SUPPORTING INFORMATION

E-factor minimized protocols for the Polystyryl-BEMP catalyzed conjugate additions of various nucleophiles to $\alpha,\beta$-unsaturated carbonyl compounds

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Experimental section

All chemicals were purchased and used without any further purification. GC analyses were performed by using Hewett-Packard HP 5890 series II equipped with a capillary column SPB-5 (30 m, 0.25 mm), a FID detector and hydrogen as gas carrier. GC-EIMS analyses were carried out by using a Hewett-Packard HP 6890 Series GC system/5973 Mass Selective Detector equipped with an electron impact ionizer at 70 eV. All 1H NMR and 13C NMR spectra were recorded at 200 MHz or 400 MHz, and at 50.3 or 100.6 MHz respectively, using a Bruker DRX-ADVANCE 200 MHz and a Bruker DRX-ADVANCE 400 MHz spectrometers. Deuterated solvents were used with the residual peak as internal standard, or TMS in the case of CDCl3. Chemical shift was reported in ppm and coupling constants in Hertz. All melting points were measured with Buchi Melting Point 510 apparatus and are uncorrected. Microanalyses were realized by using a Carlo Erba Elemental analyzer mod. 1106. Thin Layer Chromatography analyses were performed on silica gel on aluminum plates and UV and/or KMnO4 were used as revealing systems. Column chromatographies were performed by using silica gel 230-400 mesh and eluting as reported below. PS-BEMP was purchased from Aldrich.

Compounds 4, 5, 7, 8, 11, 12, 14, 16, 17, 18, 19, 21a-b, 22, 24a-b, 26 are known compounds, compounds 10, 23, 27a-b, 28a, 29 have been already prepared but spectroscopic data have not been reported, while compounds 6, 9, 15, 25, 28b are new compounds. Characterization data (1H NMR, 13C NMR, GC-EIMS, mp, and elemental analyses) for compounds 6, 9, 10, 15, 23, 25, 27a, 27b, 28a, 28b, 29 are reported below.

References


Representative experimental procedure.
In a screw capped vial equipped with a magnetic stirrer PS-BEMP (1) (0.048 g, 0.1 mmol, 2.1 mmol/g), trans-4-phenyl-3-buten-2-one (2a) (0.292 g, 2.0 mmol) and dimethylmalonate (3a) (0.229 ml, 2.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 24 h, methanol was added, the catalyst was recovered by filtration and the organic solvent was evaporated under vacuum to give pure dimethyl-2-(1'-phenyl-3'-oxo-butyl)malonate (4) as a colourless oil (0.541 g, 97 % yield).
**E-factor calculation (Waste produced (g)/ Product (g))**

**Batch conditions:**

Table 2, entry 1: reaction of 2a with 3a (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.146 \text{ g (2a)} + 0.132 \text{ g (3a)} + 1.58 \text{ g (MeOH)} - 0.270 \text{ g (isolated 4)}}{0.270 \text{ g}} = 5.97
\]

Table 2, entry 2: reaction of 2a with 3b (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.146 \text{ g (2a)} + 0.133 \text{ g (3b)} + 2.37 \text{ g (MeOH)} - 0.265 \text{ g (isolated 5)}}{0.265 \text{ g}} = 9.0
\]

Table 2, entry 3: reaction of 2a with 3c (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.146 \text{ g (2a)} + 0.128 \text{ g (3c)} + 1.58 \text{ g (MeOH)} - 0.247 \text{ g (isolated 6)}}{0.247 \text{ g}} = 6.5
\]

Table 2, entry 4: reaction of 2b with 3a (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.096 \text{ g (2b)} + 0.132 \text{ g (3a)} + 2.37 \text{ g (MeOH)} - 0.217 \text{ g (isolated 7)}}{0.217 \text{ g}} = 11.0
\]

Table 2, entry 5: reaction of 2b with 3b (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.096 \text{ g (2b)} + 0.133 \text{ g (3b)} + 1.58 \text{ g (MeOH)} - 0.213 \text{ g (isolated 8)}}{0.213 \text{ g}} = 7.5
\]

Table 2, entry 6: reaction of 2b with 3c (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.096 \text{ g (2b)} + 0.128 \text{ g (3c)} + 2.37 \text{ g (MeOH)} - 0.211 \text{ g (isolated 9)}}{0.211 \text{ g}} = 11.3
\]

Table 2, entry 7: reaction of 2c with 3a (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.086 \text{ g (2c)} + 0.396 \text{ g (3a)} + 1.58 \text{ g (MeOH)} - 0.186 \text{ g (isolated 10)}}{0.186 \text{ g}} = 10.1
\]

Table 2, entry 8: reaction of 2c with 3b (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.086 \text{ g (2c)} + 0.399 \text{ g (3b)} + 1.58 \text{ g (MeOH)} - 0.197 \text{ g (isolated 11)}}{0.197 \text{ g}} = 9.5
\]

Table 2, entry 9: reaction of 2c with 3c (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.086 \text{ g (2c)} + 0.128 \text{ g (3c)} + 2.37 \text{ g (MeOH)} - 0.197 \text{ g (isolated 12)}}{0.197 \text{ g}} = 12.1
\]

Table 3, entry 1: reaction of 2a with 13a (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.146 \text{ g (2a)} + 0.110 \text{ g (13a)} + 1.42 \text{ g (MeOH)} - 0.249 \text{ g (isolated 14)}}{0.249 \text{ g}} = 5.7
\]

Table 3, entry 2: reaction of 2a with 13b (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.146 \text{ g (2a)} + 0.090 \text{ g (13b)} + 1.42 \text{ g (MeOH)} - 0.225 \text{ g (isolated 15)}}{0.225 \text{ g}} = 6.4
\]

Table 3, entry 3: reaction of 2b with 13a (calculated for 1.0 mmol):  
\[
\text{E-factor} = \frac{0.096 \text{ g (2b)} + 0.110 \text{ g (13a)} + 1.42 \text{ g (MeOH)} - 0.190 \text{ g (isolated 16)}}{0.190 \text{ g}} = 7.6
\]
Table 3, entry 4: reaction of $2b$ with $13b$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.096 \text{ g (2b)} + 0.090 \text{ g (13b)} + 1.42 \text{ g (MeOH)} – 0.179 \text{ g (isolated 17)}]}{0.179 \text{ g}} = 8.0
\]

Table 3, entry 5: reaction of $2c$ with $13a$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.086 \text{ g (2c)} + 0.110 \text{ g (13a)} + 1.42 \text{ g (MeOH)} – 0.188 \text{ g (isolated 18)}]}{0.188 \text{ g}} = 7.6
\]

Table 3, entry 6: reaction of $2c$ with $13b$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.086 \text{ g (2c)} + 0.090 \text{ g (13b)} + 1.42 \text{ g (MeOH)} – 0.164 \text{ g (isolated 19)}]}{0.164 \text{ g}} = 8.8
\]

Table 4, entry 1: reaction of $2a$ with $20a$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.146 \text{ g (2a)} + 0.119 \text{ g (20a)} + 2.37 \text{ g (MeOH)} – 0.252 \text{ g (isolated 21)}]}{0.252 \text{ g}} = 9.5
\]

Table 4, entry 2: reaction of $2a$ with $20b$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.146 \text{ g (2a)} + 0.146 \text{ g (20b)} + 2.37 \text{ g (MeOH)} – 0.219 \text{ g (isolated 22)}]}{0.219 \text{ g}} = 11.2
\]

Table 4, entry 3: reaction of $2a$ with $20c$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.146 \text{ g (2a)} + 0.087 \text{ g (20c)} + 2.37 \text{ g (MeOH)} – 0.198 \text{ g (isolated 23)}]}{0.198 \text{ g}} = 12.2
\]

Table 4, entry 4: reaction of $2b$ with $20a$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.096 \text{ g (2b)} + 0.119 \text{ g (20a)} + 2.37 \text{ g (MeOH)} – 0.198 \text{ g (isolated 24)}]}{0.198 \text{ g}} = 12.1
\]

Table 4, entry 5: reaction of $2b$ with $20b$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.096 \text{ g (2b)} + 0.146 \text{ g (20b)} + 2.37 \text{ g (MeOH)} – 0.220 \text{ g (isolated 25)}]}{0.220 \text{ g}} = 10.9
\]

Table 4, entry 6: reaction of $2b$ with $20c$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.096 \text{ g (2b)} + 0.087 \text{ g (20c)} + 2.37 \text{ g (MeOH)} – 0.186 \text{ g (isolated 26)}]}{0.186 \text{ g}} = 12.7
\]

Table 4, entry 7: reaction of $2c$ with $20a$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.086 \text{ g (2c)} + 0.119 \text{ g (20a)} + 2.37 \text{ g (MeOH)} – 0.193 \text{ g (isolated 27)}]}{0.193 \text{ g}} = 12.4
\]

Table 4, entry 8: reaction of $2c$ with $20b$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.258 \text{ g (2c)} + 0.146 \text{ g (20b)} + 2.37 \text{ g (MeOH)} – 0.223 \text{ g (isolated 28)}]}{0.223 \text{ g}} = 11.5
\]

Table 4, entry 9: reaction of $2c$ with $20c$ (calculated for 1.0 mmol):
\[
E\text{-factor} = \frac{[0.172 \text{ g (2c)} + 0.087 \text{ g (20c)} + 1.58 \text{ g (MeOH)} – 0.171 \text{ g (isolated 29)}]}{0.171 \text{ g}} = 9.8
\]
Cyclic continuous-flow conditions for the reaction of 2c with 3c (calculated for 50.0 mmol):

\[ \text{E-factor} = \frac{[4.3 \text{ g (2c)} + 6.4 \text{ g (3c)} + 4.75 \text{ g (MeOH)} - 10.17 \text{ g (isolated 12)}]}{10.17 \text{ g}} = 0.52 \]
Characterization data

3-Acetyl-3-(3’-oxo-1’-phenyl-butyl)-dihydro-furan-2-one (6)

Diastereisomeric mixture isolated in 90% overall yield. Diastereoisomer A: $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ = 1.92-1.98 (m, 1H), 2.08 (s, 3H), 2.38-2.44 (m, 1H), 3.07-3.10 (m, 1H), 3.12-3.21 (m, 1H), 3.30-3.34 (m, 1H), 3.47-3.52 (m, 1H), 4.12-4.16 (m, 1H), 7-27-7.35 (m, 5H). $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) $\delta =$ 193.6, 174.0, 164.5, 138.9, 129.0, 128.3, 124.2, 66.5, 57.4, 48.8, 35.6 (2 carbons), 29.5, 28.4, 24.3. Diastereoisomer B: $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ = 2.07 (s, 3H), 2-23-2.38 (m, 2H), 2.74-2.76 (m, 2H), 3.83-3.90 (m, 2H), 4.17-4.23 (m, 1H), 7-22-7.33 (m, 5H). $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) $\delta =$ 195.3, 175.6, 163.3, 138.4, 128.7, 127.9, 124.3, 65.7, 59.1, 45.9, 44.5, 33.9, 29.3, 28.0, 24.6. GC-EIMS (m/z, %) diastereoisomer A: 258 (13), 126 (100), 115 (77), 91 (40); diastereoisomer B: 256 (94), 210 (100), 128 (96), 115 (100), 91 (83).

3-Acetyl-3-(3’-oxo-cyclohexyl)-dihydro-furan-2-one (9)

Isolated in 94% overall yield as a colourless oil. $^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$ = 1.60-1.80 (m, 2H), 2.00-2.80 (m, 1H), 2.00-2.32 (m, 4H), 2.28 (s, 3H), 2.40-2.50 (m, 2H), 2.68-2.85 (m, 1H), 2.85-2.98 (m, 1H), 4.05-4.20 (m, 1H), 4.20-4.40 (m, 1H). $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) $\delta =$ 208.3, 201.3, 201.0, 173.7, 66.2, 66.2, 65.9, 65.5, 43.2, 42.5, 41.5, 41.1, 40.8, 40.7, 26.5, 26.3, 25.4, 25.0, 24.5, 24.3, 24.0. Anal. Calc. for C$_{12}$H$_{16}$O$_4$ (FW 224): C, 64.27; H, 7.19; O, 28.54. Found: C, 64.01; H, 7.16. GC-EIMS (m/z, %) diastereoisomer A: 181 (M$^+$, 22), 112 (47), 97 (38), 43 (100); diastereoisomer B: 181 (M$^+$, 63), 112 (46), 97 (36), 43 (100).

2-Methoxycarbonyl-pentandioic acid dimethylester (10)
**4-(Butylthio)-4-phenylbutan-2-one (15)**

Isolated in 95% yield. Yellowish oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta = 0.83$ (t, $J = 7.3$ Hz, 3H), 1.20-1.40 (m, 2H), 1.40-1.53 (m, 2H), 2.09 (s, 3H), 2.19-2.40 (m, 2H), 2.96 (d, $J = 7.3$ Hz, 2H), 4.31 (t, $J = 7.3$ Hz, 1H), 7.15-7.40 (m, 5H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta = 205.6$, 142.0, 128.5, 127.7, 127.2, 50.1, 44.1, 31.2, 31.0, 30.7, 21.9, 13.6. Anal. calc. for C$_{14}$H$_{20}$OS (FW 236): C, 71.14; H, 8.53; S, 13.57. Found: C, 70.8; H 8.57; S 13.52. GC-EIMS (m/z, %) 236 (M+, 28), 179 (26), 148 (41), 104 (31), 43 (100).

**3-(3'-Oxo-1'-phenyl-butyl)-oxazolidin-2-one (23)**

Isolated in 72% yield. Yellowish oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta = 2.23$ (s, 3H), 3.01 (dd, $J = 5.7$, 16.1 Hz, 1H), 3.35 (dd, $J = 8.2$, 16.4 Hz, 1H), 3.40-3.58 (m, 2H), 4.24 (t, $J = 8.0$, 2H), 5.23 (dd, $J = 5.7$, 9.7 Hz, 1H), 7.26-7.45 (m, 5H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta = 205.6$, 157.6, 137.9, 128.8, 128.1, 127.0, 61.8, 53.7, 45.2, 42.3, 29.6. Anal. calc. for C$_{13}$H$_{15}$NO$_3$ (FW 233): C, 66.94; H, 6.48; N, 6.00. Found: C, 66.62; H, 6.45; N, 6.03.

**3-(5'-Phenyl-tetrazol-2'-yl)-cyclohexanone (25)**
Isolated in 91% overall yield as a yellow solid (m.p. = 63-65 °C). $^1$H-NMR (CDCl$_3$, 400 MHz) δ = 1.78-2.00 (m, 1H), 2.10-2.25 (m, 1H), 2.35-2.63 (m, 4H), 3.02 (dd, $J = 5.0$, 14.8 Hz, 1H), 3.16 (dd, $J = 9.9$, 14.8 Hz, 1H), 5.15-5.35 (m, 1H), 7.45-7.60 (m, 3H), 8.10-8.25 (m, 2H). $^{13}$C-NMR (CDCl$_3$, 100.6 MHz) δ = 205.8, 165.0, 130.4, 128.9, 127.2, 126.8, 61.5, 46.2, 40.4, 30.8, 21.3. Anal. Calc. for C$_{13}$H$_{14}$N$_4$O (FW 242): C, 64.45; H, 5.82; N, 23.23; O, 6.60. Found: C, 64.76; H, 5.84; N, 23.04. GC-EIMS (m/z, %) 103 (100), 76 (38).

3-Benzotriazol-1-yl-propionic acid methyl ester (27a)/3-Benzotriazol-2-yl-propionic acid methyl ester (27b)

Mixture of two regioisomeric products (27a:27b=4:1 from $^1$H-NMR). Isolated in 94% overall yield. Yellow oil. $^1$H NMR (CDCl$_3$, 400 MHz) δ = 3.13 (t, $J = 6.7$ Hz, 2H, A), 3.20 (t, $J = 7.0$ Hz, 2H, B), 3.67 (s, 3H, A), 3.73 (s, 3H, B), 4.93 (t, $J = 6.8$ Hz, 2H, A), 5.05 (t, $J = 7.0$ Hz, 2H, B), 7.35-7.42 (m, 1H A + 1H B), 7.52 (t, $J = 7.6$ Hz, 1H, A), 7.62 (d, $J = 8.3$ Hz, 1H, A), 7.82-7.95 (m, 2H, B), 8.06 (d, $J = 8.3$ Hz, 1H, A). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) δ = 171.0 (A+B), 145.8 (A), 144.3 (B), 133.1 (A), 127.5 (A); 126.4 (B), 124.0 (A), 119.9 (A), 118.0 (B), 109.5, (A), 52.1 (A+B), 51.6 (B), 43.3 (A), 34.1 (A), 33.9 (B). Anal. calc. for C$_{10}$H$_{11}$N$_3$O$_2$ (FW 205): C, 58.53; H, 5.40; N, 20.48. Found: C, 58.27; H 5.41; N 20.56. GC-EIMS (m/z, %) A: 205 (M+, 44), 104 (99), 91 (57), 87 (32), 77 (90), 64 (41), 59 (100), 51 (35); B: 205 (M+, 57), 146 (100), 91 (47), 77 (31), 64 (31), 59 (40), 55 (36).

3-(5'-Phenyl-tetrazol-2'-yl)-propionic acid methyl ester (28a)
Mixture of two regioisomeric products (28a:28b=89:11 from $^1$H-NMR). Isolated by column chromatography (petroleum ether/ethyl acetate = 3/1) in 96% overall yield. 28a: white solid. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 3.14 (t, $J$ = 7.0 Hz, 2H), 3.74 (s, 3H), 4.96 (t, $J$ = 7.0 Hz, 2H), 7.45-7.60 (m, 3H), 8.10-8.25 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ = 170.1, 165.2, 130.4, 128.9, 127.2, 126.8, 52.3, 48.4, 33.3. Anal. Calc. for C$_{11}$H$_{12}$N$_4$O$_2$ (FW 232): C, 56.89; H, 5.21; N, 24.12; O, 13.78. Found: C, 57.13; H, 5.19; N, 24.23. GC-EIMS (m/z, %) 232 (M+, 11), 159 (100), 131 (20).

3-(5'-Phenyl-tetrazol-1'-yl)-propionic acid methyl ester (28b)

\[ \text{N} \begin{array}{c} \text{O} \\ \text{Ph} \end{array} \]

Mixture of two regioisomeric products (28a:28b=89:11 from $^1$H-NMR). Isolated by column chromatography (petroleum ether/ethyl acetate = 3/1) in 96% overall yield. 28b: colourless oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 3.10 (t, $J$ = 6.8 Hz, 2H), 3.66 (s, 3H), 4.67 (t, $J$ = 6.8 Hz, 2H), 7.50-7.65 (m, 3H), 7.65-7.80 (m, 2H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ = 170.2, 154.6, 131.3, 129.3, 128.8, 123.7, 52.3, 43.4, 33.3. Anal. Calc. for C$_{11}$H$_{12}$N$_4$O$_2$ (FW 232): C, 56.89; H, 5.21; N, 24.12; O, 13.78. Found: C, 57.13; H, 5.19; N, 24.23. GC-EIMS (m/z, %) 232 (M+, 43), 131 (27), 118 (31), 104 (69), 89 (47), 77 (78), 63 (37), 59 (100), 55 (43), 51 (31).

3-(2'-Oxo-oxazolidin-3'-yl)-propionic acid methyl ester (29)

\[ \text{O} \begin{array}{c} \text{N} \\ \text{OMe} \end{array} \]

Isolated in 99% yield. Colourless oil. $^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ = 2.61 (t, $J$ = 6.6 Hz, 2H), 3.54 (t, $J$ = 6.6 Hz, 2H), 3.61 (t, $J$ = 8.5 Hz, 2H), 3.68 (s, 3H), 4.29 (t, $J$ = 8.0 Hz, 2H). $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ = 171.9, 158.3, 61.8, 51.8, 45.2, 40.1, 32.5. Anal. calc. for C$_7$H$_{11}$NO$_4$ (FW 173): C, 48.55; H, 6.40; N, 8.09. Found: C, 48.33; H 6.37; N 8.12. GC-EIMS (m/z, %) 142 (15), 129 (20), 113 (20), 100 (39), 70 (27), 56 (100), 43 (13).
$^1$H and $^{13}$C-NMR Spectra

(Diastereoisomer A)