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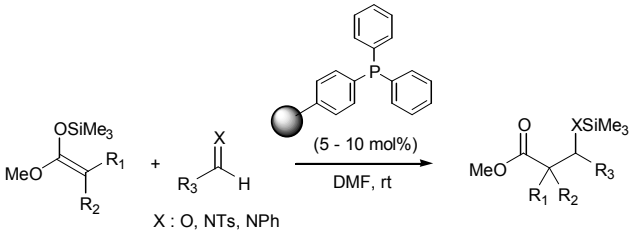

Polystyrene-supported PPh_3 (PS-PPh_3) catalyzes the aldol reaction of aldehydes and imines to give the corresponding products in good to high yields.

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Polymer-supported PPh_3 as a reusable organocatalyst for the Mukaiyama aldol and Mannich reaction

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An easily accessible and user-friendly polymer-supported phosphine PS-PPh_3 catalyzes the aldol reaction of aldehydes and imines. A broad range of aldehydes and imines could be applied under mild conditions using 5-10 mol% PS-PPh_3. PS-PPh_3 was easily recovered and reused with minimal loss of activity.

Introduction

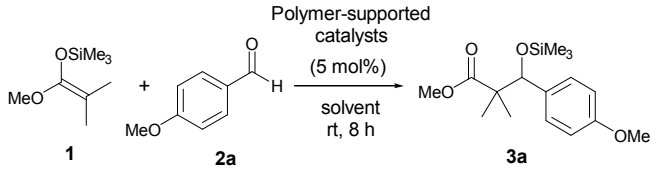
Polymer-supported catalysts have attracted much attention in recent decades due to their inherent advantages in synthetic chemistry, e.g., simplification of reaction procedures including easy recovery of the catalyst by filtration, application to automated systems, and recycling of the catalyst.[1] Polymer-supported organobases have attracted much attention in recent years. For example, polymer-supported bicyclic guanidine, 1,5,7-triazabicyclo[4,4,0]dec-5-ene polystyrene (PS-TBD), acts as a good catalyst for the Henry reaction,[2] ring-openings of epoxides,[3,4] aldol-type condensations and Michael additions.[3] Polymer-supported formamides, phosphoramide, diazaphosphorine (PS-BEMP) and phosphine (PS-PPh_3) also act as good catalysts for carbon-carbon bond forming reactions including Michael additions,[5] ring-openings of epoxides,[6] cyanosilylation,[7] allylation of aldehydes with allyltrichlorosilane and aldol reactions with trichlorosilyl enol ethers.[8,9] Recently, we have also reported cyanosilylation of aldehydes, ketones, imines and aziridines catalyzed by PS-TBD.[10] In an effort to apply polymer-supported organobases to other useful reactions, Mukaiyama aldol reactions of aldehydes and imines were examined.

The aldol reaction has become a fundamental method for forming carbon-carbon bonds in modern organic synthesis. One of the most commonly used and best understood is the Mukaiyama aldol reaction (addition of silyl enol ethers to carbonyl compounds).[11,12] This method has many advantages over the previous aldol reactions, such as mild reaction conditions, nonreversibility and lower production of side products. Therefore, several efficient catalysts have been developed in the last 40 years to realize high yields and selectivities of this reaction.[13] This reaction can be catalyzed either by a Lewis acid via activation of the electrophiles or by a Lewis base via activation of the nucleophiles. For example, the reaction could be catalyzed by fluoride,[14] phosphines,[15] lithium amides,[16] lithium acetate,[17] lithium alkoxides,[18] quaternary ammonium dendrimers,[19] ammonium phenoxide,[20] *N*-oxides,[21] *N*-methyl imidazole,[22] sodium phenoxide-phosphine oxides,[23] *N*-heterocyclic carbenes,[24] Verkade superbases[25] and dendritic HMPA.[26] Herein, we report that easily accessible and user-friendly polymer-supported phosphine PS-PPh_3 acts as an efficient and reusable catalyst for the Mukaiyama aldol and Mannnich reactions.[27, 28]

Results and discussion

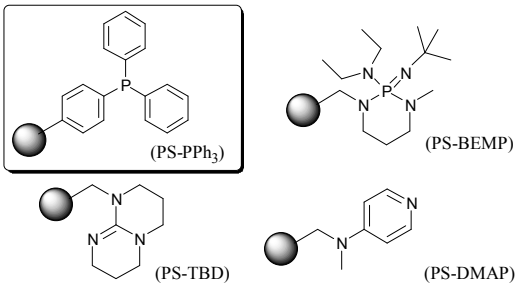
First, we examined the catalytic activity of various commercially available polymer-supported bases (Figure 1) in the reaction of 4-methoxybenzaldehyde with a trimethylsilyl enol ether derived from methyl isobutyrate. The reaction was carried out by adding the trimethylsilyl enol ether and aldehyde to DMF containing 5 mol% of the polymer-supported base at room temperature. The reaction was monitored by TLC. After the reaction was completed, EtOAc was added to the mixture and the polymer-supported base was removed by filtration. The filtrate was concentrated under vacuum and purified by column chromatography to afford the pure product. The results are summarized in Table 1. Good product yields were obtained in the presence of a catalytic amount of the PS-PPh_3. Interestingly, the product was obtained in lower yields when PS-TBD and PS-BEMP, which have higher basicity than PS-PPh_3, were used as catalysts. PS-DMAP was also used as a catalyst, however chemical yields were low. The reactions performed in THF, MeCN, CH_2Cl_2 and toluene were inferior when compared to that performed in DMF. Solvent free conditions (SFC) were also effective. However, a longer reaction time was required to obtain the product in a good yield.

Table 1 Optimization of the reaction conditions.

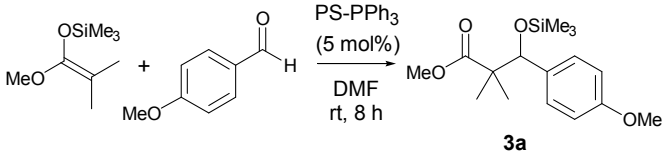


Entry	Base	Solvent	Yield (%)
1	PS-PPh_3[a]	DMF	94
2	PS-TBD	DMF	63
3	PS-BEMP[b]	DMF	55
4	PS-DMAP[c]	DMF	35
5		CH_3CN	45
6		THF	36
7		CH_2Cl_2	25
8		toluene	20
9		SFC[d]	60
10		SFC	81[e]

[a] PS-PPh_3: Diphenylphosphino-polystyrene. [b.] PS-BEMP: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine polystyrene. [c.] PS-DMAP: *N*-(Methyl polystyrene)-4-(methylamino)pyridine. [d] SFC: solvent free condition. [e] Reaction time: 24 h.



The recovery and reuse of PS-PPh_3 are illustrated in Scheme 1 for the reaction of 4-methoxybenzaldehyde with a trimethylsilyl enol ether. After the reaction was completed, ethyl acetate was added to the reaction mixture and the catalyst was recovered by filtration. The recovered catalyst was washed (H_2O, NH_3, acetone), dried and then reused. The catalyst maintained its catalytic activity after three runs.

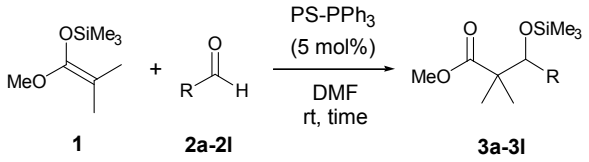


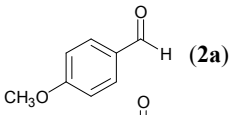
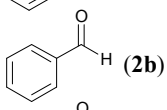
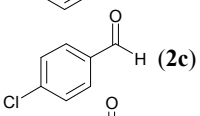
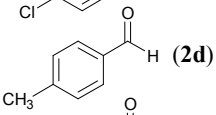
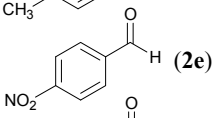
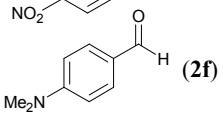
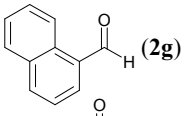
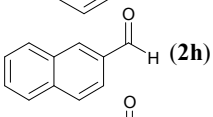
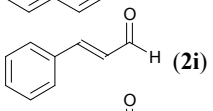
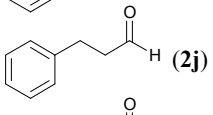
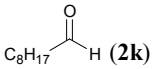
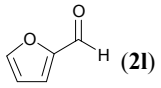
Runs	Yield (%)
1st	94
2nd	90
3rd	86
4th	92

Scheme 1. Reuse of recovered PS-PPh_3.

In order to clarify the scope of this reaction, several aldehydes were examined in the presence of 10 mol% PS-PPh_3 (Table 2). Aromatic aldehydes with either electron-donating or electron-withdrawing groups afforded the corresponding products in high yields. Compared with the aromatic aldehyde, the aliphatic aldehyde required a longer reaction time, which was similar to that for other Lewis base catalysts. Heteroaromatic aldehydes also worked well.

Table 2 PS-PPh_3 catalyzed Mukaiyama aldol reaction of various aldehydes.

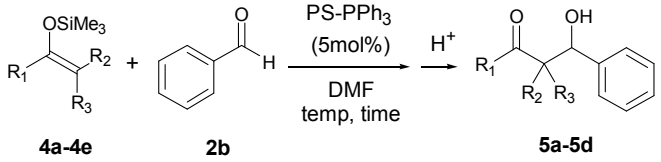


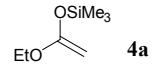
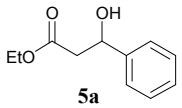
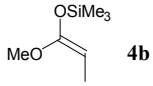
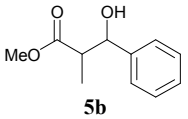
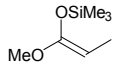
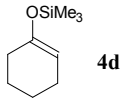
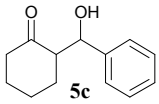
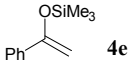
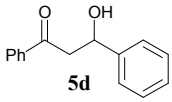
Entry	Aldehyde	product	time	Yield (%)[a,b]
1	 (**2a**)	**3a**	8 h	94
2	 (**2b**)	**3b**	8 h	91
3	 (**2c**)	**3c**	4 h	95
4	 (**2d**)	**3d**	6 h	88
5	 (**2e**)	**3e**	8 h	85
6	 (**2f**)	**3f**	8 h	90
7	 (**2g**)	**3g**	8 h	86
8	 (**2h**)	**3h**	4 h	95
9	 (**2i**)	**3i**	8 h	93
10	 (**2j**)	**3j**	24 h	87
11	 (**2k**)	**3k**	24 h	91
12	 (**2l**)	**3l**	4 h	84

[a]Isolated yield.

This PS-PPh_3 catalyzed Mukaiyama aldol reaction was also examined by using other silyl enol ethers (Table 3). Good product yields were obtained trimethylsilyl enol ether derived from ethyl acetate. In this case, the reaction also proceeded smoothly when 1 mol % of PS-PPh_3 was used. Moderate *syn*-diastereoselectivity was observed irrespective of the geometry of the silyl enol ether derived from methyl propionate. This trend is the same as previous reports. Unfortunately, we had no success with ketone silyl enol ethers under these conditions.

Table 3 PS-PPh_3 catalyzed aldol reaction of various silyl enol ethers.

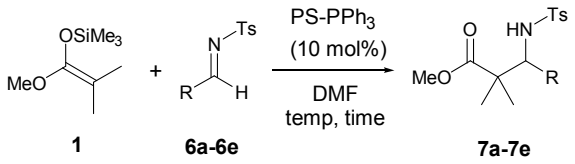


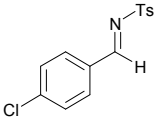
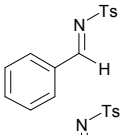
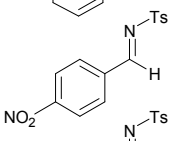
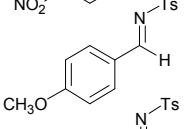
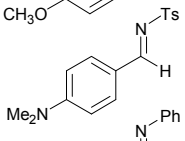
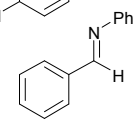
Entry	silyl enol ethers	time	products	Yield (%)[a,b] (*syn* : *anti*)
1	 **4a**	0.5 h	 **5a**	85
2[c]		8 h		84
3	 **4b** (*E* : *Z* = 81 : 19)	4 h	 **5b**	90 (66 : 34)
4	 **4c** (*E* : *Z* = 21 : 79)	4 h		74 (70 : 30)
5	 **4d**	24 h	 **5c**	trace
6	 **4e**	24 h	 **5d**	trace

[a]Isolated yield. [b] In this cace, silyl ether product was unstable, then product was obtained as OH form after hydrolysis. [c] 1 mol% of PS-PPh_3 was used.

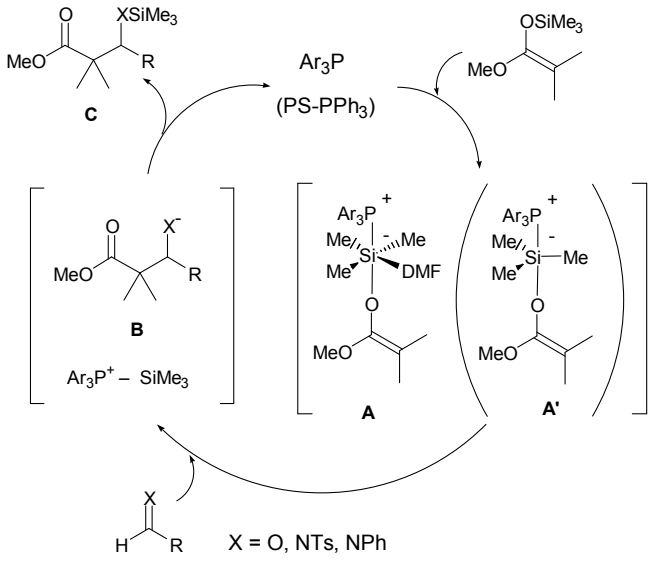
Furthermore, we have extended the present catalytic system to the reaction with imines (Mannich reaction).[29,30,31] The corresponding β-amino esters were obtained in moderate to good yields in the presence of 10 mol% PS-PPh_3 (Table 4). In this case, the reaction rates were influenced by the type of substituent on the benzene ring. When aromatic aldimines having electron-donating groups were used, the reaction proceeded more slowly compared with those using aldimines having electron-withdrawing groups. The product was obtained in lower yields when other polymer-supported organobases such as PS-TBD and PS-BEMP were used instead of PS-PPh_3 (Table 4, entries 1 vs. 2,3). We also examined three component Mannich reaction between silyl enol ether **1**, benzaldehyde (**2b**) and tosylamine, unfortunately the product was obtained as a mixture of aldol product **3b** and Mannich product **7b**.

Table 4 PS-PPh_3 catalyzed aldol reaction of various Imines.



Entry	Aldehyde		temperature	time	Yield (%)[a]
1		(**6a**)	r.t	18 h	85 (**7a**)
2[b]		(**6a**)	r.t.	18 h	33 (**7a**)
3[c]		(**6a**)	r.t.	18 h	20 (**7a**)
4		(**6b**)	40 °C	12 h	82 (**7b**)
5		(**6c**)	**r.t.**	12 h	90 (**7c**)
6		(**6d**)	40 °C	24 h	74 (**7d**)
7		(**6e**)	40 °C	24 h	56 (**7e**)
8		(**6e**)	**r.t.**	18 h	82 (**7f**)

[a]Isolated yield. [b]PS-TBD was used instead of PS-PPh_3. [c]PS-BEMP was used instead of PS-PPh_3.



Scheme 2. Proposed mechanism.

A possible mechanism is illustrated in Scheme 2. First, phosphorus atom of PS-PPh_3 coordinates the silicon atom of the silyl enol ether to form activated hexa coordinated silicon species **A** or penta coordinated silicon species **A'** and the O-Si bond is activated. Next, the nucleophilicity of the enol ether is enhanced and readily reacts with an electrophile to produce the alkoxide or amino ion **B** and silylphosphonium salt. Finally, immediate silylation occurs to give the silylated adduct **C** with regeneration of PS-PPh_3. This mechanism is similar to that of previously reported Lewis base catalyzed aldol reactions. [13a, 16-25, 31]

Experimental

All reactions were performed under an argon atmosphere using oven-dried glassware. Flash column chromatography was performed using silica gel Wakogel C-200. Preparative thin-layer chromatography was carried out on silica gel Wakogel B-5F. Dehydrate DMF, THF, toluene and CH_3CN were purchased from Wako Chemical. Other commercially available reagents was used as received without further purification. Yields refer to isolated compounds estimated to be >95% pure, as determined by ^1H NMR spectroscopy. IR spectra were recorded on a JUSCO FT/IR-430 spectrometer. ^1H and ^{13}C NMR spectra were determined for solutions in $CDCl_3$ with Me_4Si as internal standard on a Bruker Avance III instrument. HRMS data were measured on a JEOL JMS-700 mass spectrometer.

General procedure for PS-PPh_3 catalyzed Mukaiyama aldol reaction of aldehyde with silyl ketene acetals

To a suspension of PS-PPh_3 (0.05mmol) in DMF (1 mL) was added aldehyde (1.0 mmol) and silyl ketene acetal (1.25 mmol) at room temperature. After the reaction was complete (as determined by TLC), EtOAc (5 ml) was added to the mixture and PS-PPh_3 was separated by filtration. The filtrate was concentrated under vacuum and purified by column chromatography on silica gel (EtOAc:hexane = 1:3) to give the corresponding product. The recovered catalyst is reusable after washing (acetone, NH_4OH and water) and drying in vacuo.

General procedure for PS-PPh_3 catalyzed Mannich reaction of imine with silyl ketene acetals

To a suspension of PS-PPh_3 (0.10 mmol) in DMF (1 mL) was added imine (1.0 mmol) and silyl ketene acetal (1.25 mmol) at room temperature or 30 °C. After the reaction was complete (as determined by TLC), EtOAc (15 ml) was added to the mixture and PS-PPh_3 was separated by filtration. The filtrate was washed with brine and water and dried over anhydrous Na_2SO_4, then evaporated. The crude mixture was purified by preparative TLC (EtOAc:hexane = 1:1) to afford the corresponding product.

Methyl 3-(4-methoxyphenyl)-2,2-dimethyl-3-trimethylsilyloxy-propionate (3a)[32]: Colorless oil; yield: 303 mg (94 %); ^1H NMR (500 MHz, CDCl3): δ 0.09 (s, 9H), 0.93 (s, 3H), 1.06 (s, 3H), 3.63 (s, 3H), 3.75 (s, 3H), 4.88 (s, 1H), 6.77 (d, J = 8.6 Hz, 5H), 7.13 (d, J = 8.6 Hz, 5H); ^{13}C NMR (125 MHz, CDCl3) δ =0.0, 19.1, 21.7, 49.1, 51.6, 55.2, 78.8, 112.8, 128.8, 133.0, 158.9, 177.4; HRMS (FAB): m/z: calcd for $C_{16}H_{27}O_4Si$: 323.1679; found: 323.1961 $[M + H]^+$.

Methyl 2,2-dimethyl-3-phenyl-3-trimethylsilyloxypropionate (3b)[17c]: Colorless oil; yield: 255 mg (91 %); ^1H NMR (500 MHz, CDCl3): δ 0.04 (s, 9H), 0.97 (s, 3H), 1.11 (s, 3H), 3.66 (s, 3H), 4.96 (s, 1H), 4.92 (s, 1H), 7.22-7.32 (m, 5H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.0, 19.0, 22.0, 49.1, 51.7, 79.2, 127.4, 127.8, 140.7, 177.3; HRMS (FAB): m/z: calcd for $C_{15}H_{25}O_3Si$: 281.1573; found: 281.1568 $[M + H]^+$.

Methyl 3-(4-chlorophenyl)-2,2-dimethyl-3-trimethylsilyloxy-propionate (3c)[17c]: White solid; m.p. 53 °C; yield: 299 mg (95 %); ^1H NMR (500 MHz, CDCl3): δ 0.06 (s, 9H), 0.94 (s, 3H), 1.08 (s, 3H), 3.64 (s, 3H), 7.18 (d, J = 8.4 Hz, 5H), 7.23 (d, J = 8.6 Hz, 5H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.0, 19.2, 21.4, 48.9, 51.7, 78.5, 127.6, 129.2, 133.1, 139.5, 177.0; HRMS (FAB): m/z: calcd for $C_{15}H_{24}ClO_3Si$: 315.1183; found: 315.1175 $[M + H]^+$.

Methyl 3-(4-methylphenyl)-2,2-dimethyl-3-trimethylsilyloxy-propionate (3d)[33]: Colorless oil; yield: 259 mg (88 %); ^1H NMR (500 MHz, CDCl3): δ 0.07 (s, 9H), 0.96 (s, 3H), 1.09 (s, 3H), 2.30 (s, 3H), 3.65 (s, 3H), 4.91 (s, 1H), 7.05 (d, J = 8.0 Hz, 5H), 7.13 (d, J = 8.0 Hz, 5H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.0, 19.1, 21.1, 21.7, 49.0, 51.6, 79.0, 127.7, 128.1, 136.9, 137.8, 177.5; HRMS (FAB): m/z: calcd for $C_{16}H_{27}O_3Si$: 295.1729; found: 295.1727$[M + H]^+$.

Methyl 2,2-dimethyl-3-(4-Nitromethoxyphenyl)-3-trimethyl-silyloxypropionate (3e)[33]: White solid; m.p. 116 °C; yield: 275 mg (85 %); ^1H NMR (500 MHz, CDCl3): δ 0.04 (s, 9H), 0.97 (s, 3H), 1.11 (s, 3H), 3.65 (s, 3H), 5.03 (s, 1H), 7.43 (d, J = 8.5 Hz, 5H), 8.13 (d, J = 8.5 Hz, 5H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.0, 19.7, 21.3, 49.1, 52.0, 78.3, 122.8, 128.5, 147.4, 148.7, 176.5.; HRMS (FAB): m/z: calcd for $C_{15}H_{24}NO_5Si$: 326.1424; found: 326.1417 $[M + H]^+$.

Methyl 3-[4-(dimethylamino)phenyl]-2,2-dimethyl-3-trimethyl-silyloxypropionate (3f)[17c]: White solid; m.p. 76 °C; yield: 291 mg (90 %); ^1H NMR (500 MHz, CDCl3): δ 0.08 (s, 9H), 0.94 (s, 3H), 1.07 (s, 3H), 2.92 (S, 6H), 3.64 (s, 3H), 4.86 (s, 1H), 6.55-6.70 (m, 2H), 7.05-7.15 (m, 2H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.0, 18.9, 21.9, 40.7, 49.2, 51.7, 79.1, 111.4, 128.7, 149.8, 177.6; HRMS (FAB): m/z: calcd for $C_{17}H_{30}NO_3Si$: 324.1995; found: 324.2007 [M + H]$^+$.

Methyl 2,2-dimethyl-3-(naphthalene-1-yl)-3-trimethylsilyloxy-propionate (3g)[34] : Colorless oil; yield: 285 mg (86 %); ^1H NMR (500 MHz, CDCl3): δ -0.11 (s, 9H), 0.93 (s, 3H), 1.21 (s, 3H), 3.64 (s, 3H), 6.00 (s, 1H), 7.40-7.51 (m, 3H), 7.69 (d, J = 7.4 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 7.4 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ = -0.1, 18.5, 23.0, 50.0, 51.8, 72.9, 123.2, 124.8, 125.0, 125.7, 127.0, 127.9, 128.8, 131.6, 133.2,

136.8, 177.5; HRMS (FAB): *m/z*: calcd for $C_{19}H_{27}O_3Si$: 331.1729; found: 331.1736 $[M + H]^+$.

Methyl 2,2-dimethyl-3-(naphthalene-2-yl)-3-trimethylsilyloxy-propionate (3h)[35]: White solid; m.p. 70 °C; yield: 315 mg (95 %); ^{1}H NMR (500 MHz, CDCl3): δ -0.05 (s, 9H), 1.02 (s, 3H), 1.15 (s, 3H), 3.67 (s, 3H), 5.13 (s, 1H), 7.40-7.47 (m, 3H), 7.67 (d, *J* = 4.4 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.81 (d, *J* = 7.4 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.0, 19.2, 21.8, 49.3, 51.7, 79.3, 125.7, 125.9, 126.1, 126.6, 127.0, 127.6, 128.0, 132.8, 133.0, 138.5, 177.3; HRMS (FAB): *m/z*: calcd for $C_{19}H_{27}O_3Si$: 331.1729; found: 331.1715 $[M + H]^+$.

Methyl (4*E*)-2,2-dimethyl-5-phenyl-3-trimethylsilyloxypent-4-enoate (3i)[33]: Colorless oil; yield: 285 mg (93 %); ^{1}H NMR (500 MHz, CDCl3): δ 0.00 (s, 9H), 1.02 (s, 3H), 1.11 (s, 3H), 3.59 (s, 3H), 4.40 (d, *J* = 7.0 Hz, 1H), 6.03 (dd, *J* = 7.0, 16.0 Hz, 1H), 6.41 (d, *J* = 16.0 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.24 (dd, *J* = 7.2, 7.5 Hz, 2H), 7.28 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.3, 19.8, 21.2, 48.5, 51.8, 78.5, 126.4, 127.6, 128.6, 128.8, 132.0, 136.8, 177.1; HRMS (FAB): *m/z*: calcd for $C_{17}H_{27}O_3Si$: 307.1729; found: 307.1740 $[M + H]^+$.

Methyl 2,2-dimethyl-5-phenyl-3-trimethylsilyloxypentanoate (3j)[33]: Colorless oil; yield: 268 mg (87 %); ^{1}H NMR (500 MHz, CDCl3): δ 0.14 (s, 9H), 1.08 (s, 3H), 1.16 (s, 3H), 1.61-1.66 (m, 2H), 2.40-2.55 (m, 2H), 3.64 (s, 3H), 3.97 (d, *J* = 12.0 Hz, 1H), 7.16-7.22 (m, 2H), 7.24-7.29 (m, 2H); ^{13}C NMR (125 MHz, CDCl3) δ =0.9, 20.3, 21.6, 33.5, 35.2, 48.4, 51.8, 77.5, 125.8, 128.3, 128.4, 142.2, 177.6; HRMS (FAB): *m/z*: calcd for $C_{17}H_{29}O_3Si$: 309.1886; found: 309.1876 $[M]^+$.

Methyl 2,2-dimethyl3-trimethylsilyloxy-dodecanoate (3k)[17c]: Colorless oil; yield: 288 mg (91 %); ^{1}H NMR (500 MHz, CDCl3): δ 0.09 (s, 9H), 0.85 (t, *J* = 8.1 Hz, 3H), 1.04 (s, 3H), 1.11 (s, 3H), 1.11-1.45 (m, 12H), 1.53-1.64 (m, 2H), 3.64 (s, 3H), 3.83 (d, *J* = 9.1 Hz, 1H); ^{13}C NMR (125 MHz, CDCl3) δ = 0.7, 14.1, 20.1, 21.6, 22.6, 27.0, 29.2, 29.5, 29.7, 31.8, 32.8, 48.2, 51.5, 77.7, 177.8; HRMS (FAB): *m/z*: calcd for $C_{17}H_{37}O_3Si$: 317.2512; found: 317.2523 $[M + H]^+$.

Methyl 3-(2-furyl)-2,2-dimethyl-3-trimethylsilyloxy-propionate (3l)[17c]: Colorless oil; yield: 242 mg (84 %); ^{1}H NMR (500 MHz, CDCl3): δ 0.00 (s, 9H), 1.04 (s, 3H), 1.23 (s, 3H), 3.68 (s, 3H), 5.00 (s, 1H), 6.20 (d, *J* = 3.2 Hz, 1H), 6.31 (d, *J* = 3.2 Hz, 1H), 7.32-7.34 (m, 1H); ^{13}C NMR (125 MHz, CDCl3) δ = -0.3, 19.6, 21.2, 48.6, 51.8, 73.5, 107.9, 109.9, 141.5, 154.4, 176.8; HRMS (FAB): *m/z*: calcd for $C_{13}H_{23}O_4Si$: 271.1366; found: 271.1363 $[M + H]^+$.

E**thyl 3-3-hydroxy-3-phenylpropionate (5a)[33]:** Colorless oil; yield: 165 mg (85 %); ^{1}H NMR (500 MHz, CDCl3): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.70 (dd, *J* = 3.9, 16.4 Hz, 1H), 2.76 (dd, *J* = 9.0, 16.4 Hz, 1H), 3.30-3.34 (brs, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 5.13 (dd, *J* = 2.8, 8.8 Hz, 1H), 7.28-7.31 (m, 1H), 7.35-7.39 (m, 4H); ^{13}C NMR (125 MHz, CDCl3) δ = 14.1, 43.2, 60.9, 70.3, 125.6, 127.8, 128.5, 142.4, 172.4; HRMS (FAB): *m/z*: calcd for $C_{11}H_{15}O_3$: 195.1021; found: 195.1010 $[M + H]^+$.

M**ethyl 3-3-hydroxy-2-methyl-3-phenylpropionate (5b)[17c]:** *syn* / *anti* mixture: Colorless oil; yield: 175 mg (90 %); HRMS (FAB): *m/z*: calcd for $C_{11}H_{15}O_3$: 195.1021; found: 195.1033 $[M + H]^+$. *syn* Isomer: ^{1}H NMR (500 MHz, CDCl3): δ 1.12 (d, *J* = 7.2 Hz, 3H), 2.78 (dq, *J* = 4.1, 7.2 Hz, 1H), 2.93-2.98 (brs, 3H), 3.67 (s, 3H), 5.10 (d, *J* = 4.0 Hz, 1H), 7.23-7.30 (m, 1H), 7.31-7.39 (m, 4H); ^{13}C NMR (125 MHz, CDCl3) δ = 10.6, 46.3, 51.8, 73.5, 125.9, 127.5, 128.2, 141.3, 176.2.; *anti* Isomer: ^{1}H NMR (500 MHz, CDCl3): δ 1.00 (d, *J* = 7.2 Hz, 3H), 2.83 (dq, *J* = 7.2, 8.4 Hz, 1H), 2.90-3.05 (brs, 3H), 3.72 (s, 3H), 4.74 (d, *J* = 8.4 Hz, 1H), 7.25-7.30 (m, 1H), 7.31-7.42 (m, 4H); ^{13}C NMR (125 MHz, CDCl3) δ = 14.4, 47.1, 51.8, 76.4, 126.6, 128.1, 128.5, 141.5, 176.3.

Methyl 4-chlorophenyl-2,2-Dimethyl-3-(tosylamino)-propionate (7a)[31e]: White solid; m.p. 145 °C; yield: 332 mg (84 %); ^{1}H NMR (500 MHz, CDCl3): δ 1.03 (s, 3H), 1.31 (s, 3H), 2.30 (s, 3H), 3.58 (s, 3H), 4.27 (d, *J* = 9.5 Hz, 1H), 6.13 (d, *J* = 9.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.94-7.00 (m, 4H), 7.35 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ = 21.3, 22.5, 24.9, 46.9, 52.2, 64.3, 126.8, 128.0, 129.1, 129.3, 135.7, 137.5, 143.0, 176.4; HRMS (FAB): *m/z*: calcd for $C_{19}H_{23}ClNO_4S$: 396.1036; found: 396.1022 $[M + H]^+$.

Methyl 2,2-dimethyl-3-phenyl-3-(tosylamino)propionate (7b) [31e] : White solid; m.p. 130 °C; yield: 285 mg (82 %); ^{1}H NMR (500 MHz, CDCl3): δ 1.08 (s, 3H), 1.26 (s, 3H), 2.24 (s, 3H), 3.60 (s, 3H), 4.38 (d, *J* = 9.9 Hz, 1H), 6.30 (d, *J* = 9.9 Hz, 1H), 6.88 (d, *J* = 7.0 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 2H), 9.68-7.10 (m, 5H), 7.39 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ = 21.2, 221., 24.2, 41.3, 52.0, 64.5, 126.7, 127.2, 127.7, 127.8, 128.9, 136.9, 137.4, 142.5, 176.4; HRMS (FAB): *m/z*: calcd for $C_{19}H_{24}NO_4S$: 362.1426; found: 362.1429 $[M + H]^+$.

Methyl 2,2-dimethyl-3-(4-nitrophenyl)-3-(tosylamino)-propionate (7c) [31e]: White solid; m.p. 180 °C; yield: 365 mg (90 %); ^{1}H NMR (500 MHz, CDCl3): δ 1.05 (s, 3H), 1.33 (s, 3H), 2.26 (s, 3H), 3.59 (s, 3H), 4.39 (d, *J* = 9.3 Hz, 1H), 6.30 (d, *J* = 9.3 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ = 21.4, 22.5, 24.9, 46.8, 52.4, 64.2, 123.0, 126.8, 129.0, 129.2, 137.3, 143.4, 144.7, 147.1, 176.1; HRMS (FAB): *m/z*: calcd for $C_{19}H_{23}N_2O_6S$: 407.1277; found: 407.1273 $[M + H]^+$.

Methyl 3-(4-methoxyphenyl)- 2,2-dimethyl-3-(tosylamino)-propionate (7d) [31e]: White solid; m.p. 114 °C; yield: 289 mg (64 %); ^{1}H NMR (500 MHz, CDCl3): δ 1.04 (s, 3H), 1.25 (s, 3H), 2.25 (s, 3H), 3.57 (s, 3H), 3.68 (s, 3H), 4.29 (d, *J* = 9.2 Hz, 1H), 6.12 (d, *J* = 9.2 Hz, 1H), 6.53 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 7.81 (dd, *J* = 8.5, 8.8 Hz, 2H); ^{13}C NMR

(125 MHz, CDCl3) δ = 21.5, 22.5, 24.6, 47.6, 52.2, 55.4, 64.3, 113.1, 126.9, 129.0, 129.1, 129.4, 137.7, 142.4, 158.8, 176.4; HRMS (FAB): *m*/*z*: calcd for $C_{20}H_{26}NO_5S$: 392.1532; found: 392.1540 $[M + H]^+$.

Methyl 3-[4-(dimethylamino)phenyl]-2,2-dimethyl-3-(tosylamino)-propionate (7e) [31e]**:** White solid; m.p. 155 °C; yield: 226 mg (56 %); ^{1}H NMR (500 MHz, CDCl3): δ 1.04 (s, 3H), 1.25 (s, 3H), 2.23 (s, 3H), 2.82 (s, 6H), 3.57 (s, 3H), 4.23 (d, *J* = 9.6 Hz, 1H), 5.99 (d, *J* = 9.6 Hz, 1H), 6.34 (d, *J* = 7.1 Hz, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (125 MHz, CDCl3) δ = 21.3, 22.2, 24.5, 40.4, 47.3, 51.9, 64.4, 111.9, 126.9, 128.6, 128.8, 142.0, 149.7, 162.5, 176.8; HRMS (FAB): *m*/*z*: calcd for $C_{20}H_{26}NO_5S$: 392.1532; found: 392.1540 $[M + H]^+$.

Methyl 2,2-dimethyl-3-phenyl-3-(phenylamino)propionate (7f) [31e]**:** Colorless oil; yield: 234 mg (82 %); ^{1}H NMR (500 MHz, CDCl3): δ 1.13 (s, 3H), 1.24 (s, 3H), 2.23 (s, 3H), 3.62 (s, 3H), 4.46 (s, 1H), 4.70 (br, 1H), 6.46 (d, *J* = 8.5 Hz, 2H), 6.56 (dd, *J* = 8.5, 8.8 Hz, 1H), 7.00 (d, *J* = 8.5, 8.8 Hz, 2H), 7.20-7.28 (m, 5H). ^{13}C NMR (125 MHz, CDCl3) δ = 20.7, 24.5, 47.0, 52.0, 64.3, 113.3, 117.2, 127.4, 128.0, 128.2, 129.0, 139.2, 146.9, 177.0; HRMS (FAB): *m*/*z*: calcd for $C_{18}H_{22}NO_2$: 284.1651; found: 286.1648 $[M + H]^+$

Conclusions

In conclusion, we demonstrated the easily accessible and user-friendly polymer-supported phosphine PS-PPh_3 catalyzed Mukaiyama aldol and Mannich reactions. A broad range of aldehydes and imines could be applied under mild conditions using 5-10 mol% PS-PPh_3. Furthermore, PS-PPh_3 was easily recovered and reused with minimal loss of activity after three runs. These reactions provide a simple and environmentally friendly method for the synthesis of β-hydroxy esters and β-amino esters.

Notes and references

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1 Recent reviews, see (a) C. A. McNamara, M. J. Dixon, M. Bradley, *Chem. Rev.,* 2002, **102**, 3275-3300; (b) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.,* 2003, **103**, 3401-3429; (c) F. Cozzi, *Adv. Synth. Catal.,* 2006, **348**. 1367-1390; (d) W. J. Sommer, M. Weck, *Cood. Chem. Rev.,* 2007, **251**, 860-873; (e) C. K. Kwong, R. Huang, M. Zhang, P. H. Toy, *Chem. Eur. J.,* 2007, **13**, 2369-2376; (f) M. R. Buchmeiser, *Chem. Rev*., 2009, **109**, 303-321; (g) Z. Wang. G. Chen, K. Ding, *Chem. Rev*., 2009, **109**, 322-359; (h) S. Ikegami, H. Hamamoto, *Chem. Rev*., 2009, **109**, 583-593; (i) J. Lu, P. H. Toy, *Chem. Rev*., 2009, **109**, 815-838; (j) T. E. Kristensen, T. Hansen, *Eur. J. Org. Chem.,* 2010, **17**, 3179-3204. (j) Y. Zhang, S. N. Riduan, *Chem. Soc. Rev*., 2012, **41**, 2093-2094.

2 D. Simoni, R. Rondanin, M. Morini, R. Baruchello, F. P. Invidiata, *Tetrahedron Lett.,* 2000, **41**, 1607-1610.

3 F. Fringuelli, F. Pizzo, C. Vittoriani, L. Vaccaro, *Chem. Commun*., 2004, 2756-2757

4 (a) F. Fringuelli, F. Pizzo, C. Vittoriani, L. Vaccaro,. *Eur. J. Org. Chem*., 2006, 1231-1236; (b) D. Lanari, R. Balini, A. Palmieri, F. Pizzo, L. Vaccaro, *Eur. J. Org. Chem*., 2011, 2874-2884.

5 (a) D. Bensa, T. Constantieux, J. Rodriguez, *Synthesis*, 2004, 923-927. (b) A, W. Pilling, J. Boehmer, D. J. Dixon, *Angew. Chem. Int. Ed*., 2007, **46**, 5428-5430. (c) A. W. Pilling, J. Boehmer, D. J. Dixon, *Chem. Commun.*, 2008, 832-834. (d) R. Ballini, L. Barboni, L. Castrica, F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, *Adv. Synth. Catal*., 2008, **350**, 1218-1224. (e) Bonollo, D. Lanari, J. M. Longo, L. Vaccaro, *Green. Chem*., 2012, **14**, 164-169.

6 T. Angelini, F. Fringuelli, D. Lanari, F. Pizzo, L. Vaccaro, *Tetrehedron Lett.*, 2010, **51**, 1566-1569

7 G. Strappaveccia, D. Lanari, D. Gelman, F. Pizzo, O. Rosati, M. Curini, L. Vaccaro, *Green Chem.* 2013, **15**, 199-204.

8 C. Ogawa, M. Sugiura, S. Kobayashi, *Chem. Commun*., 2003, 191-193.

9 R. A. Flowers II, X. Liu, C. Timmons, G. Li, *Euro. J. Org. Chem.*, 2004, 2988-2990.

10 (a) S. Matsukawa, S. Fujikawa *Tetrahedron Lett*., 2012, **53**, 1075-1077. (b) S. Matsukawa, T. Harada, S. Yasuda, *Org. Biomol. Chem.*, 2012, **10**, 4886-4890. (c) S. Matsukawa, K. Tsukamoto, S. Yasuda, T. Harada, *Synthesis*, 2013, **45**, 2959-2965.

11 (a) T. Mukaiyama, K. Narasaka, K. Banno, *Chem. Lett*., 1973, 1011–1114. (b) T. Mukaiyama, K. Banno, K. Narasaka, *J. Am. Chem. Soc.,* 1974, **96**, 7503–7509. (c) T. Mukaiyama, T. Izawa, K. Saigo, *Chem. Lett.,* 1974, 323–326.

12 For selected reviews, see: (a) T. Mukaiyama, *Org. React.,* 1982, **28**, 203-331. (b) T. Mukaiyama, S. Kobayashi, *Org. React.,* 1994, **46**, 1-103. (c) S. G. Nelson, *Tetrahedron:Asymmetry,* 1998, **9**, 357-389. (d) H. Groger, E. M. Vogl, M. Shibasaki, *Chem.Eur. J*., 1998, **4**, 1137-1141. (e) R. Mahrwald, *Chem. Rev*., 1999, **99**, 1095-1120. (f) T. Mukaiyama, *Tetrahedron*, 1999, **55**, 8609-8670. (g) T. Mukaiyama, *Angew. Chem., Int. Ed.,* 2004, **43**, 5590-5614. (h) Modern Aldol Reactions, Vol. 1,2 (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, 2004. (i) E. M. Carreira, A. Fettes, C. Marti, *Org. React.,* 2006, **67**, 1-216. (j) M. Shibasaki, S. Matsunaga, *Chem. Soc. Rev.,* 2006, **35**, 269-279. (k) J. Gawronski, N. Wascinska, J. Gajewy, *Chem. Rev*., 2008, **108**, 5227–5252. (l) T. Kitanosono, S. Kobayashi, *Adv. Synth. Catal*., 2013, **355**, 3095-3118.

13 (a) G. L. Beutner, S. E. Denmark, *Angew. Chem. Int. Ed.*, 2013, **52**, 9086-9096. (b) S. B. J. Kan, K. K. H. Ng, I. Paterson, *Angew. Chem. Int. Ed*., 2013, **52**, 9097-9108. (c) J. Matsuo, M. Murakami, *Angew. Chem. Int. Ed.*, 2013, **52**, 9109-9118.

14 (a) R. Noyori, I. Nishida, J. Sakata, J. *J. Am. Chem. Soc.,* 1983, **105**, 1598-1608. (b) E. Nakamura, M. Shimizu, I. Kuwajima, J. Sakata, K. Yokoyama, R. Noyori, *J. Org. Chem.,* 1983, **48**, 932-945.

15 S. Matsukawa, N. Okano, T. Imamoto, *Tetrahedron Lett.,* 2000, **41**, 103–107.

16 T. Mukaiyama, H. Fujisawa, T. Nakagawa, *Hel*V. *Chim. Acta,* 2002, **85**, 4518

17 (a) T. Nakagawa, H. Fujisawa, T. Mukaiyama, *Chem. Lett*., 2003, **32**, 696–697. (b) H. Fujisawa, E. Takahashi, T. Mukaiyama, *Eur. J.*

Chem., 2006, **12**, 5082–5093. (c) T. Nakagawa, H. Fujisawa, Y. Nagata, T. Mukaiyama, *Bull. Chem. Soc. Jpn*., 2004, **77**, 1555-1567.

18 H. Fujisawa, T. Nakagawa, T. Mukaiyama, *Adv. Synth. Catal*., 2004, **346**, 1241–1246.

19 T. Mizugaki, C. E. Hetrick, M. Murata, K. Ebitani, M. D. Amiridis, K. Kaneta, *Chem. Lett.,* 2005, 420-421

20 H. Fujisawa, Y. Nagata, Y. Sato, T. Mukaiyama, *Chem. Lett.,* 2005, **34**, 842-843.

21 Hagiwara, H.; Inoguchi, H.; Fukushima, M.; Hoshi, T.; Suzuki, T. *Synlett,* 2005, 2388.

22 Hagiwara, H.; Inoguchi, H.; Fukushima, M.; Hoshi, T.; Suzuki, T. *Tetrahedron Lett*., 2006, ***47***, 5371

23 M. Hatano, E. Takagi, K. Ishihara, *Org. Lett.,* 2007, **9**, 4527–4530.

24 J. J. Song, Z. Tan, J. T. Reeves, N. K. Yee, C. H. Senanayake, *Org. Lett*., 2007, **9**, 1013-1016.

25 V. R. Chintareddy, K. Wadhwa, J. G. Verkade, *J. Org. Chem.,* 2009, **74**, 8118-8132

26 F. Mummy, R. Haag, *Synlett*, 2012, 2672-2676.

27 For some recent PPh_3 catalyzed reactions, see: (a) D. B. Ramachary, C. Venkaiah , P. M. Krishna, *Org. Lett.*, 2013, **15**, 4714-4717. (b) L. Nicolas, P. Angibaud, I. Stansfield, L. Meerpoel, S. Reymond, J. Cossy, *Tetrahedron Lett*., 2014, **55**, 849-852. (c) W. Li, J. Zhang, *Org. Lett.*, 2014, **16**, 162-165. (d) E. Li, P. Jia, L. Liang, Y. Huang, *ACS Catal.* 2014, **4**, 600-603. (e) W. Dong, P. Hu, J. Hu, X. Tong, *Tetrahedron Lett.* 2014, **55**, 1682-1685.

28 Silica-supported TBD catalyzed Mukaiyama aldol reactions have also been reported. However, a high temperature is required and chemical yield is not high. See: Srivastava, R. *J. Mol. Cat. A: Chem.* **2007**, *264*, 146-152

29 (a) I. Ojima, S. Inaba, K. Yoshida, *Tetrahedron Lett*., 1977, 3643-3646. (b) I. Ojima, S. Inaba, M. Nagai, *Synthesis* 1991, 545-547.

30 Reviews, see: (a) M. Arend, B. Westermann, N. Risch, *Angew. Chem. Int. Ed*., 1998, **37**, 1044-1070. (b) S. Kobayashi, H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069-1094. (c) A. Cordova, *Acc. Chem. Res.*, 2004, 37, 102-112. (d) G. K. Friestad, A. K. Mathies, *Tetrahedron*, 2007, **63**, 2541-2569. (e) D. Ferraris, *Tetrahedron*, 2007, 63, 9581-9597. (f) B. Yin, Y. Zhang, L.W. Xu, *Synthesis,* 2010, 3583-3595. (g) M. Hatano, K. Ishihara, *Synthesis,* 2010, 3785-3801. (h) S. Kobayashi, Y. Mori, Y. J. S. Fossey, M. M. Salter, *Chem. Rev.,* 2011, **111**, 2626-2704. (i) P. Merino, T. Tejero, *Synlett,* 2011, 1965. (j) P. S. Bhadury, H. Li, *Synlett*, 2012, 1108-1131.

31 Lewis base catalyzed reactions, see: (a) H. Fujisawa, E. Takahashi, T. Nakagawa, T. Mukaiyama, *Chem. Lett.*, 2003, **32**, 1036-1037. (b) E. Takahashi, H. Fujisawa, T. Mukaiyama, *Chem. Lett*., 2004, **33**, 936-937. (c) S. Matsukawa, K. Obu, *Chem. Lett.*, 2004, **33**, 1626-1627. (d) E. Takahashi, H. Fujisawa, T. Mukaiyama, *Chem. Lett.*, 2005, **34**, 84-85. (e) H. Fujisawa, E. Takahashi, T. Mukaiyama *Chem. Eur. J.* 2006, **12**, 5082-5093.

32 N. Giuseppone, P. Van de Weghe, M. Mellah, J. Collin *Tetrahedron,* 1998, **54**, 13129-13148.

33 G. Onodera, T Toeda, N. Toda, D. Shibagishi, R. Takeuchi *Tetrahedron*, 2010, **66**, 9021-9031.

34 K. Gedrich, M. Heitbaum, A. Notzon, I. Senkovska, R. Fröhlich, J. Getzschmann, U. Mueller, F. Glorius, S. Kaskel *Chem. Euro. J*., 2011, **17**, 2099-2106.

35 M. Abe, M. Ikeda, Y. Shirodai, M. Nojima *Tetrahedron Lett*. 1996, **37**, 5901-5904.