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$PhI(OAc)_2$-promoted umpolung acetoxylation of enamides for the synthesis of α-acetoxy ketones

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Umpolung is a fundamental concept in organic chemistry, which provides an alternative strategy for the synthesis of target compounds which were not easily accessible by conventional methods. Herein, a mild and efficient $PhI(OAc)_2$-promoted umpolung acetoxylation reactions of enamides was developed for the synthesis of α-acetoxy ketones. The reaction tolerates a wide range of functional groups and affords α-acetoxy ketones in good to excellent yields. $PhI(OAc)_2$ serves as a source of acetoxy in the reaction.

umpolung, enamides, acetoxylation, hypervalent iodine reagents, α-acetoxy ketones

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1 Introduction

α-Acetoxy ketones represent an important class of intermediates in organic synthesis [1–4], medicinal industries, and biological system (Scheme 1) [5–8]. Accordingly, various methods such as oxidation of enolates, ketones, and terminal alkynes [9–15], acetylation of α-bromo and α-hydroxyl ketones [6,16], and copper-catalyzed insertion of O–H bond of carboxylic acids into α-diazo ketones [17] have been developed for the formation of α-acetoxy ketones. Despite this progress, most of these reactions require expensive and toxic heavy metals oxidants [18,19], which would hamper their applications in synthetic organic chemistry. Therefore, development of novel and environmentally friendly strategies towards α-acetoxy ketones is still highly desirable.

Umpolung or polarity inversion provides an alternative route to afford the desirable products that are hardly synthesized using regular approaches [20–26]. Hypervalent iodine reagents due to their high electrophilicity have been used to achieve umpolung of electronegative compounds, such as enolates and ketones [27–32]. Recently, Wirth and co-workers [33] have developed pioneering research on the hypervalent iodine reagents promoted functionalizatons of silyl enol ethers through umpolung strategy (Scheme 2(a)). Enamides are nitrogen analogs of silyl enol ethers. The C_β-position is a nucleophilic center and is prone to electrophilic attack [34]. With this idea in mind and our interest in the enamides transformations [35–39], we hypothesized that hypervalent iodine reagents promoted transformation of enamides may be achieved through an umpolung process. The C_β-position of enamides react with $PhI(OAc)_2$ to give intermediate **A**. Then, intramolecular nucleophilic displacement by acetoxy affords intermediate **B** with release of iodobenzene to achieve umpolung [9,30]. Hydrolysis of intermediate **B** in the presence of H_2O affords α-acetoxy

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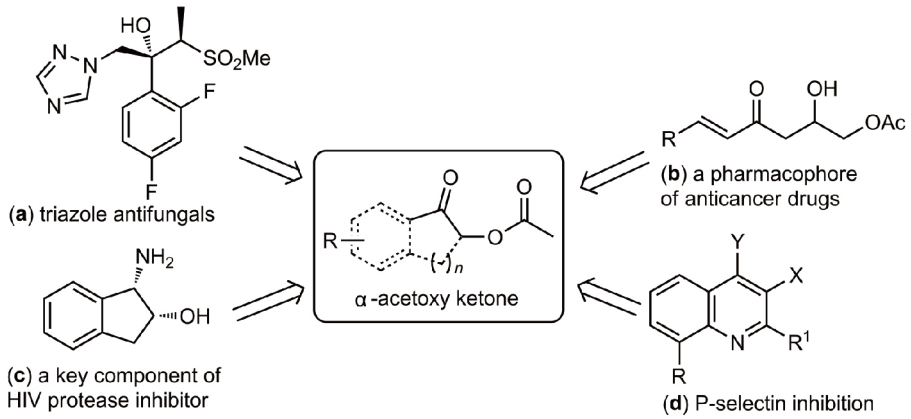
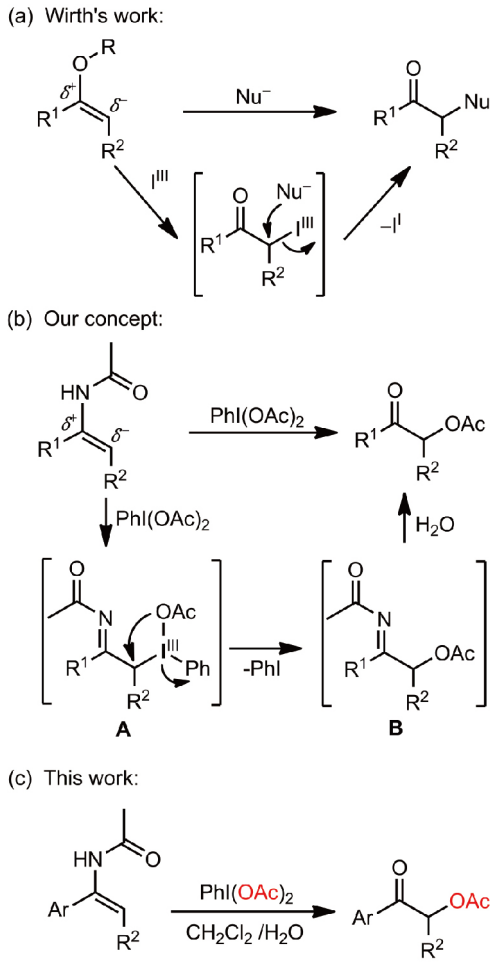


Scheme 1 α-Acetoxy ketones as precursors for molecules of medicinal and biological importance.



Scheme 2 Umpolung strategy for constructing of α-acetoxy ketones.

ketone (Scheme 2(b)). However, till date the umpolung reactions of enamides have been much less developed [40,41]. To achieve this conception, two main challenges that needed to be addressed were as follows: (1) the enamides easily decomposes under acidic conditions [42–47]; (2) the enamides would be oxidized to give imides in the presence of strong oxidant [48,49]. A practical solution is to use mild hypervalent iodine oxidant under neutral conditions. Herein, we report a facile and efficient $PhI(OAc)_2$-promoted umpolung acetoxylation reaction of enamides for the synthesis of α-acetoxy ketones under mild conditions (Scheme 2(c)).

2 Experimental

2.1 Typical procedure for umpolung acetoxylation of enamides

A 10-mL round flask was charged with $PhI(OAc)_2$ (0.24 mmol, 77.3 mg) and enamides **1** (0.2 mmol, 1.0 equiv.) in CH_2Cl_2/H_2O (2.0 mL, *v*/*v*=1:1). The flask was heated to 50 °C under vigorous stirring. Upon completion (detected by thin layer chromatography (TLC)) of the reaction, the reaction mixture was cooled down to room temperature. It was quenched with H_2O (5 mL) and extracted with EtOAc (2×10 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and then evaporated in vacuo. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (*v*/*v*=6:1) as the eluent to afford the corresponding product **2**.

2.2 Characterization data of α-acetoxy ketones

2-Oxo-2-phenylethyl acetate (**2a**). Yield: 77% (27.4 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.92 (d, *J*=8.0 Hz, 2 H), 7.61 (t, *J*=7.2 Hz, 1 H), 7.49 (t, *J*=7.6 Hz, 2 H), 5.35 (s, 2 H), 2.23(s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.1, 170.4, 134.1, 133.9, 128.8, 127.7, 66.0, 20.5. HRMS Calcd. (ESI) *m*/*z* for $C_{10}H_{10}NaO_3$: $[M+Na]^+$ 201.0522, found: 201.0527.

2-Oxo-2-*p*-tolylethyl acetate (**2b**). Yield: 69% (26.4 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, *J*=8.4 Hz, 2 H), 7.29 (d, *J*=8 Hz, 2 H), 5.33 (s, 2 H), 2.42 (s, 3 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.7, 170.5, 144.9, 131.6, 129.5, 127.8, 65.9, 21.7, 20.6. HRMS Calcd. (ESI) *m*/*z* for $C_{11}H_{12}NaO_3$: $[M+Na]^+$ 215.0679, found: 215.0672.

2-Oxo-2-*o*-tolylethyl acetate (**2c**). Yield: 75% (28.8 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (d, J=7.6 Hz, 1 H), 7.42 (t, J=7.2 Hz, 1 H), 7.29 (d, J=7.6 Hz, 2 H), 5.18 (s, 2 H), 2.52 (s, 3 H), 2.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.7, 170.4, 139.0, 134.3, 132.2, 132.1, 128.0, 125.7, 67.2, 21.1, 20.5. HRMS Calcd. (ESI) m/z for $C_{11}H_{12}NaO_3$: $[M+Na]^+$ 215.0679, found: 215.0671.

2-(3,4-Dimethylphenyl)-2-oxoethyl acetate (**2d**). Yield: 94% (38.7 mg), white solid, m.p. 74–75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (s, 1 H), 7.64 (d, J=7.6 Hz, 1 H), 7.23 (d, J=8.0 Hz, 1 H), 5.31 (s, 2 H), 2.31 (s, 3 H), 2.31 (s, 3 H), 2.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.9, 170.4, 143.5, 137.2, 129.9, 128.8, 125.3, 65.9, 20.5, 20.0, 19.7. HRMS Calcd. (ESI) m/z for $C_{12}H_{14}NaO_3$: $[M+Na]^+$ 229.0835, found: 229.0835.

2-(2,5-Dimethylphenyl)-2-oxoethyl acetate (**2e**). Yield: 90% (37.1 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (s, 1 H), 7.23 (d, J=8 Hz, 1 H), 7.16 (d, J=8 Hz, 1 H), 5.18 (s, 2 H), 2.46 (s, 3 H), 2.36 (s, 3 H), 2.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.7, 170.4, 135.8, 135.3, 134.2, 132.9, 132.1, 128.5, 67.2, 20.8, 20.6, 20.5. HRMS Calcd. (ESI) m/z for $C_{12}H_{14}NaO_3$: $[M+Na]^+$ 229.0835, found: 229.0835.

2-(2,4-Dimethylphenyl)-2-oxoethyl acetate (**2f**). Yield: 96% (39.6 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54 (d, J=8 Hz, 1 H), 7.09–7.07 (m, 2 H), 5.19 (s, 2 H), 2.50 (s, 3 H), 2.36 (s, 3 H), 2.21 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 194.7, 170.4, 143.0, 139.6, 133.1, 131.2, 128.4, 126.3, 67.0, 21.4, 21.3, 20.5. HRMS Calcd. (ESI) m/z for $C_{12}H_{14}NaO_3$: $[M+Na]^+$ 229.0835, found: 229.0832.

2-Oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethyl acetate (**2g**). Yield: 89% (41.1 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62–7.60 (m, 2 H), 7.15 (d, J=8.4 Hz, 1 H), 5.30 (s, 2 H), 2.80 (t, J=6.4 Hz, 4 H), 2.22 (s, 3 H), 1.83–1.79 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.9, 170.4, 144.1, 137.7, 131.6, 129.5, 128.6, 124.7, 65.9, 29.6, 29.3, 22.8, 22.6, 20.5. HRMS Calcd. (ESI) m/z for $C_{14}H_{16}NaO_3$: $[M+Na]^+$ 255.0992, found: 255.0982.

2-(Biphenyl-4-yl)-2-oxoethyl acetate (**2h**). Yield: 80% (40.6 mg), white solid, m.p. 108–109 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.98 (d, J=8.4 Hz, 2 H), 7.69 (d, J=8.4 Hz, 2 H), 7.61 (d, J=7.2 Hz, 2 H), 7.47 (t, J=7.2 Hz, 2 H), 7.41 (d, J=7.2 Hz, 1 H), 5.36 (s, 2 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.7, 170.4, 146.5, 139.5, 132.8, 128.9, 128.4, 128.3, 127.4, 127.2, 66.0, 20.5. HRMS Calcd. (ESI) m/z for $C_{16}H_{14}NaO_3$: $[M+Na]^+$ 277.0835, found: 277.0829.

2-(4-Methoxyphenyl)-2-oxoethyl acetate (**2i**). Yield: 77% (32.0 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.90 (d, J=8.8 Hz, 2 H), 6.95 (d, J=8.8 Hz, 2 H), 5.30 (s, 2 H), 3.87 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.6, 170.5, 164.0, 130.0, 127.1, 114.0, 65.7, 55.5, 20.6. HRMS Calcd. (ESI) m/z for $C_{11}H_{12}NaO_4$: $[M+Na]^+$ 231.0628, found: 231.0624.

2-(3-Methoxyphenyl)-2-oxoethyl acetate (**2j**). Yield: 81% (33.7 mg), colourless liquid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48–7.44 (m, 2 H), 7.39 (t, J=8 Hz,1 H), 7.16–7.13 (m, 1 H), 5.32 (s, 2 H), 3.85 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.0, 170.4, 159.9, 135.4, 129.8, 120.3, 120.1, 112.0, 66.0, 55.4, 20.5. HRMS Calcd. (ESI) m/z for $C_{11}H_{12}NaO_4$: $[M+Na]^+$ 231.0628, found: 231.0629.

2-(3,4-Dimethoxyphenyl)-2-oxoethyl acetate (**2k**). Yield: 85% (40.5 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53–7.48 (m, 2 H), 6.90 (d, J=8.4 Hz, 1 H), 5.31 (s, 2 H), 3.95 (s, 3 H), 3.93 (s, 3 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.6, 170.4, 153.8, 149.2, 127.2, 122.1, 110.1, 109.8, 65.6, 56.0, 55.9, 20.5. HRMS Calcd. (ESI) m/z for $C_{12}H_{14}NaO_5$: $[M+Na]^+$ 261.0733, found: 261.0727.

2-(Benzo[d][1,3]dioxol-5-yl)-2-oxoethyl acetate (**2l**). Yield: 76% (33.7 mg), yellow solid, m.p. 80–81 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.49 (dd, J_1=1.6 Hz, J_2=8 Hz, 1 H), 7.39 (d, J=1.6 Hz, 1 H), 6.86 (d, J=8.4 Hz, 1 H), 6.06 (s, 2 H), 5.26 (s, 2 H), 2.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.1, 170.4, 152.3, 148.3, 128.8, 123.9, 108.1, 107.5, 101.9, 65.7, 20.5. HRMS Calcd. (ESI) m/z for $C_{11}H_{10}NaO_5$: $[M+Na]^+$ 245.0420, found: 245.0415.

2-(4-Acetamidophenyl)-2-oxoethyl acetate (**2m**). Yield: 43% (20.2 mg), yellow liquid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.34 (s, 1 H), 7.92 (d, J=8.8 Hz, 2 H), 7.73 (d, J=8.8 Hz, 2 H), 5.40 (s, 2 H), 2.14 (s, 3 H), 2.09 (s, 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 191.2, 169.9, 169.1, 144.3, 129.1, 128.4, 118.3, 66.2, 24.2, 20.4. HRMS Calcd. (ESI) m/z for $C_{12}H_{13}NNaO_4$: $[M+Na]^+$ 258.0737, found: 258.0730.

2-(4-(*tert*-Butoxycarbonylamino)phenyl)-2-oxoethyl acetate (**2n**). Yield: 64% (37.5 mg), white solid, m.p. 126–127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, J=8.8 Hz, 2 H), 7.49 (d, J=8.8 Hz, 2 H), 7.02 (s, 1 H), 5.30 (s, 2 H), 2.22 (s, 3 H), 1.52 (s, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.7, 170.5, 152.1, 143.7, 129.2, 128.5, 117.5, 81.3, 65.8, 28.2, 20.6. HRMS Calcd. (ESI) m/z for $C_{15}H_{19}NNaO_5$: $[M+Na]^+$ 316.1155, found: 316.1153.

2-(4-Fluorophenyl)-2-oxoethyl acetate (**2o**). Yield: 76% (29.8 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.97–7.93 (m, 2 H), 7.16 (t, J=8.4 Hz, 2 H), 5.30 (s, 2 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 190.6, 170.4, 166.1 (d, J_{CF}=254.5 Hz), 130.6 (d, J_{CF}=3.1 Hz), 130.4 (d, J_{CF}=9.4 Hz), 116.1 (d, J_{CF}=21.9 Hz), 65.8, 20.5. HRMS Calcd. (ESI) m/z for $C_{10}H_9FNaO_3$: $[M+Na]^+$ 219.0428, found: 219.0421.

2-(4-Chlorophenyl)-2-oxoethyl acetate (**2p**). Yield: 83% (35.2 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87 (d, J=6.8 Hz, 2 H), 7.47 (d, J=6.8 Hz, 2 H), 5.31 (s, 2 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.0, 170.4, 140.4, 132.4, 129.2, 129.1, 65.8, 20.5. HRMS Calcd. (ESI) m/z for $C_{10}H_9ClNaO_3$: $[M+Na]^+$ 235.0132, found: 235.0135.

2-(2-Chlorophenyl)-2-oxoethyl acetate (**2q**). Yield: 95% (40.3 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ

7.62 (d, *J*=7.2 Hz, 1 H), 7.45–7.42 (m, 2 H), 7.38–7.34 (m, 1 H), 5.20 (s, 2 H), 2.18 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ* 195.2, 170.3, 135.7, 132.8, 131.5, 130.5, 129.9, 127.1, 68.2, 20.4. HRMS Calcd. (ESI) *m*/*z* for $C_{10}H_9ClNaO_3$ $[M+Na]^+$ 235.0132, found: 235.0133.

2-(4-Bromophenyl)-2-oxoethyl acetate (**2r**). Yield: 95% (48.6 mg), white solid, m.p. 81–82 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.77 (d, *J*=8.8 Hz, 2 H), 7.62 (d, *J*=8.4 Hz, 2 H), 5.28 (s, 2 H), 2.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 191.2, 170.3, 132.8, 132.1, 129.2, 129.1, 65.8, 20.5. HRMS Calcd. (ESI) *m*/*z* for $C_{10}H_9BrNaO_3$: $[M+Na]^+$ 278.9627, found: 278.9624.

2-(4-Iodophenyl)-2-oxoethyl acetate (**2s**). Yield: 70% (42.6 mg), white solid, m.p. 116–117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.85 (d, *J*=8.4 Hz, 2 H), 7.62 (d, *J*=8.4 Hz, 2 H), 5.28 (s, 2 H), 2.22 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 191.6, 170.3, 138.1, 133.3, 129.0, 102.0, 65.7, 20.5. HRMS Calcd. (ESI) *m*/*z* for $C_{10}H_9INaO_3$: $[M+Na]^+$ 326.9489, found: 326.9484.

2-Oxo-2-(4-(trifluoromethyl)phenyl)ethyl acetate (**2t**). Yield: 73% (35.9 mg), white solid, m.p. 69–71 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.03 (d, *J*=8 Hz, 2 H), 7.76 (d, *J*=8.4 Hz, 2 H), 5.34 (s, 2 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 191.5, 170.3, 136.8, 135.1 (d, J_{CF_3}=32.6 Hz), 128.1, 125.9 (d, J_{CF_3}=3.5 Hz), 124.7, 122.0, 66.0, 20.4. HRMS Calcd. (ESI) *m*/*z* for $C_{11}H_9F_3NaO_3$: $[M+Na]^+$ 269.0396, found: 269.0396.

2-(4-Nitrophenyl)-2-oxoethyl acetate (**2u**). Yield: 85% (37.9 mg), yellow liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.35 (d, *J*=8.8 Hz, 2 H), 8.09 (d, *J*=8.8 Hz, 2 H), 5.35 (s, 2 H), 2.24 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 191.1, 170.2, 150.7, 138.6, 128.9, 124.0, 66.0, 20.4. HRMS Calcd. (ESI) *m*/*z* for $C_{10}H_9NNaO_5$: $[M+Na]^+$ 246.0373, found: 246.0370.

2-(Naphthalen-2-yl)-2-oxoethyl acetate (**2v**). Yield: 88% (40.1 mg), brown solid, m.p. 76–77 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.39 (s, 1 H), 7.96–7.92 (m, 2 H), 7.90–7.85 (m, 2 H), 7.62–7.59 (m, 1 H), 7.57–7.55 (m, 1 H), 5.46 (s, 2 H), 2.25 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 192.0, 170.4, 135.8, 132.3, 131.4, 129.5, 129.4, 128.8, 128.8, 127.8, 127.0, 123.2, 66.0, 20.5. HRMS Calcd. (ESI) *m*/*z* for $C_{14}H_{12}NaO_3$: $[M+Na]^+$ 251.0679, found: 251.0675.

1-Oxo-1-phenylpropan-2-yl acetate (**2w**). Yield: 40% (15.4 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.95 (d, *J*=7.2 Hz, 2 H), 7.60 (t, *J*=7.6 Hz, 1 H), 7.49 (t, *J*=8.0 Hz, 2 H), 6.00–5.95 (m, 1 H), 2.15 (s, 3 H), 1.52 (d, *J*=7.2 Hz, 3 H). HRMS Calcd. (ESI) *m*/*z* for $C_{11}H_{12}NaO_3$: $[M+Na]^+$ 215.0679, found: 215.0670.

1-Oxo-2,3-dihydro-1*H*-inden-2-yl acetate (**2x**). Yield: 79% (30.0 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.79 (d, *J*=8 Hz, 1 H), 7.65 (t, *J*=7.6 Hz, 1 H), 7.47–7.40 (m, 2 H), 5.43 (dd, J_1=4.8 Hz, J_2=8 Hz, 1 H), 3.66 (dd, J_1=8 Hz, J_2=16.8 Hz, 1 H), 3.05 (dd, J_1=4.8 Hz, J_2=17.2 Hz, 1 H), 2.19 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 200.6, 170.4, 150.3, 135.8, 134.4, 128.1, 126.6, 124.4, 74.0, 33.3, 20.7. HRMS Calcd. (ESI) *m*/*z* for $C_{11}H_{10}NaO_3$: $[M+Na]^+$ 213.0522, found: 213.0516.

1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl acetate (**2y**). Yield: 63% (25.7 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.03 (d, *J*=8 Hz, 1 H), 7.51 (t, *J* =7.6 Hz, 1 H), 7.33 (t, *J*=7.6 Hz, 1 H), 7.27 (d, *J*=2 Hz, 1 H), 5.57–5.53 (m, 1 H), 3.26–3.11 (m, 1 H), 3.10–3.06 (m, 1 H), 2.40–2.37 (m, 1 H), 2.31–2.26 (m, 1 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 193.0, 170.2, 143.0, 133.9, 131.5, 128.6, 127.8, 126.9, 74.5, 29.1, 27.9, 20.8. HRMS Calcd. (ESI) *m*/*z* for $C_{12}H_{12}NaO_3$: $[M+Na]^+$ 227.0679, found: 227.0679.

Ethyl 2-acetoxy-3-oxo-3-phenylpropanoate (**2aa**). Yield: 6% (3.0 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 8.02–8.00 (m, 2 H), 7.64 (t, *J*=7.2 Hz, 1 H), 7.51 (d, *J*=8.0 Hz, 2 H), 6.33 (s, 1 H), 4.28–4.23 (m, 2 H), 2.24 (s, 3 H), 1.22 (t, *J*=7.2 Hz, 3 H). HRMS Calcd. (ESI) *m*/*z* for $C_{13}H_{14}NaO_5$: $[M+Na]^+$ 273.0733, found: 273.0729.

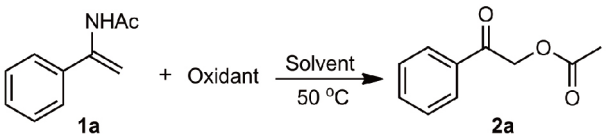
2-Oxo-2-phenylethyl 4-methylbenzenesulfonate (**4**). Yield: 63% (36.5 mg), white solid, m.p. 71–72 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.86–7.82 (m, 4 H), 7.61 (t, *J*=7.6 Hz, 1 H), 7.47 (t, *J*=8.0 Hz, 2 H), 7.34 (d, *J*=8.4 Hz, 2 H), 5.27 (s, 2 H), 2.44 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ* 190.2, 145.3, 134.2, 133.6, 132.5, 129.9, 128.9, 128.1, 127.9, 69.9, 21.6. HRMS Calcd. (ESI) *m*/*z* for $C_{15}H_{14}SNaO_4$: $[M+Na]^+$ 313.0505, found: 313.0512.

2-(Acetylimino)-2-phenylethyl acetate (**B**). Yield: 12% (5.3 mg), colourless liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) *δ* 7.75 (d, *J*=7.6 Hz, 2 H), 7.52 (t, *J*=8.0 Hz, 1 H), 7.45 (t, *J*=7.6 Hz, 2 H), 5.26 (s, 2 H), 2.28 (s, 3 H), 2.14 (s, 3 H). HRMS Calcd. (ESI) *m*/*z* for $C_{12}H_{13}NNaO_3$: $[M+Na]^+$ 242.0788, found: 242.0784.

3 Results and discussion

We initiated the investigation by using *N*-(1-phenylvinyl)-acetamide as substrate in the presence of (diacetoxy)iodobenzene at 50 °C in CH_2Cl_2 solvent, and the product α-acetoxy ketones **2a** was obtained only in 10% yield along with imides byproducts [48,49]. Encouraged by this preliminary result, we tried to optimize the reaction conditions (Table 1). Firstly, different solvents, such as dimethyl sulfoxide (DMSO) and CH_3CN were screened. However, improvement in the yield was not observed (entries 2 and 3). The reaction mechanism indicates that the presence of H_2O is important for promoting this reaction. Indeed, the yield of **2a** was improved to 34% when the 10 equiv. of H_2O was added in CH_2Cl_2 (entry 4). Further optimization of the reaction conditions showed that the reaction was most productive when a mixed solvent of CH_2Cl_2/H_2O (1:1) was used (entry 5). Slightly lower yield (70%) was obtained when H_2O was employed as the solvent

Table 1 Optimization of reaction conditions [a)]



Entry	Oxidant	Additive	Solvent	Yield of **2a** (%)
1	$PhI(OAc)_2$		CH_2Cl_2	10
2	$PhI(OAc)_2$		DMSO	0
3	$PhI(OAc)_2$		CH_3CN	5
4	$PhI(OAc)_2$	H_2O	CH_2Cl_2	34 [b)]
5	$PhI(OAc)_2$		CH_2Cl_2/H_2O	77
6	$PhI(OAc)_2$		H_2O	70
7	DMP		CH_2Cl_2/H_2O	58
8	1-Acetoxy-1,2-benziodoxole-3(1*H*)-one		CH_2Cl_2/H_2O	0
9	PhIO	HOAc	CH_2Cl_2/H_2O	51 [c)]
10	Koser's reagent	HOAc	CH_2Cl_2/H_2O	0 [c),d)]
11	*m*-CPBA	HOAc, PhI	CH_2Cl_2/H_2O	18 [e)]
12	$PhI(OAc)_2$		CH_2Cl_2/H_2O	22 [f)]
13	$PhI(OAc)_2$		CH_2Cl_2/H_2O	53 [g)]
14	$PhI(OAc)_2$		CH_2Cl_2/H_2O	40 [h)]

a) Reaction conditions: **1a** (0.2 mol, 1.0 equiv.), hypervalent iodine reagents (0.24 mmol, 1.2 equiv.), solvent (2 mL), CH_2Cl_2/H_2O (1:1, 2 mL), T=50 °C, isolated yield; b) H_2O (10 equiv.) was added; c) HOAc (2.4 equiv.) was added; d) the 2-oxo-2-phenylethyl 4-methylbenzenesulfonate **4** was formed in 63% yield; e) PhI (10 mol%), AcOH (5.0 equiv.) and *m*-CPBA (2.0 equiv.); f) $PhI(OAc)_2$ (0.5 equiv.) was used; g) 30 °C; h) 70 °C; DMP=Dess-Martin periodinane.

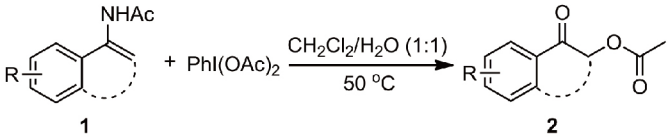
(entry 6). Moreover, we also observed that other hypervalent iodine reagents, such as Dess-Martin periodinane and 1-acetoxy-1,2-benziodoxole-3(1*H*)-one were inferior to $PhI(OAc)_2$ (entries 7 and 8). It should be noted that the α-acetoxy ketone **2a** was obtained in 51% yield using PhIO combined with 2.4 equiv. of HOAc as the oxidant (entry 9). When Koser's reagent/AcOH was used as the oxidant, the 2-oxo-2-phenylethyl 4-methylbenzenesulfonate **4** instead of α-acetoxy ketone **2a** was obtained in 63% yield (entry 10). Furthermore, when *in-situ* generated $PhI(OAc)_2$ (PhI, AcOH and *m*-CPBA) [9] was employed as the umpolung reagent, only 18% yield of the desired product **2a** was obtained (entry 11). The yield was decreased to 22% when 0.5 equiv. of $PhI(OAc)_2$ was used (entry 12). Finally, we have varied the reaction temperature, it was found that the conversion was decreased at 30 °C (entry 13). However, the yield was decreased when the reaction was conducted at 70 °C, due to the byproducts (imides and acetophenone) were prominent. (entry 14).

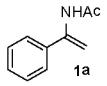
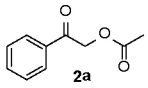
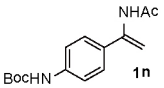
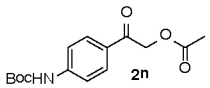
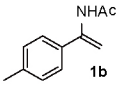
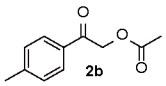
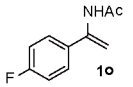
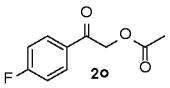
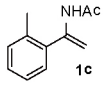
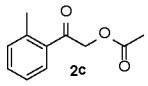
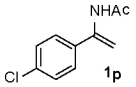
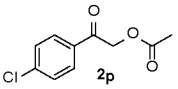
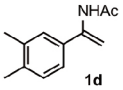
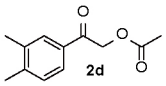
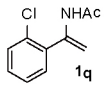
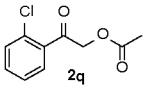
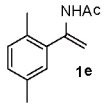
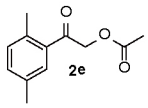
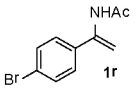
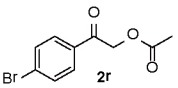
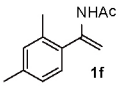
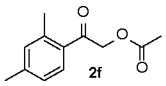
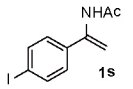
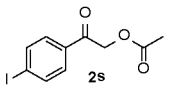
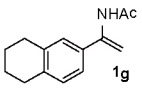
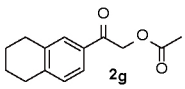
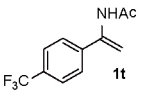
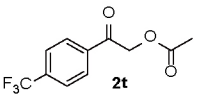
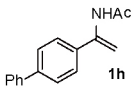
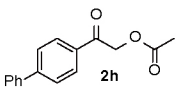
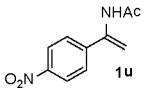
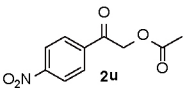
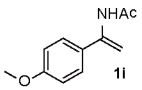
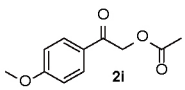
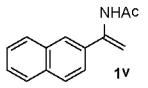
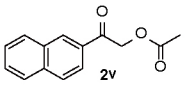
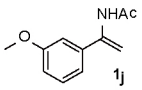
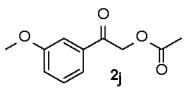
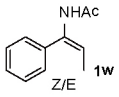
Having established the optimized reaction conditions, we have surveyed the scope of various enamides toward umpolung acetoxylation reaction as summarised in Table 2. The reaction displayed good functional-group tolerance and proved to be a general method for the synthesis of α-acetoxy ketones. A variety of *para*-, *meta*-, and *ortho*-substituents on the aromatic ring of the enamides furnished the desired products in good to excellent yields. Notably, the reaction was successfully performed on a gram scale affording α-acetoxy ketone **2a** in 74% yield (entry 1). Enamides with methyl, alkyl, and phenyl on the aromatic ring afforded the corresponding products in 69%–96% yields (entries 2–8). Enamides with strong electron-donating groups such as methoxy, dimethoxy, [1,3]dioxole, and amino substituted enamides were converted into desired products in good to high yields (entries 9–14). Notably, aryl enamides with fluoro, chloro, and sensitive functional groups such as bromo and iodo, provided the best results with up to 95% yield of the α-acetoxy ketones (entries 15–19). The strong electron-withdrawing groups, such as trifuoromethyl and nitro were well tolerated to produce the corresponding products in high yields (entries 20 and 21). This reaction also afforded 88% yield for β-naphthyl-substituted enamide **1v** (entry 22). Interestingly, β-substituted enamides such as **1w**, **1x** and **1y**, also underwent the reaction smoothly to give the corresponding products **2w**, **2x** and **2y** in 40%, 79% and 63% yield, respectively (entries 23–25). However, only a trace of the desired α-acetoxy ketone **2z** was observed when aliphatic enamide such as *N*-cyclohexenylacetamide **1z** was used as the substrate (entry 26).

Furthermore, *N*-unsubstitued enamines and enol carbonates were investigated for further extending the substrate scope (Scheme 3). However, the desired ethyl 2-acetoxy-3-oxo-3-phenylpropanoate **2aa** was obtained in only 6% yield, with 52% recovery of the enamine **1aa** (Scheme 3(a)). No reaction occurred when enol carbonate **1ab** was employed as the substrate (Scheme 3(b)).

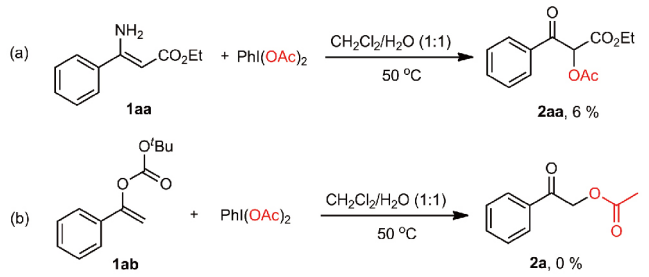
To gain insight into the reaction mechanism, the control experiments were performed (Scheme 4). Firstly, when *N*-(1-

Table 2 Reaction of enamides with $PhI(OAc)_2$ [a)]

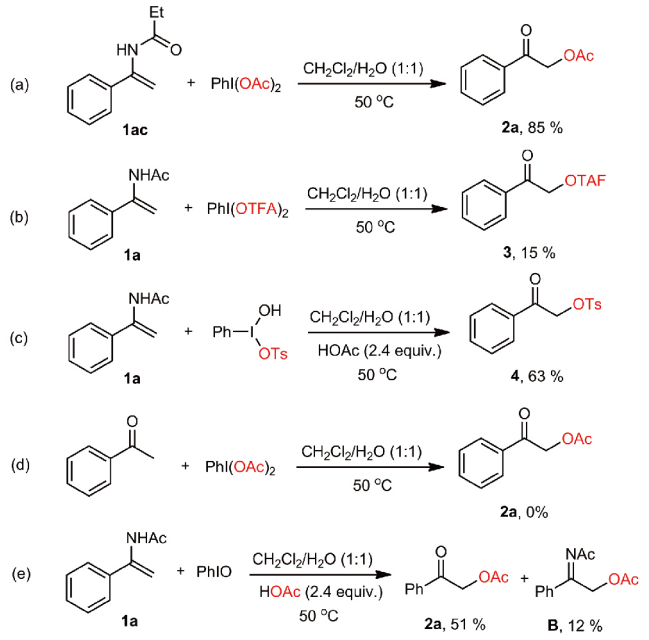


Entry	Substrate	Product	Yield (%) [b)]	Entry	Substrate	Product	Yield (%) [b)]
1			77 (74)[c)]	14			64
2			69	15			76
3			75	16			83
4			94	17			95
5			90	18			95
6			96	19			70
7			89	20			73
8			80	21			85
9			77	22			88
10			81	23			40
11			85	24			79
12			76	25			63
13			43	26			trace

a) Reaction conditions: **1** (0.2 mol), $PhI(OAc)_2$ (0.24 mmol, 1.2 equiv.), CH_2Cl_2/H_2O (1:1, 2 mL), T=50 °C; b) isolated yield; c) **1a** (10.0 mmol), $PhI(OAc)_2$ (12.0 mmol, 1.2 equiv.) CH_2Cl_2/H_2O (1:1, 20 mL), T=50 °C.



Scheme 3 Reaction of enamino esters, and enol carbonates with $PhI(OAc)_2$ (color online).



Scheme 4 Control experiments for studying the reaction mechanism (color online).

phenylvinyl)propionamide **1ac** was utilized for this transformation, α-acetoxy ketone **2a** was obtained in 85% yield (Scheme 4(a)). Giving the corresponding α-acetoxy ketone **3** in 15% yield when $PhI(OTFA)_2$ was used instead of $PhI(OAc)_2$ (Scheme 4(b)). Similarly, when Koser's reagent/HOAc was used as the oxidant, the 2-oxo-2-phenylethyl 4-methylbenzenesulfonate **4** was formed in 63% yield (Scheme 4(c)). These results suggested that the acetoxy group on the products came from $PhI(OAc)_2$ other than enamides [50]. Furthermore, the reaction failed to provide α-acetoxy ketone **2a** when acetophenone was used instead of enamide (Scheme 4(d)) [13]. This result indicated that acetophenone was not the intermediate in thereaction. The α-acetoxy ketone **2a** was obtained in 51% yield along with intermediate **B** in 12% yield when using PhIO combine with 2.4 equiv. of HOAc as the oxidant (Scheme 4(e)). This result confirmed the aforementioned reaction mechanism as well.

4 Conclusions

In summary, we have developed an efficient umpolung acetoxylation of enamides for the synthesis of α-acetoxy ketones. $PhI(OAc)_2$ was used as environmentally benign and inexpensive reagent for umpolung of enamides. The reaction displayed good functional-group tolerance and furnished the desired products in good to excellent yields under mild reaction conditions. The control experiments demonstrated that the acetoxy group in products came from $PhI(OAc)_2$.

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Conflict of interest The authors declare that they have no conflict of interest.

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