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Tandem olefin metathesis–elimination reactions. A new route to doubly unsaturated carbonyl derivatives

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ABSTRACT

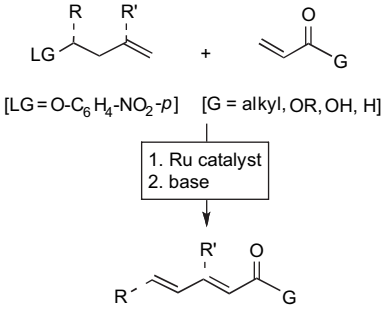
Cross-metathesis between an activated olefin and an ethereal derivative of homoallylic alcohols leads to products that are subject to facile elimination resulting in α,β,γ,δ-unsaturated esters, ketones, acids, and aldehydes in high yields.

1. Introduction

Harnessing the power of olefin metathesis chemistry[1] has led to a wealth of new opportunities in organic synthesis. As these are oftentimes ruthenium-catalyzed processes, additional advantage can be taken of the metal for further bond constructions in a one-pot tandem fashion. Some recent examples of such sequential catalysis include a cross-metathesis (CM)/Wittig olefination by Murelli and Snapper,[2a] and Paul and Andrade,[2b] ring-closing metathesis (RCM) or CM/cis-dihydroxylation from Blechert's group,[3] and a three-step process involving RCM/transfer hydrogenation/hydrogenation by Grubbs.[4] Many possible alternatives on this theme can be envisioned, however, where tandem reactions might involve metathesis either preceded or followed by a bond-forming event that is not necessarily mediated by Ru. In this report, we describe one such sequence leading to multiple centers of unsaturation in conjugation with a carbonyl activating group (Scheme 1).[5] Such conjugated dienic carbonyl derivatives are common structural subunits in natural products[6] as well as useful intermediates in synthesis.[7] Thus, there are several routes to dienone and dienoates that rely mainly on either more modern cross-coupling chemistry (e.g., the boron Heck reaction)[8] or a traditional approach (i.e., Wittig or Wittig-like)[9] or both.[2] On the other hand, the combination offered by an initial olefin cross-metathesis followed by an elimination provides novel and highly efficient inroads to these unsaturated arrays under very mild conditions.

2. Results and discussion

As an olefinic coupling partner equivalent to butadiene in a metathesis reaction, a simple known[10] ether derivative of homoallyl alcohol, **1**, was prepared anticipating that its subsequent elimination would be facile. Other leaving groups could easily be envisioned, but no others were tried in this study. Upon exposure of **1** to ethyl vinyl ketone (3 equiv) in refluxing CH_2Cl_2 (DCM) and in the presence of 5% of the phosphine-free Grubbs–Hoveyda second generation (GH-2) catalyst (**3**),[11] *E*-enone **2** was formed in essentially quantitative yield (entry 1, Table 1). The catalyst loading could be reduced to 2% without significant change in outcome (entry 2). Other catalysts such as **4**[12] (entry 4) and **5**[13] (entries 5–7) were also screened. Both were found to be less effective under these standard conditions, not a surprising outcome given the electron-rich tricyclohexylphosphine present in each, and the reduced rates at which these ligands dissociate from the metal center.[11b] Reactions at room temperature take place, although for the allotted time (15 h, entry 3) they were incomplete. Competing homocoupling of the enone for reactions run at higher concentrations accounts in part for lower yields (e.g., entry 5 vs 7).



Scheme 1.

Butadiene equivalent **1** smoothly couples with a variety of type-2 conjugated partners to give products **6a**–**6e**, as illustrated in Table 2. All of the precursor enones and enoates used are commercially available materials. Independent of their nature, elimination could

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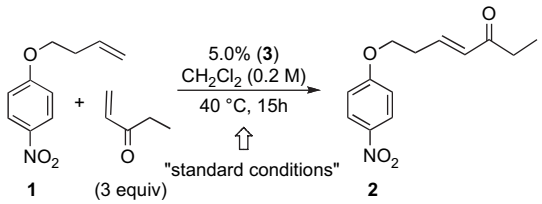
be effected by DBU (2 equiv) in DCM at ambient temperature within an hour at a concentration of 0.25 M. Again, conversions to dienes **7a**–**7e** were virtually 100% and isolated yields, likewise, were very high. Attempts to replace DBU with Et_3N were unsuccessful; elimination did not occur at room temperature.

Table 1
Optimization of the CM reaction of butadiene equivalent **1**[a]



Entry	Change from standard conditions	Yield[b] (%)
1	None	99
2	2.0% **3** instead of 5.0% **3**	95
3	2.0% **3** instead of 5.0% **3** at 22 °C	72
4	5.0% **4** instead of 5.0% **3**	88
5	5.0% **5** instead of 5.0% **3** in 0.5 M soln	38
6	5.0% **5** instead of 5.0% **3** in 0.5 M soln at 22 °C	29
7	5.0% **5** instead of 5.0% **3**	68

[a] Using 3 equiv ethyl vinyl ketone.
[b] Isolated yield of chromatographically pure materials.

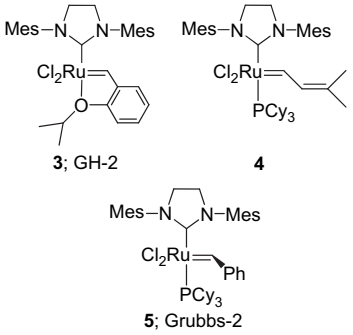
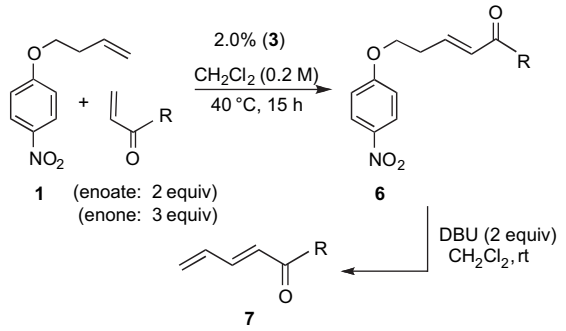


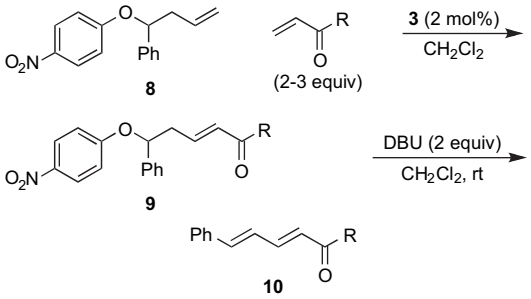
Table 2
Synthesis of α,β,γ,δ-unsaturated carbonyl compounds[a]



Entry	R	Yield of **6**[b] (%)	Yield of **7**[b] (%)
1	O-*t*-Bu	**6a** (96)	**7a** (98)
2	OMe	**6b** (89)	**7b** (100[c])
3	*O*-2-Ethylhexyl	**6c** (93)	**7c** (99)
4	Me	**6d** (92)	**7d** (100[c])
5	Et	**6e** (95)	**7e** (96)

[a] Metathesis reactions were conducted at 0.2 M for 15 h at 40 °C; elimination reactions were conducted at 0.25 M for 1 h at 22 °C.
[b] Isolated yield of chromatographically pure materials.
[c] Conversion was measured by GC–MS.

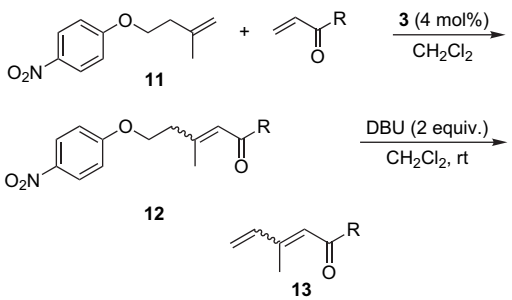
Table 3
Synthesis of δ-substituted α,β,γ,δ-unsaturated carbonyl derivatives[a]



Entry	R	Yield of **9**[b] (%)	Yield of **10**[b] (%)
1	O-*t*-Bu	**9a** (93)	**10a** (97)
2	OMe	**9b** (93)	**10b** (92)
3	*O*-2-Ethylhexyl	**9c** (96)	**10c** (99)
4	Me	**9d** (95)	**10d** (99)
5	Et	**9e** (97)	**10e** (98)
6	OH	**9f** (75)	**10f** (88[c])
7	H	**9g** (55, 96[d])	**10g** (90)

[a] Metathesis reactions were conducted at 0.2 M for 15 h at 40 °C; elimination reactions were conducted at 0.25 M for 1 h at 22 °C.
[b] Isolated yield of chromatographically pure materials.
[c] 3 equiv DBU.
[d] Based on recovered starting material.

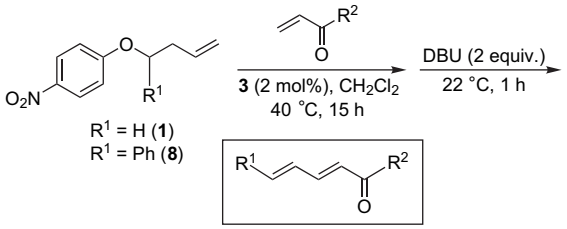
A substituted analog of **1**, ether **8** (from a Mitsunobu coupling on the corresponding commercially available alcohol precursor), also ultimately led to a variety of conjugated carbonyl-containing products (Table 3). In addition to the enoates and enones (entries 1–5) also examined earlier (see Table 2), both acrylic acid (2 equiv, entry 6) and acrolein (3 equiv, entry 7) could be employed. Initial products **9** are easily isolated and subsequently converted to doubly unsaturated carbonyl derivatives **10** under otherwise identical conditions as used previously (DBU, DCM, rt, 1 h). With a 1-substituted 3-butenol-derived ether such as **8**, δ-substituted α,β,γ,δ-unsaturated products are to be expected (e.g., **10**). Moving the substituent to the 3-position, as in the case of **11**, or what translates into the eventual β-site in the dienic product, affords initially, e.g., β,β-disubstituted enoate **12a** or enone **12b** (Scheme 2). The increased steric hindrance associated with the 1,1-disubstituted olefin in **11** slows the metathesis reactions with both an acrylate and an enone; additional catalyst was required (4 mol %) as was a higher reaction concentration (0.40 M). As expected from such metathesis reactions on 1,1-disubstituted alkenes,[14] both geometrical isomers were isolated as a roughly 1:1 mixture of *E*/*Z* products. Elimination from the separated pure *E*-isomer of **12a** led to *E*/*Z*-dienoates **13a** in a 5:1 *E*/*Z* ratio favoring the *E*-product, suggesting that some equilibration is occurring. The pure *Z*-isomer of **12a** gave an inverted 1:5 ratio favoring the *Z*-product. Continued



R = O-*t*-Bu: **12a** (50%); **13a** (94%)
R = Et: **12b** (65%); **13b** (94%)

Scheme 2. Synthesis of β-substituted α,β,γ,δ-unsaturated carbonyl compounds.

Table 4
One-pot synthesis of conjugated diene carbonyl compounds[a]



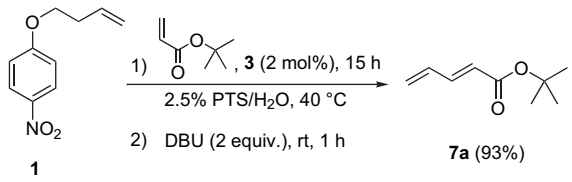
Entry	R^1, R^2	Yield[b] (%)
1	R^1=Ph, R^2=Et	**10e** (96)
2	R^1=Ph, R^2=*O*-*t*-Bu	**10a** (93)
3	R^1=H, R^2=*O*-2-ethylhexyl	**7c** (95)

[a] Reactions were conducted at 0.2 M.
[b] Isolated yield of chromatographically pure materials.

heating (90 min) at 40 °C of the initial 1:1 mix of *E*/*Z*-**12a** did not alter the relative amounts of dienic materials formed. Likewise, similar treatment of each isomer for extended times ultimately afforded the same 1:1 ratio.

The potential for both the cross-metathesis and the elimination steps to be carried out in a tandem, one-pot sequence was demonstrated with educts **1** and **8** (Table 4). Thus, following initial metathesis to either an enone (with **8**, entry 1) or an enoate (with **8**, entry 2; with **1**, entry 3), introduction of DBU to the mixture at room temperature led smoothly to the desired doubly unsaturated products **10e**, **10a**, and **7c** in high overall isolated yields.

Lastly, we have recently reported that the amphiphile 'PTS' (**14**),[15] present only to the extent of ca. 2.5% (by weight), allows for cross-metathesis within nanometer micelles in pure water.[16] Hence, application of this 'green' chemistry to the one-pot process at hand leads from olefin **1** and *tert*-butyl acrylate to dienoate **7a** in high overall yield (Scheme 3).



Scheme 3. Cross-metathesis/elimination in PTS/H_2O.

3. Conclusions

Homoallylic alcohols derivatized as their *p*-nitrophenol derivatives readily participate in olefin cross-metathesis reactions, both in traditional methylene chloride solution and in neat water using a small percentage of the nonionic surfactant PTS. The resulting initial products, which are activated carbonyl derivatives and can be isolated, have been shown to subsequently undergo elimination at room temperature under the influence of DBU to form doubly unsaturated derivatives. This new two-step sequence can also be effected in a single pot operation in high overall yields.

4. Experimental

4.1. General

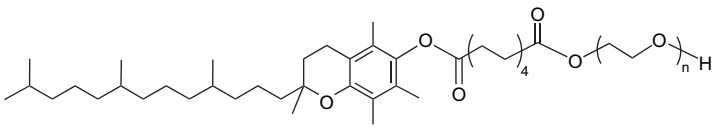
Melting points are uncorrected. Column chromatography was performed using Silicycle Silica-P 60 Å flash silica gel. Thin-layer-chromatographic analysis was conducted using commercially available EMD silica gel 60 F_{254} plates. Nuclear Magnetic Resonance spectra were obtained on a Varian Inova system, in $CDCl_3$, with proton and carbon resonances at 400 and 100 MHz, respectively, and are referenced to the residual solvent signal at 7.27 and 77.23 ppm, respectively. Infrared spectra were obtained either neat or by thin film on NaCl plates using a JASCO FT/IR-430 series spectrometer and are reported in cm^{-1}. Mass spectral data were acquired on either a VF Autospec or an analytical VG-70-250 HF spectrometer. Grubbs-2 and Grubbs–Hoveyda second generation catalysts were obtained from Materia, Inc. and stored in a glove box under an Ar atmosphere.

4.2. 1-(But-3-enyloxy)-4-nitrobenzene (1)

To a solution of 4-nitrophenol (0.40 g, 2.88 mmol) and K_2CO_3 (0.99 g, 7.16 mmol) in CH_3CN (20 mL) was added 4-bromo-1-butene (0.59 mL, 5.76 mmol), and the mixture was refluxed for 18 h. The solution was filtered through Celite and the filtrate concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2, washed with water, dried, and the solvent was removed under reduced pressure to give a yellow residue, which was chromatographed (hexanes–ethyl acetate, 24:1) to give **1** (0.55 g, 99%) as a pale yellow liquid. The spectroscopic data obtained for the product was in accord with that previously reported for this compound.[10]

4.3. 1-Nitro-4-(1-phenylbut-3-enyloxy)benzene (8)

Preparation of **8** follows from a known procedure,[17] using 4-nitrophenol (1.07 g, 7.70 mmol), 1-phenylbut-3-en-1-ol (1.04 g, 7.00 mmol), triphenylphosphine (2.02 g, 7.70 mmol), and di-(4-chlorobenzyl)azodicarboxylate (2.95 g, 8.05 mmol). Column chromatography (eluting with 10% EtOAc/hexanes) afforded the product as a pale yellow liquid (1.41 g, 75%); IR (neat): 3081, 3032, 2979, 2913, 2844, 1642, 1593, 1510, 1454, 1342, 1298, 1253, 1173, 1112, 1078, 1002, 921, 860, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J=9.2 Hz, 2H), 7.38–7.28 (m, 5H), 6.90 (d, J=9.2 Hz, 2H), 5.89–5.78 (m, 1H), 5.24 (dd, J=7.6, 5.6 Hz, 1H), 5.17–5.10 (m, 2H), 2.84–2.77 (m, 1H), 2.68–2.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 141.4, 139.9, 133.4, 128.9, 128.3, 126.0, 125.8, 118.4, 115.9, 80.7, 42.8; MS (ESI): m/z 292 (M+Na); HRMS (ESI) calcd for $C_{16}H_{15}NO_3Na$ $[M+Na]^+$=292.0950, found 292.0943.



14 (PTS; n = ca. 13)

4.4. 1-(3-Methylbut-3-enyloxy)-4-nitrobenzene (11)

Preparation of **11** was achieved according to a known procedure,[17] using 4-nitrophenol (1.07 g, 7.70 mmol), 3-methylbut-3-en-1-ol (0.71 mL, 7.00 mmol), triphenylphosphine (2.02 g,

7.70 mmol), and di-(4-chlorobenzyl)azodicarboxylate (2.95 g, 8.05 mmol). Column chromatography (eluting with 5% EtOAc/hexanes) afforded the product as a yellow liquid (1.28 g, 88%); IR (neat): 3081, 2939, 1651, 1595, 1518, 1471, 1377, 1347, 1299, 1260, 1173, 1111, 1039, 1012, 896, 846 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J=9.2 Hz, 2H), 6.96 (d, J=9.2 Hz, 2H), 4.88 (d, J=1.2 Hz, 1H), 4.81 (d, J=1.2 Hz, 1H), 4.18 (t, J=6.8 Hz, 2H), 2.55 (t, J=6.8 Hz, 2H), 1.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 142.0, 126.1, 114.6, 112.7, 67.4, 37.0, 22.9; MS (EI) m/z (%): 207 (M, 7), 179 (5), 152 (4), 69 (100); HRMS (EI) calcd for $C_{11}H_{13}NO_3$ $[M]^+$=207.0895, found 207.0903.

4.5. General procedure for cross-metathesis

The general procedure is illustrated by the preparation of dienone **9e**. To a solution of olefin **8** (135 mg, 0.50 mmol) and ethyl vinyl ketone (149 μL, 1.5 mmol) in CH_2Cl_2 (2.5 mL) was added **3** (6.3 mg, 0.01 mmol, 2.0 mol %), and the mixture was refluxed for 15 h. The flask was fitted with a condenser and refluxed under argon for 15 h. The reaction mixture was then reduced in volume to 0.5 mL and purified directly on a silica gel column, eluting with 6:1 hexanes–ethyl acetate to provide **9e** (158 mg, 97%) as a pale yellow liquid. IR (neat): 3085, 3033, 2978, 2938, 1699, 1674, 1632, 1592, 1510, 1455, 1419, 1342, 1253, 1200, 1173, 1112, 979, 917, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, J=9.2 Hz, 2H), 7.38–7.27 (m, 5H), 6.89 (d, J=9.2 Hz, 2H), 6.83 (dt, J=16.0, 7.2 Hz, 1H), 6.17 (d, J=16.0 Hz, 1H), 5.34 (dd, J=7.6, 4.8 Hz, 1H), 2.97–2.89 (m, 1H), 2.83–2.76 (m, 1H), 2.54 (q, J=7.2 Hz, 2H), 1.07 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.8, 162.8, 141.7, 140.6, 139.3, 132.9, 129.2, 128.7, 125.9, 125.8, 115.9, 79.7, 41.4, 33.7, 8.1; MS (ESI): m/z 364 (M+K), 348 (M+Na), 326 (M+H); HRMS (ESI) calcd for $C_{19}H_{19}NO_4Na$ $[M+Na]^+$=348.1212, found 348.1209.

4.5.1. (E)-tert-Butyl 5-(4-nitrophenoxy)pent-2-enoate (**6a**)

From olefin **1** (97 mg, 0.50 mmol) following the general procedure using *tert*-butyl acrylate (146 μL, 1.0 mmol) and catalyst **3** (6.3 mg, 0.01 mmol), elution with 19:1 hexanes–ethyl acetate, afforded **6a** (141 mg, 96%) as a colorless liquid. IR (neat): 3115, 3087, 2979, 2934, 1709, 1656, 1595, 1509, 1473, 1391, 1367, 1340, 1265, 1173, 1111, 1029, 981, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J=9.2 Hz, 2H), 6.96 (d, J=9.2 Hz, 2H), 6.91 (dt, J=15.6, 6.8 Hz, 1H), 5.90 (d, J=15.6 Hz, 1H), 4.17 (t, J=6.4 Hz, 2H), 2.72 (qd, J=6.8, 1.6 Hz, 2H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 163.8, 142.4, 141.8, 126.1, 125.8, 114.6, 80.7, 67.0, 31.7, 28.3; MS (ESI): m/z 316 (M+Na), 294 (M+H); HRMS (ESI) calcd for $C_{15}H_{19}NO_5Na$ $[M+Na]^+$=316.1161, found 316.1161.

4.5.2. (E)-Methyl 5-(4-nitrophenoxy)pent-2-enoate (**6b**)

From olefin **1** (124 mg, 0.64 mmol) following the general procedure using methyl acrylate (173 μL, 1.92 mmol) and catalyst **3** (8.0 mg, 0.013 mmol), elution with 9:1 hexanes–ethyl acetate, afforded **6b** (143 mg, 89%) as a white solid. Mp=41–43 °C; IR (thin film): 3114, 3086, 2951, 1722, 1660, 1607, 1594, 1512, 1469, 1437, 1342, 1299, 1262, 1219, 1173, 1111, 1031, 978, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J=9.2 Hz, 2H), 7.04 (dt, J=16.0, 6.8 Hz, 1H), 6.96 (d, J=9.2 Hz, 2H), 6.00 (dt, J=16.0, 1.2 Hz, 1H), 4.18 (t, J=6.4 Hz, 2H), 3.76 (s, 3H), 2.75 (qd, J=6.4, 1.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 163.7, 144.2, 141.9, 126.1, 123.7, 114.6, 66.8, 51.8, 31.9; MS (ESI): m/z 274 (M+Na), 252 (M+H); HRMS (ESI) calcd for $C_{12}H_{13}NO_5Na$ $[M+Na]^+$=274.0691, found 274.0696.

4.5.3. (E)-2-Ethylhexyl 5-(4-nitrophenoxy)pent-2-enoate (**6c**)

From olefin **1** (97 mg, 0.50 mmol) following the general procedure using *O*-2-ethylhexyl acrylate (209 μL, 1.0 mmol) and catalyst **3** (6.3 mg, 0.01 mmol), elution with 11:1 hexanes–ethyl acetate, afforded **6c** (163 mg, 93%) as a pale yellow liquid. IR (neat): 3064, 3033, 2959, 2930, 2860, 1719, 1659, 1606, 1593, 1514, 1495, 1455, 1380, 1342, 1253, 1198, 1171, 1112, 1021, 978, 875, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, J=9.2 Hz, 2H), 7.00 (dt, J=15.6, 6.8 Hz, 1H), 6.95 (d, J=9.2 Hz, 2H), 5.98 (d, J=15.6 Hz, 1H), 4.17 (t, J=6.4 Hz, 2H), 4.07 (dd, J=10.8, 5.6 Hz, 1H), 4.04 (dd, J=10.8, 6.0 Hz, 1H), 2.76–2.71 (m, 2H), 1.63–1.59 (m, 1H), 1.38–1.28 (m, 8H), 0.91–0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 163.7, 143.6, 141.8, 126.1, 124.2, 114.6, 67.1, 66.9, 38.9, 31.9, 30.6, 29.1, 24.0, 23.1, 14.2, 11.2; MS (ESI): m/z 372 (M+Na); HRMS (ESI) calcd for $C_{19}H_{27}NO_5Na$ $[M+Na]^+$=372.1787, found 372.1792.

4.5.4. (E)-6-(4-Nitrophenoxy)hex-3-en-2-one (**6d**)

From olefin **1** (97 mg, 0.50 mmol) following the general procedure using methylvinyl ketone (122 μL, 1.50 mmol), and catalyst **3** (6.3 mg, 0.01 mmol), elution with 4:1 hexanes–ethyl acetate afforded **6d** (108 mg, 92%) as a white solid. Mp=56–57 °C; IR (thin film): 3079, 3023, 2952, 1699, 1678, 1631, 1594, 1501, 1426, 1337, 1271, 1210, 1179, 1112, 1020, 990, 858, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J=9.2 Hz, 2H), 6.98 (d, J=9.2 Hz, 2H), 6.87 (dt, J=16.0, 6.8 Hz, 1H), 6.23 (dt, J=16.0, 1.6 Hz, 1H), 4.20 (t, J=6.4 Hz, 2H), 2.78 (qd, J=6.0, 1.2 Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.4, 163.7, 142.8, 141.8, 133.5, 126.1, 114.6, 66.8, 32.1, 27.3; MS (ESI): m/z 258 (M+Na), 236 (M+H); HRMS (ESI) calcd for $C_{12}H_{13}NO_4Na$ $[M+Na]^+$=258.0742, found 258.0738.

4.5.5. (E)-7-(4-Nitrophenoxy)hept-4-en-3-one (**6e**)

From olefin **1** (97 mg, 0.50 mmol) following the general procedure using ethyl vinyl ketone (150 μL, 1.50 mmol) and catalyst **3** (6.3 mg, 0.01 mmol), elution with 4:1 hexanes–ethyl acetate, afforded **6e** (119 mg, 95%) as a white solid. Mp=44–46 °C; IR (thin film): 3086, 2977, 2938, 1698, 1673, 1633, 1607, 1593, 1512, 1469, 1341, 1299, 1262, 1174, 1111, 1025, 978, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J=9.2 Hz, 2H), 6.96 (d, J=9.2 Hz, 2H), 6.89 (dt, J=16.0, 7.2 Hz, 1H), 6.26 (dt, J=16.0, 1.2 Hz, 1H), 4.19 (t, J=6.4 Hz, 2H), 2.76 (qd, J=6.4, 1.2 Hz, 2H), 2.61 (q, J=7.2 Hz, 2H), 1.12 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 163.7, 141.8, 141.4, 132.3, 126.1, 114.6, 66.9, 33.7, 32.1, 8.1; MS (CI) m/z (%): 250 (M+H, 15), 178 (11), 140 (55), 111 (100); HRMS (CI) calcd for $C_{13}H_{16}NO_4$ $[M+H]^+$=250.1079, found 250.1083.

4.5.6. (E)-tert-Butyl 5-(4-nitrophenoxy)-5-phenylpent-2-enoate (**9a**)

From olefin **8** (135 mg, 0.50 mmol) following the general procedure using *tert*-butyl acrylate (146 μL, 1.00 mmol) and catalyst **3** (6.3 mg, 0.01 mmol), elution with 19:1 hexanes–ethyl acetate, afforded **9a** (172 mg, 93%) as a colorless liquid. IR (neat): 3063, 2979, 2932, 1711, 1656, 1593, 1513, 1495, 1455, 1422, 1391, 1367, 1342, 1253, 1152, 1112, 1009, 981, 917, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, J=9.2 Hz, 2H), 7.38–7.28 (m, 5H), 6.91–6.85 (m, 3H), 5.85 (d, J=15.6 Hz, 1H), 5.31 (dd, J=7.6, 4.8 Hz, 1H), 2.94–2.86 (m, 1H), 2.78–2.73 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 162.9, 142.0, 141.7, 139.5, 129.2, 128.6, 126.3, 125.9, 116.0, 80.7, 79.7, 41.1, 28.3; MS (ESI): m/z 408 (M+K), 392 (M+Na), 370 (M+H); HRMS (ESI) calcd for $C_{21}H_{23}NO_5Na$ $[M+Na]^+$=392.1474, found 392.1467.

4.5.7. (E)-Methyl 5-(4-nitrophenoxy)-5-phenylpent-2-enoate (**9b**)

From olefin **8** (108 mg, 0.40 mmol) following the general procedure using methyl acrylate (108 μL, 1.20 mmol) and catalyst **3** (5.0 mg, 0.008 mmol), elution with 7:1 hexanes–ethyl acetate, afforded **9b** (122 mg, 93%) as a pale yellow liquid. IR (neat): 3084, 3031, 2951, 2844, 1721, 1660, 1593, 1513, 1495, 1454, 1436, 1342, 1251, 1201, 1172, 1112, 1023, 979, 917, 862, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.10–8.06 (m, 2H), 7.37–7.29 (m, 5H), 6.99 (dt, J=15.6, 7.2 Hz, 1H), 6.91–6.87 (m, 2H), 5.92 (d, J=15.6 Hz, 1H), 5.34 (dd, J=7.2, 4.4 Hz, 1H), 3.71 (s, 3H), 2.96–2.89 (m, 1H), 2.82–2.76 (m,

1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 162.8, 143.5, 141.7, 139.3, 129.2, 128.6, 125.9, 125.8, 124.2, 115.9, 79.5, 51.7, 41.2; MS (ESI): *m*/*z* 350 (M+Na); HRMS (ESI) calcd for $C_{18}H_{17}NO_5Na$ $[M+Na]^+$= 350.1004, found 350.1010.

4.5.8. (*E*)-2-Ethylhexyl 5-(4-nitrophenoxy)-5-phenylpent-2-enoate (**9c**)

From olefin **8** (108 mg, 0.40 mmol) following the general procedure using *O*-2-ethylhexyl acrylate (167 μL, 0.80 mmol) and catalyst **3** (5.0 mg, 0.008 mmol), elution with 11:1 hexanes–ethyl acetate, afforded **9c** (164 mg, 96%) as a pale yellow liquid. IR (neat): 3064, 3033, 2959, 2930, 2860, 1719, 1658, 1601, 1593, 1516, 1495, 1455, 1380, 1342, 1253, 1198, 1171, 1112, 1021, 980, 862, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (d, *J*=9.2 Hz, 2H), 7.38–7.28 (m, 5H), 6.97 (dt, *J*=15.6, 7.2 Hz, 1H), 6.89 (d, *J*=9.2 Hz, 2H), 5.93 (dt, *J*=15.6, 1.2 Hz, 1H), 5.33 (dd, *J*=7.6, 4.8 Hz, 1H), 4.06 (dd, *J*=10.8, 6.0 Hz, 1H), 4.03 (dd, *J*=10.8, 6.0 Hz, 1H), 2.97–2.89 (m, 1H), 2.83–2.76 (m, 1H), 1.62–1.56 (m, 1H), 1.39–1.32 (m, 2H), 1.28 (br s, 6H), 0.91–0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 162.8, 143.0, 141.7, 139.3, 129.2, 128.6, 125.9, 124.7, 115.9, 79.6, 67.0, 41.2, 38.9, 30.5, 29.0, 23.9, 23.1, 14.2, 11.2; MS (ESI): *m*/*z* 464 (M+K), 448 (M+Na), 426 (M+H); HRMS (ESI) calcd for $C_{25}H_{31}NO_5Na$ $[M+Na]^+$=448.2100, found 448.2113.

4.5.9. (*E*)-6-(4-Nitrophenoxy)-6-phenylhex-3-en-2-one (**9d**)

From olefin **8** (108 mg, 0.40 mmol) following the general procedure using methylvinyl ketone (97 μL, 1.20 mmol) and catalyst **3** (5.0 mg, 0.008 mmol), elution with 4:1 hexanes–ethyl acetate, afforded **9d** (119 mg, 95%) as a white solid. Mp=95–97 °C; IR (thin film): 3084, 3033, 2923, 1698, 1676, 1630, 1593, 1509, 1454, 1423, 1341, 1298, 1252, 1173, 1112, 980, 918 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J*=9.2 Hz, 2H), 7.37–7.27 (m, 5H), 6.88 (d, *J*=9.2 Hz, 2H), 6.80 (dt, *J*=16.0, 7.2 Hz, 1H), 6.14 (d, *J*=16.0 Hz, 1H), 5.36 (dd, *J*=7.6, 4.8 Hz, 1H), 2.97–2.90 (m, 1H), 2.84–2.75 (m, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 162.7, 142.0, 141.6, 139.2, 134.0, 129.2, 128.6, 125.8, 125.8, 115.9, 79.5, 41.3, 27.2; MS (ESI): *m*/*z* 334 (M+Na); HRMS (ESI) calcd for $C_{18}H_{17}NO_4Na$ $[M+Na]^+$=334.1055, found 334.1056.

4.5.10. (*E*)-5-(4-Nitrophenoxy)-5-phenylpent-2-enoic acid (**9f**)

From olefin **8** (108 mg, 0.40 mmol) following the general procedure using acrylic acid (55 μL, 0.80 mmol) and catalyst **3** (5.0 mg, 0.008 mmol), elution with 4:1 hexanes–ethyl acetate, afforded **9f** (94 mg, 75%) as a white solid. Mp=38–41 °C; IR (thin film): 3032, 2917, 1697, 1653, 1607, 1593, 1514, 1495, 1454, 1422, 1342, 1298, 1253, 1173, 1112, 1011, 980, 911, 863, 846 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J*=9.2 Hz, 2H), 7.39–7.29 (m, 5H), 7.11 (dt, *J*=15.6, 7.2 Hz, 1H), 6.89 (d, *J*=9.2 Hz, 2H), 5.93 (d, *J*=15.6 Hz, 1H), 5.36 (dd, *J*=7.6, 4.8 Hz, 1H), 3.00–2.92 (m, 1H), 2.87–2.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 162.7, 146.2, 141.8, 139.1, 129.3, 128.8, 125.9, 125.8, 124.0, 116.0, 79.4, 41.2; MS (ESI): *m*/*z* 336 (M+Na); HRMS (ESI) calcd for $C_{17}H_{15}NO_5Na$ $[M+Na]^+$=336.0848, found 336.0853.

4.5.11. (*E*)-5-(4-Nitrophenoxy)-5-phenylpent-2-enal (**9g**)

From olefin **8** (108 mg, 0.40 mmol) following the general procedure using acrolein (80 μL, 1.20 mmol) and catalyst **3** (5.0 mg, 0.008 mmol), elution with 4:1 hexanes–ethyl acetate, afforded **9g** (65 mg, 55%, 96% based on recovered starting material) as a colorless liquid. IR (neat): 3112, 3084, 3033, 2918, 2828, 2739, 1686, 1638, 1607, 1593, 1509, 1493, 1454, 1422, 1342, 1298, 1251, 1173, 1133, 1113, 1004, 975, 917, 862, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (d, *J*=8.0 Hz, 1H), 8.09 (d, *J*=9.2 Hz, 2H), 7.40–7.30 (m, 5H), 6.90 (d, *J*=9.2 Hz, 2H), 6.78 (dt, *J*=15.6, 7.2 Hz, 1H), 6.20 (ddt, *J*=15.6, 8.0, 1.2 Hz, 1H), 5.40 (dd, *J*=7.6, 4.4 Hz, 1H), 3.10–3.02 (m, 1H), 2.97–2.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 162.6, 152.1, 141.9, 139.0, 135.6, 129.4, 128.9, 126.0, 125.8, 116.0, 79.3, 41.5; MS (ESI): *m*/*z* 320 (M+Na); HRMS (ESI) calcd for $C_{17}H_{15}NO_4Na$ $[M+Na]^+$= 320.0899, found 320.0900.

4.5.12. *tert*-Butyl-3-methyl-5-(4-nitrophenoxy)pent-2-enoate (**12a**)

From olefin **11** (165 mg, 0.80 mmol) following the general procedure using *tert*-butyl acrylate (58 μL, 0.40 mmol) and catalyst **3** (10.0 mg, 0.016 mmol), elution with 13:1 hexanes–ethyl acetate, afforded **12a** (61 mg, 50%, *E*/*Z*=1:1) as a pale yellow liquid. The *E*/*Z* ratios were determined by relative integrations of the vinylic methyl resonances at 2.21 and 1.99 ppm. *(E)-Isomer.* R_f=0.55 (4:1 hexanes–ethyl acetate); IR (neat): 3114, 3087, 2978, 1712, 1651, 1593, 1516, 1390, 1342, 1299, 1259, 1173, 1142, 1111, 1032, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*=9.6 Hz, 2H), 6.95 (d, *J*=9.6 Hz, 2H), 5.69 (q, *J*=1.2 Hz, 1H), 4.19 (t, *J*=6.8 Hz, 2H), 2.63 (t, *J*=6.8 Hz, 2H), 2.21 (d, *J*=1.2 Hz, 3H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 163.8, 153.0, 141.8, 126.1, 120.0, 114.6, 80.2, 66.6, 39.9, 28.4, 18.9; MS (CI) *m*/*z* (%): 308 (M+H, 3), 252 (21), 234 (100), 113 (30), 95 (12); HRMS (CI) calcd for $C_{16}H_{22}NO_5$ $[M+H]^+$=308.1498, found 308.1493. *(Z)-Isomer.* R_f=0.61 (4:1 hexanes–ethyl acetate); IR (neat): 3114, 3087, 2978, 2934, 1708, 1649, 1595, 1510, 1470, 1366, 1333, 1253, 1174, 1142, 1112, 1086, 1052, 1032, 1011, 901, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (d, *J*=9.2 Hz, 2H), 6.98 (d, *J*=9.2 Hz, 2H), 5.74 (q, *J*=1.2 Hz, 1H), 4.24 (t, *J*=6.8 Hz, 2H), 3.09 (t, *J*=6.8 Hz, 2H), 1.99 (d, *J*=1.2 Hz, 3H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 164.1, 154.1, 141.6, 126.1, 120.4, 114.7, 80.2, 67.8, 33.0, 28.4, 26.5; MS (CI) *m*/*z* (%): 308 (M+H, 26), 252 (71), 234 (25), 169 (11), 113 (100); HRMS (CI) calcd for $C_{16}H_{22}NO_5$ $[M+H]^+$=308.1498, found 308.1489.

4.5.13. 5-Methyl-7-(4-nitrophenoxy)hept-4-en-3-one (**12b**)

From olefin **11** (207 mg, 1.00 mmol) following the general procedure using ethyl vinyl ketone (50 μL, 0.50 mmol) and catalyst **3** (12.6 mg, 0.02 mmol), elution with 8:1 hexanes–ethyl acetate, afforded **12b** (85 mg, 65%, *E*/*Z*=5:4) as a pale yellow liquid. The *E*/*Z* ratios were determined by relative integrations of the vinylic methyl resonances at 2.22 and 2.02 ppm. *(E)-Isomer.* R_f=0.50 (3:1 hexanes–ethyl acetate); IR (neat): 2937, 1688, 1625, 1608, 1593, 1513, 1471, 1341, 1299, 1261, 1173, 1111, 1030, 847 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (d, *J*=9.2 Hz, 2H), 6.95 (d, *J*=9.2 Hz, 2H), 6.16 (s, 1H), 4.21 (t, *J*=6.4 Hz, 2H), 2.65 (t, *J*=6.4 Hz, 2H), 2.48 (q, *J*=7.6 Hz, 2H), 2.22 (s, 3H), 1.08 (t, *J*=7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.7, 163.8, 152.6, 141.8, 126.1, 125.3, 114.6, 66.5, 40.2, 37.7, 19.5, 8.2; MS (EI) *m*/*z* (%): 263 (M, 6), 245 (10), 234 (100), 152 (36), 125 (24), 124 (48), 95 (47), 57 (47); HRMS (EI) calcd for $C_{14}H_{17}NO_4$ $[M]^+$=263.1158, found 263.1161. *(Z)-Isomer.* R_f=0.62 (3:1 hexanes–ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (d, *J*=9.2 Hz, 2H), 6.97 (d, *J*=9.2 Hz, 2H), 6.21 (s, 1H), 4.24 (t, *J*=6.4 Hz, 2H), 3.04 (t, *J*=6.4 Hz, 2H), 2.47 (q, *J*=7.2 Hz, 2H), 2.02 (s, 3H), 1.07 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.4, 164.1, 154.5, 141.6, 126.1, 125.4, 114.7, 68.0, 37.6, 33.8, 27.1, 8.1; HRMS (EI) calcd for $C_{14}H_{17}NO_4$ $[M]^+$=263.1158, found 263.1149.

4.6. General procedure for the preparation of doubly unsaturated carbonyl derivatives

The general procedure is illustrated by the preparation of **10c**. DBU (0.10 mL, 0.68 mmol) was added dropwise to a solution of **9c** (145 mg, 0.34 mmol) in CH_2Cl_2 (1.4 mL) and the reaction mixture was stirred at 22 °C for 1 h. HCl (3 mL, 1.0 M) was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried, and the solvent was removed under reduced pressure to give a light yellow residue, which was chromatographed (hexanes–ethyl acetate, 20:1) to give **10c** (97 mg, 99%) as a colorless liquid. IR (neat): 3060, 3028, 2959, 2860, 1710,

1627, 1461, 1382, 1343, 1237, 1173, 1132, 999, 947, 916, 878, 838 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.48–7.40 (m, 3H), 7.38–7.30 (m, 3H), 6.93–6.84 (m, 2H), 6.01 (d, J=15.6 Hz, 1H), 4.11 (dd, J=10.8, 6.0 Hz, 1H), 4.08 (dd, J=10.8, 6.0 Hz, 1H), 1.67–1.61 (m, 1H), 1.43–1.32 (m, 8H), 0.94–0.90 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 144.6, 140.5, 136.2, 129.2, 129.0, 127.3, 126.4, 121.6, 67.0, 39.0, 30.6, 29.1, 24.0, 23.2, 14.3, 11.2; MS (EI) m/z (%): 286 (M, 12), 174 (48), 157 (29), 129 (100), 128 (40); HRMS (EI) calcd for $C_{19}H_{26}O_2$ $[M]^+$=286.1933, found 286.1927.

*4.6.1. (E)-2-Ethylhexyl penta-2,4-dienoate (**7c**)*

From enoate **6c** (18.6 mg, 0.053 mmol) following the general procedure using DBU (16 μL, 0.11 mmol), elution with 20:1 hexanes–ethyl acetate, afforded **7c** (11 mg, 99%) as a colorless liquid. IR (neat): 3091, 2960, 2861, 1717, 1643, 1601, 1463, 1417, 1381, 1305, 1265, 1200, 1143, 1009, 922, 868 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 (dd, J=15.6, 10.8 Hz, 1H), 6.46 (dt, J=18.0, 10.0 Hz, 1H), 5.92 (d, J=15.6 Hz, 1H), 5.61 (d, J=16.8 Hz, 1H), 5.49 (d, J=10.4 Hz, 1H), 4.08 (dd, J=11.2, 6.0 Hz, 1H), 4.05 (dd, J=11.2, 6.0 Hz, 1H), 1.61–1.59 (m, 1H), 1.42–1.29 (m, 8H), 0.92–0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.3, 144.7, 135.0, 125.7, 122.5, 67.1, 39.0, 30.6, 29.1, 24.0, 23.2, 14.3, 11.2; MS (CI) m/z (%): 211 (M+H, 80), 113 (35), 99 (95), 81 (100), 71 (39), 57 (48); HRMS (CI) calcd for $C_{13}H_{23}O_2$ $[M+H]^+$=211.1698, found 211.1695.

*4.6.2. 5-Methylhepta-4,6-dien-3-one (**13b**)*

From enone **12b** (21 mg, 0.08 mmol) following the general procedure using DBU (24 μL, 0.16 mmol), elution with 13:1 hexanes–ethyl acetate, afforded **13b** (9.3 mg, 94%, E/Z=3.4:1) as a colorless liquid. The E/Z ratios were determined by relative integrations of the γ-methine resonances at 6.37 and 7.74 ppm. IR (neat): 2925, 1686, 1593, 1459, 1377, 1241, 1127, 1035, 920, 865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ for cis: 7.74 (dd, J=17.6, 10.8 Hz, 1H), 6.07 (s, 1H), 5.62 (d, J=17.6 Hz, 1H), 5.45 (d, J=10.8 Hz, 1H), 2.48 (q, J=7.2 Hz, 2H), 1.99 (d, J=1.2 Hz, 3H), 1.08 (t, J=7.2 Hz, 3H); for trans: 6.37 (dd, J=17.6, 10.8 Hz, 1H), 6.14 (s, 1H), 5.66 (d, J=17.6 Hz, 1H), 5.44 (d, J=10.8 Hz, 1H), 2.51 (q, J=7.2 Hz, 2H), 2.24 (d, J=1.2 Hz, 3H), 1.09 (t, J=7.2 Hz, 3H)]; MS (EI) m/z (%): 124 (M, 25), 109 (11), 95 (100), 67 (78).

4.7. General procedure for one-pot synthesis of conjugated diene carbonyl compounds in CH_2Cl_2

The general procedure is illustrated by the preparation of **10e**. To a solution of **8** (85 mg, 0.316 mmol) and ethyl vinyl ketone (94 μL, 0.947 mmol) in CH_2Cl_2 (1.6 mL) was added **3** (4.0 mg, 0.0064 mmol, 2.0 mol %), and the mixture was refluxed for 15 h. Then the reaction mixture was cooled to 22 °C, and DBU (94 μL, 0.63 mmol) was added dropwise and stirred for another 1 h at the same temperature. HCl (1.0 M, 3 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried, and the solvent was removed under reduced pressure to give a brown residue, which was chromatographed (hexane–ethyl acetate, 13:1) to give **10e** (56 mg, 96%) as a white solid.

4.8. Procedure for one-pot synthesis in PTS/H_2O (7a)

Olefin **1** (39 mg, 0.20 mmol), *tert*-butyl acrylate (59 μL, 0.40 mmol), and catalyst **3** (2.53 mg, 0.004 mmol) were sequentially added to a Teflon-coated-stir-bar-containing Biotage 2–5 mL microwave reactor vial at room temperature, and sealed with a septum. An aliquot of PTS/H_2O (2.5% by weight, 1.0 mL) was added via syringe and the resulting emulsion was allowed to stir at 40 °C for 15 h. Then DBU (60 μL, 0.60 mmol) was added dropwise to the reaction mixture and stirred for another 1 h at 22 °C. The homogeneous reaction mixture was then diluted with EtOAc (5 mL), filtered through a bed of silica gel layered over Celite, and the bed washed (3×10 mL) with EtOAc. The volatiles were removed in vacuo to afford the crude material, which was subsequently purified by flash chromatography on silica gel (eluting with 5.0% EtOAc/hexanes) to yield **7a** as a white solid (29 mg, 93%).

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