Tetrahedron Letters 50 (2009) 6256–6260

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Expedient synthesis of 3-substituted cycloalkanones via a Pd-catalyzed decarboxylative protonation protocol

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ARTICLE INFO

Article history:
Received 17 August 2009
Revised 31 August 2009
Accepted 1 September 2009
Available online 6 September 2009

Keywords:
Cycloalkanones
Decarboxylative protonation
Palladium
C–H activation

ABSTRACT

We developed an efficient method for the introduction of $-CH_2EWG$ moiety at the β-position of 2-cycloalken-1-ones via a Pd-catalyzed decarboxylative protonation protocol.

After the findings of Pd-catalyzed decarboxylative protonation and allylation of allyl esters by Tsuji,[1a–c] the concepts found many useful applications.[1–3] Recently we applied the Pd-catalyzed decarboxylative protonation for the synthesis of various 1,5-dicarbonyl and related compounds from modified Baylis–Hillman adducts having allyl ester moiety.[3]

1,5-Dicarbonyl and related scaffolds constituted important backbone of many natural substances.[4] Especially, 1,5-dicarbonyl compounds having cycloalkanone moiety have been found in many natural substances including jasmonates, magnolion, and cucurbates.[5] In these respects, the syntheses of 1,5-dicarbonyl and related compounds have received much attention.[5,6] The Mukaiyama–Michael type reaction of cycloalkenones with trimethylsilyl enol ethers or trimethylsilyl ketene acetals under the influence of DBU,[6a] $InCl_3$,[6b] TASF,[6c] $Bu_2Sn(OTf)_2$,[6d] or $TiCl_4$[6e] have been reported. Michael addition of dimethyl malonate to cycloalkenone and the following dealkoxycarbonylation with LiI/DMSO under refluxing condition has also been reported.[6f] Similar approach with *tert*-butyl acetoacetate was reported and TFA was used in this case for the removal of *tert*-butyl ester moiety to produce cyclic 1,5-dicarbonyl compound.[6g] However, the reported methods suffer from moderate yields[6a–e,i] or the use of drastic conditions.[6f] In these respects, development of an expedient procedure for the synthesis of cyclic 1,5-dicarbonyl and related compounds is still highly required, and we wish to report an efficient alternate procedure involving a Pd-catalyzed decarboxylative protonation.

During the studies on the synthetic applicability of Pd-catalyzed decarboxylative protonation,[3] we reasoned out that the introduction of $-CH_2EWG$ moiety at the β-position of cycloalkenones could be easily achieved under mild conditions. The strategy involved a sequential conjugate addition of allyl ester **2** to cycloalkenone **1** and a Pd-catalyzed decarboxylative protonation process, as shown in Scheme 1.

In order to check the feasibility of our rationale, we prepared compound **3a** from 2-cyclopenten-1-one (**1a**) and allyl acetoacetate (**2a**) in 79% (K_2CO_3/CH_3CN, rt, 24 h) as a diastereomeric mixture (1:1).[7,8] We examined the reaction of **3a** under various Pd-catalyzed reaction conditions (Scheme 2, see also entry 1 in Table 1).[1–3] When the reaction of **3a** was carried out under the influence of $Pd(OAc)_2/PPh_3/Et_3N/HCOOH$ in CH_3CN at room temperature (condition A)[1–3] compound **4a** was obtained in good yield (86%).[8] The result was similar at refluxing temperature (condition B, 84%). When the reaction was conducted in aqueous CH_3CN in the presence of Et_3N at room temperature (condition C), **4a** was obtained in 91%. However, cyclopentene derivative **5a**[8,9d] was isolated in 16%, unexpectedly, at refluxing temperature (condition D),[1–3] along with **4a** (71%) as the major product. The structure of compound **5a** was confirmed by its spectroscopic data (^1H, ^{13}C, IR, and Mass).[8,9d]

The formation of **4a** could be explained as in our previous Letter[3] involving π-allylpalladium carboxylate (**I**) and π-allylpalladium intermediate (**II**). When we use Et_3N/HCOOH conditions

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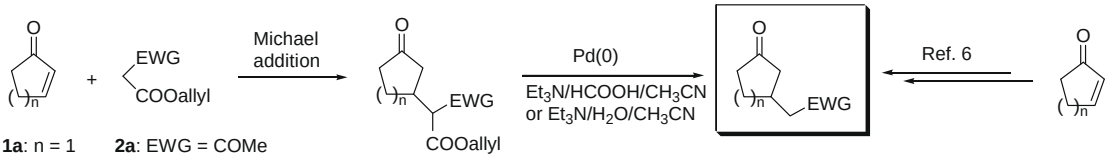
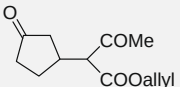
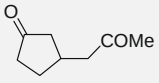
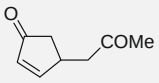
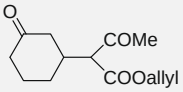
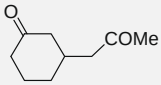
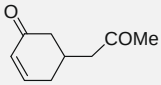
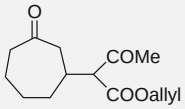
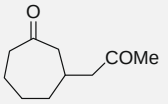
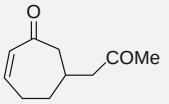
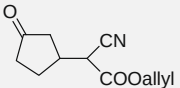
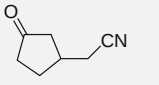
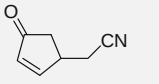
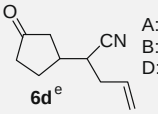
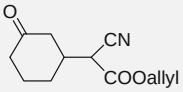
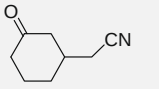
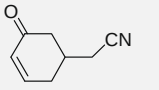
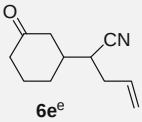
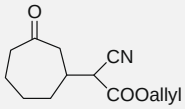
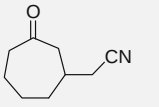
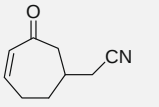
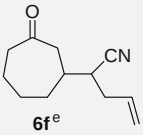
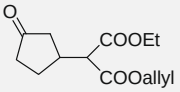
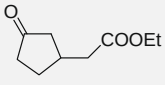
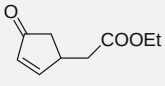
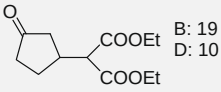
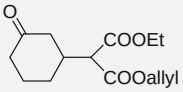
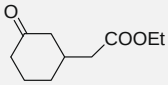
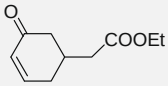
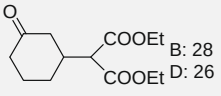
doi:10.1016/j.tetlet.2009.09.014

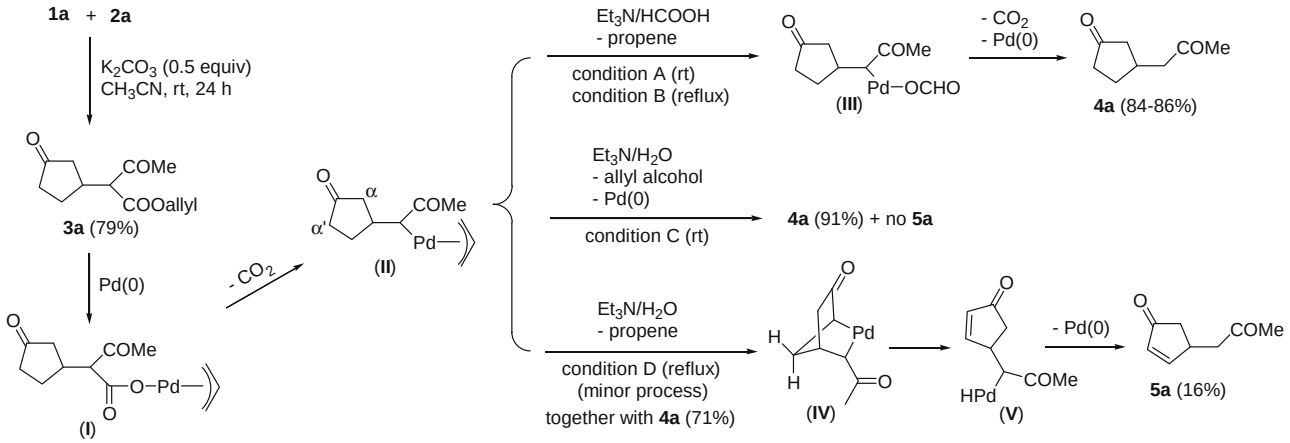


Scheme 1.

Table 1
Pd-catalyzed decarboxylative protonation

Entry	Substrate[a,e] (%)		Product[b,c,d] (%)	
1	 **3a** (79)	 **4a** A: 86 B: 84 C: 91 D: 71	 **5a** A: 0 B: 0 C: 0 D: 16	
2	 **3b** (61)	 **4b** A: 84 B: 85 C: 88 D: 72	 **5b** A: 0 B: 0 C: 0 D: 12	
3	 **3c** (46)	 **4c** A: 86 B: 87 C: 89 D: 95	 **5c** A: 0 B: 0 C: 0 D: 0	
4	 **3d** (70)	 **4d** A: 0 B: 59 D: 55	 **5d** A: 0 B: 0 D: 8	 **6d**[e] A: 0 B: 7 D: 31
5	 **3e** (67)	 **4e** A: 0 B: 73 D: 49	 **5e** A: 0 B: 0 D: 14	 **6e**[e] A: 0 B: 13 D: 23
6	 **3f** (67)	 **4f** B: 80 D: 61	 **5f** B: 0 D: 0	 **6f**[e] B: 11 D: 29
7	 **3g** (86)	 **4g** B: 61 D: 42	 **5g** B: 0 D: 16	 **7g** B: 19 D: 10
8	 **3h** (82)	 **4h** B: 63 D: 45	 **5h** B: 0 D: 4	 **7h** B: 28 D: 26

[a] Conditions of Michael addition: K_2CO_3 (0.5 equiv), CH_3CN, rt, 24 h (for entries 1, 2, 4–6); TBAF (2.0 equiv), THF, rt, 24 h (for entry 3); TBD (0.5 equiv), toluene, rt, 3 h (for entries 7 and 8).
[b] $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and Et_3N (1.3 equiv) are common.
[c] Condition A: HCOOH (1.0 equiv), CH_3CN, rt, 1 h; condition B: HCOOH (1.0 equiv), CH_3CN, reflux, 1 h; condition C: CH_3CN/H_2O (9:1), rt, 2 h; condition D: CH_3CN/H_2O (9:1), reflux, 2 h.
[d] Reaction time of nitrile-containing substrates (entries 4–6) is 18 h.
[e] Compounds **3a–h** and **6d–f** were isolated as a diastereomeric mixture (ca. 1:1 in every case).



Scheme 2.

(conditions A and B), (**II**) was changed into (**III**) with liberation of propene, and the following decarboxylation produced **4a** as documented in the literature.[1–3] As reported by us[3a] and others[1d] in similar systems, the formation of compound **4a** under the conditions of aqueous CH_3CN/Et_3N (conditions C and D) might involve the liberation of allyl alcohol. However, the mechanism for the formation of **5a** has to be addressed. The mechanism could be postulated tentatively as shown in Scheme 2: (i) C–H activation at the α′-position of (**II**) to form the bicyclic palladacycle (**IV**),[10] (ii) β′-H elimination to form a ring-opened intermediate (**V**), and the final reductive removal of Pd(0) to generate **5a**.[8,9d] As described above (vide supra) compound **5a** was observed only under the condition of D, albeit in low yield. The overall mechanism is very similar with that of Pd(0)-catalyzed intramolecular redox reaction reported by Hogenauer and Mulzer.[10] They also observed the critical role of CH_3CN/H_2O at elevated temperature as in our case.[10,11]

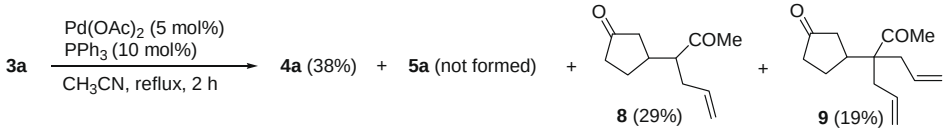
Irrespective of the formation of **5a** in low yield under condition D, we obtained our desired compound **4a** in good yield. Thus, we decided to examine the synthesis of 3-substituted cycloalkanones via a Pd-catalyzed decarboxylation, systematically. Various starting materials **3b–h** were prepared by the reactions of 2-cyclopenten-1-one (**1a**), 2-cyclohexen-1-one (**1b**), 2-cycloheptene-1-one (**1c**) and allyl acetoacetate (**2a**), allyl cyanoacetate (**2b**), allyl ethyl malonate (**2c**) in good to moderate yields, as summarized in Table 1. As a base catalyst, K_2CO_3, TBAF,[7c] and TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene)[7a,b] were used depending on the substrates (see footnote a in Table 1). In all cases the compounds **3b–h** were obtained as a diastereomeric mixture (*syn/anti*, 1:1) and we used them without separation. The Pd-catalyzed decarboxylative protonation reactions were carried out under the conditions A–D, and the results are summarized in Table 1.

The reaction of acetyl derivatives **3b** and **3c** (entries 2 and 3) showed a similar reactivity with that of **3a**. All conditions produced decarboxylative protonation products **4b** and **4c** in good yields (72–95%). Cyclohexene derivative **5b** was isolated in 12% under the condition D. However, we could not observe the formation of **5c** in the case of cycloheptane derivative **3c** (entry 3) even under the condition D. The reason is not clear at this stage, however, the formation of the corresponding palladacycle intermediate might be somewhat difficult than other cases.

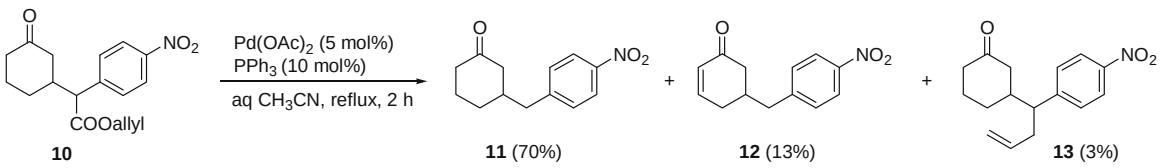
For the nitrile-substituted substrates **3d–f** (entries 4–6), we could not observe the formation of desired product **4d–f** at room temperature. At refluxing temperature (conditions B and D), compounds **4d–f** were isolated in moderate yields (49–80%). Under the condition D, cycloalkene derivatives **5d** and **5e** were isolated similarly, albeit in low yields (8–14%). Cycloheptene derivative **5f** was not formed similarly (see, entry 3). Instead, decarboxylative allylation products **6d–f** were isolated in low yields (7–31%).

The reactions with ester-substituted substrates, **3g** and **3h**, were sluggish at room temperature (entries 7 and 8). Condition B provided products **4g** and **4h** in better yields (61–63%) than the condition D (42–45%). Compounds **5g** and **5h** were formed under condition D similarly (4–16%). It is interesting to note that transesterification products **7g** and **7h** were isolated (10–28%), and this is the major reason for the low yields of desired **4g** and **4h**.

The reaction of **3a** under anhydrous CH_3CN was examined, as shown in Scheme 3. Compound **4a** was isolated as the major product (38%) along with mono-allyl compound **8** (29%, *syn/anti* = 1:1)



Scheme 3.



Scheme 4.

and diallyl compound **9** (19%). As the last examination, we tried the reaction of *p*-nitrobenzyl derivative **10**,[3b] as shown in Scheme 4. The reaction produced protonation product **11** (70%) along with cyclohexene derivative **12** (13%) and allyl compound **13** (3%).

In summary, we synthesized various cycloalkanone derivatives having $-CH_2EWG$ moiety at the β-position from 2-cycloalken-1-ones by using a combination of a base-catalyzed conjugate addition with allyl ester and a Pd-catalyzed decarboxylative protonation. Interestingly, cycloalkenone derivatives were formed in some cases via the Pd(0)-catalyzed intramolecular redox reaction.

Acknowledgements

This work was supported by National Research Foundation of Korea Grant funded by the Korean Government (2009-0070633). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

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8. *Typical procedure for the synthesis of* **4a** *and* **5a** (*condition D*): a mixture of 2-cyclopenten-1-one (**1a**, 165 mg, 2.0 mmol), allyl acetoacetate (**2a**, 429 mg, 3.0 mmol), and K_2CO_3 (138 mg, 1.0 mmol) in CH_3CN (5 mL) was stirred at room temperature for 24 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 4:1) compound **3a** was isolated as colorless oil, 356 mg (79%) as a *syn/anti* mixture (1:1). A mixture of compound **3a** (224 mg, 1.0 mmol), $Pd(OAc)_2$ (12 mg, 5 mol %), PPh_3 (27 mg, 10 mol %), Et_3N (132 mg, 1.3 mmol), in aqueous CH_3CN (H_2O/CH_3CN = 1:9, 3 mL) was heated to reflux under nitrogen atmosphere for 2 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 8:2:1) compounds **4a** (100 mg, 71%) and **5a** (22 mg, 16%) were isolated as colorless oils. Other compounds were synthesized similarly and the representative spectroscopic data of selected compounds **4a**,[9j] **4f**, **5a**,[9d] **5b**, **5e**, **5h**, **6d**, **6e**, **6f**, **8**, **9**, and **12** are as follows. Known compounds were identified by comparison their spectroscopic data with the reported, **4b**,[6d,g] **4c**,[9i] **4d**,[9c] **4e**,[9k] **4g**,[9a,6b] **4h**,[6b] **5d**,[9h] **5g**,[9b,f] **7g**,[9a] **7h**,[9l] **10**,[3b] **11**,[3b] **13**.[3b]
Compound **4a**:[9j] 71%; colorless oil; IR (film) 1741, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.44–1.59 (m, 1H), 1.74–1.85 (m, 1H), 1.96–2.69 (m, 7H), 2.17 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.21, 30.19, 32.17, 38.21, 44.59, 48.91, 207.14, 218.59; ESIMS *m/z* 140 (M^++1).
Compound **4f**: 61%; yellow oil; IR (film) 2244, 1699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38–1.73 (m, 3H), 1.90–2.19 (m, 4H), 2.30–2.65 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.70, 25.15, 27.83, 33.04, 36.00, 43.75, 48.62, 117.87, 211.46; ESIMS *m/z* 151 (M^++1). Anal. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.67; H, 8.88; N, 9.12.
Compound **5a**:[9d] 16%; colorless oil; IR (film) 1714, 1261, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.93 (dd, *J* = 18.9 and 2.4 Hz, 1H), 2.19 (s, 3H), 2.57–2.74 (m, 3H), 3.35–3.45 (m, 1H), 6.18 (dd, *J* = 5.7 and 2.1 Hz, 1H), 7.64 (d, *J* = 5.7 and 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.11, 36.44, 41.00, 47.90, 134.35, 166.98, 206.09, 209.01; ESIMS *m/z* 138 (M^++1). Anal. Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.67; H, 7.43.
Compound **5b**: 12%; colorless oil; IR (film) 1714, 1678 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86–2.79 (m, 7H), 2.16 (s, 3H), 6.02–6.07 (m, 1H), 6.92–6.98 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.46 (2C), 31.53, 43.86, 48.67, 129.75, 149.24, 198.83, 206.65; ESIMS *m/z* 152 (M^++1). Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.24; H, 8.03.
Compound **5e**: 14%; colorless oil; IR (film) 2247, 1682, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.27–2.65 (m, 7H), 6.07–6.14 (m, 1H), 6.95–7.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.24, 30.72, 31.90, 43.00, 117.21, 130.00, 147.78, 196.83; ESIMS *m/z* 135 (M^++1). Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.34; H, 6.54; N, 10.12.
Compound **5h**: 4%; colorless oil; IR (film) 1731, 1681, 1259 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.01–2.68 (m, 7H), 4.15 (q, *J* = 7.2 Hz, 2H), 6.03–6.07 (m, 1H), 6.93–6.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.21, 31.50, 31.83, 39.98, 43.80, 60.61, 129.78, 149.10, 171.56, 198.65; ESIMS *m/z* 182 (M^++1). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.86; H, 7.55.
Compound **6d**: 31% (1:1 mixture); yellow oil; IR (film) 2239, 1743, 1406 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.72–1.85 (m, 1H), 1.97–2.55 (m, 8H), 2.70–2.80 (m, 1H), 5.21–5.28 (m, 2H), 5.76–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.77, 27.66, 34.86, 35.08, 36.50, 36.52, 37.99, 38.05, 38.19, 38.29, 41.66, 42.93, 119.33, 119.36, 119.65, 119.70, 132.51, 132.58, 215.60, 215.72; ESIMS *m/z* 163 (M^++1). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.43; H, 8.35; N, 8.29.
Compound **6e**: 23% (1:1 mixture); yellow oil; IR (film) 2237, 1714, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.53–1.78 (m, 2H), 1.84–2.74 (m, 10H), 5.18–5.26 (m, 2H), 5.71–5.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.42, 24.51, 27.30, 29.86, 33.78, 33.89, 37.42, 37.51, 39.23, 39.32, 40.90, 40.95, 43.49, 46.09, 119.25, 119.27, 119.58, 119.68, 132.60, 132.64, 209.00, 209.09; ESIMS *m/z* 177 (M^++1). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.61; H, 8.76; N, 7.87.
Compound **6f**: 29% (1:1 mixture); yellow oil; IR (film) 2237, 1701, 1447 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32–1.77 (m, 3H), 1.86–2.07 (m, 4H), 2.27–2.77 (m, 7H), 5.18–5.26 (m, 2H), 5.72–5.86 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.79 (2C), 27.75, 28.11, 32.58, 33.97, 34.11, 35.74, 36.89, 37.21, 38.24, 38.35, 43.65, 43.72, 45.34, 48.21, 119.21, 119.24, 119.85, 119.87, 132.74, 132.76, 211.85, 211.88; ESIMS *m/z* 191 (M^++1). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.42; H, 9.10; N, 7.23.
Compound **8**: 29% (1:1 mixture); yellow oil; IR (film) 1743, 1709, 1357 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45–1.62 (m, 1H), 1.78–1.96 (m, 1H), 2.05–2.65 (m, 8H), 2.14 (s, 3H 0.5), 2.17 (s, 3H 0.5), 5.02–5.17 (m, 2H), 5.62–5.78 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.40, 28.09, 30.48, 30.70, 34.09, 35.28, 37.92, 38.28, 38.43, 38.50, 42.96, 43.36, 57.61, 57.97, 117.53 (2C), 134.30, 134.38, 210.66, 210.77, 217.54, 217.72; ESIMS *m/z* 180 (M^++1).
Compound **9**: 19%; yellow oil; IR (film) 1743, 1698, 1355 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.66–1.81 (m, 1H), 2.04–2.20 (m, 3H), 2.18 (s, 3H), 2.24–2.59 (m, 7H), 5.09–5.19 (m, 4H), 5.66–5.81 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.54, 28.29, 37.90, 38.08, 38.53, 40.46, 42.41, 55.27, 118.69, 118.73, 133.46 (2C), 211.36, 217.62; ESIMS *m/z* 220 (M^++1).
Compound **12**: 13%; yellow oil; IR (film) 1678, 1517, 1345 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04–2.54 (m, 5H), 2.81 (d, *J* = 6.6 Hz, 2H), 6.04–6.08 (m, 1H), 6.91–6.97 (m, 1H), 7.32 (d, *J* = 8.7 Hz, 2H), 8.18 (d, *J* = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.62, 36.63, 41.69, 43.86, 123.80, 129.81, 130.00, 146.79,

146.73, 148.84, 198.58; ESIMS *m/z* 231 (M^++1). Anal. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.46; H, 5.87; N, 5.05.

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11. In order to increase the yield of **5a**, we tried the reaction of **3a** under $Pd(OAc)_2$ (5 mol %)/PPh_3 (10 mol %)/Et_3N (1.3 equiv) in aqueous CH_3CN in a sealed tube at 110–120 °C, however, we did not observe better results. In order to increase the proportion of C-bound Pd-intermediate (**II**),[3b] we reduced the ratio of PPh_3/Pd as follows: $Pd(OAc)_2$ (10 mol %)/PPh_3 (5 mol %)/Et_3N (1.3 equiv) in aqueous CH_3CN at refluxing temperature. However, the results were almost the same with those of entry 3 (condition D), unfortunately.