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An expedient synthesis of β-aralkyl cycloalkanones via the sequential conjugate addition of allyl arylacetates and Pd-catalyzed decarboxylative protonation protocol

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ABSTRACT

An expedient protocol for the synthesis of β-aralkyl cycloalkanones was developed via the conjugate addition of allyl arylacetate to cycloalkenones and the following Pd-catalyzed decarboxylative protonation strategy.

Introduction of carbon nucleophile at the β-position of cycloalkenone in a Michael fashion is an important chemical transformation in organic synthesis.[1,2] Conjugate addition of organometallic compounds in the presence of copper salt is the most common and efficient method.[1a,b] Besides organocopper reagents, organozinc in combination with $(AlMeO)_n$[1c] and RLi/RMgX in combination with $BeCl_2$[1d] have also been used for the reaction. However, the preparation of functionalized organometallic compounds and their use in organic synthesis are often faced with some problems like functional group incompatibility. Especially, the preparation of nitro-containing organometallic compounds is difficult due to the reactivity of nitro group, although nitroaryl Grignard reagents can be generated at low temperature and used efficiently in some cases.[3a] In these contexts, conjugate addition of nitrobenzyl group at the β-position of cycloalkenones is regarded as a tedious matter.[2,3]

After Tsuji's brilliant contributions,[4a–d] Pd-catalyzed decarboxylative protonation and allylation have been used widely in organic synthesis.[4–6] As is often the case the corresponding π-allylpalladium carboxylate intermediate cannot lose carbon dioxide without an electron-accommodating group.[4–6] Many functional groups have been reported as the suitable electron-accommodating moieties including ester, nitrile, and acetyl groups.[4,5] Recently, Tunge and co-workers used electron-deficient aryl and heterocyclic moieties as the electron-accommodating group in their Pd-catalyzed decarboxylative allylation.[6]

Very recently, we used the Pd-catalyzed decarboxylative protonation protocol elegantly for the synthesis of 1,5-dicarbonyls and related compounds from Baylis–Hillman adducts.[5] During the project we imagined that we could introduce *p*-nitrobenzyl moiety at the β-position of 2-cyclohexene-1-one (**1a**) as shown in Scheme 1. The strategy was the sequential conjugate addition of allyl *p*-nitrophenylacetate (**2a**) to form **3a** and the following Pd-catalyzed decarboxylative protonation of **3a** to make **4a**.

The conjugate addition of **2a** to **1a** was carried out in the presence of TBD (1,5,7-triazabicyclo[4.4.0]dec-5-ene)[7] in toluene to produce **3a** in high yield (84%) in short time. The Pd-catalyzed decarboxylative protonation of **3a** was carried out under the influence of Et_3N/HCOOH in CH_3CN to produce **4a** in high yield (90%) in short time (1 h).[8] The reaction of **3a** in aqueous CH_3CN[5] produced **4a** in low yield (67%) together with some intractable side products. The plausible mechanism for the reaction is depicted in Scheme 1: the sequential (i) oxidative addition of *O*-allyl bond of **3a** to Pd(0) to form the π-allylpalladium carboxylate (**I**), (ii) loss of CO_2 to form two canonical *C*-π-allylpalladium (**II**) and *O*-π-allylpalladium (**III**) intermediates, (iii) formation of palladium formate (**IV**) with liberation of propene, and (iv) liberation of CO_2 and Pd(0) to produce product **4a**.

Encouraged by the successful results, we prepared allyl esters **3a–k** by the reaction of four cycloalkenones **1a–d** and five allyl arylacetates **2a–e,** which have a suitable electron-accommodating moiety. Most of the starting materials were prepared by the catalytic action of TBD,[7] however, the reaction of allyl pyridylacetate (**2d**) was not efficient with TBD thus TBAF (*n*-tetrabutylammonium fluoride, THF solution)[9] was used as the catalyst (entries 4 and 9).

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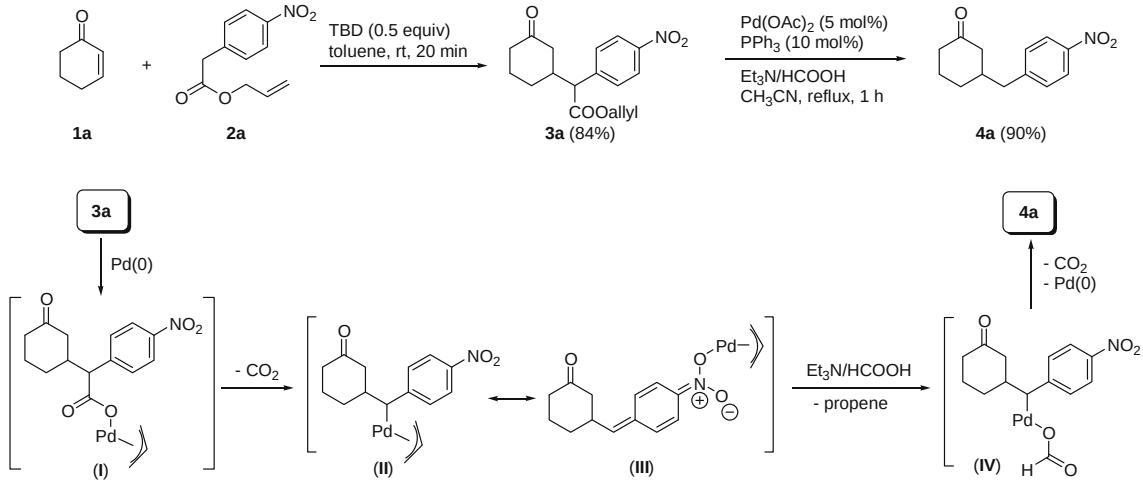


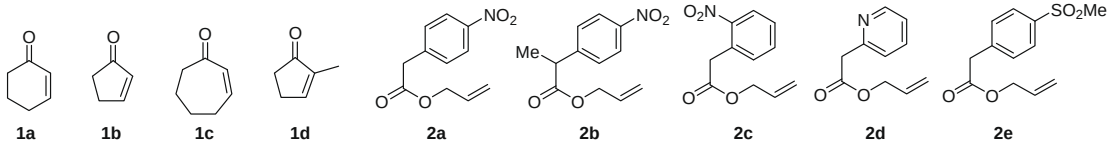
Scheme 1.

As summarized in Table 1, the yields of starting materials **3a–k** were moderate to good (58–89%). Most of the starting materials were isolated as a 1:1 *syn/anti* mixture except **3b** (2:1 mixture). The starting material **3k**, prepared from **1d** and **2a**, has three stereocenters and showed the formation of four stereoisomers. Two isomers of cis-form were observed in trace amounts (<5%, 1:1 mixture) while the two isomers of trans-form were observed in large amounts (>95%, 1:1 mixture) in its ^{1}H NMR spectrum, as reported in a similar case.[10] With these substrates **3a–k**, we synthesized our desired products **4a–k** in high yields (75–95%) under the conditions of $Pd(OAc)_2/PPh_3/Et_3N/HCOOH$ in refluxing CH_3CN in short time. It is interesting to note that the reaction of **3e** in CH_3CN showed almost no reaction presumably due to the weak electron accommodating capability of $-SO_2Me$ group than the nitro group in other cases. However, we could obtain **4e** in 75% yield when we used DMF as a solvent for long time (6 h), very fortunately. The results are summarized in Table 1.

As shown in Scheme 2, we examined the Pd-mediated decarboxylative allylation reaction with **3a** and obtained **5** in 63% isolated yield. The reaction was carried out in non-polar solvent such as toluene with relatively larger amounts of PPh_3 (Pd/PPh_3 = 0.125) as deeply studied by Tsuji and co-workers.[4,11] In the reaction, decarboxylative protonation product **4a** (23%) was also isolated. Decarboxylative allylation of **3b** produced compound **6** in 83% yield similarly under the same conditions together with **4b** (8% yield). When we used small amounts of PPh_3 (Pd/PPh_3 = 2.5) in the reaction of **3b**, we obtained compound **7** in 53% isolated yield via the Pd-catalyzed decarboxylation–elimination mechanism.[11,12]

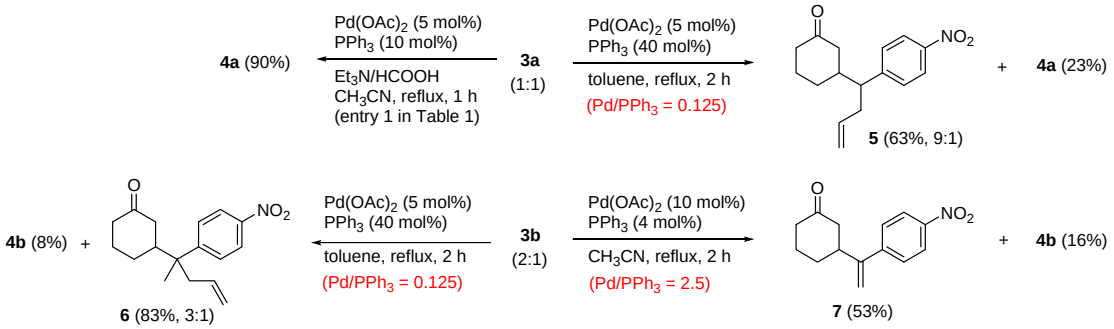
It is interesting to note that the stereoisomeric ratio was changed after the reaction in some examples (**4b** from **3b** in entry 2 in Table 1; **5** from **3a** and **6** from **3b** in Scheme 2). The results could be a strong evidence for the involvement of the intermediate (**III**) in the reaction mechanism, as exemplified for the conversion of **3b** to **4b** in Scheme 3. The configuration of chiral center in (**II**) could be epimerized via the canonical structure (**III**). In this manner **3b** (2:1 mixture) was converted into **4b** (1:1 mixture) although we did not determine their *syn/anti* stereochemistry.

Table 1
Synthesis of β-aralkyl cycloalkanones **4**

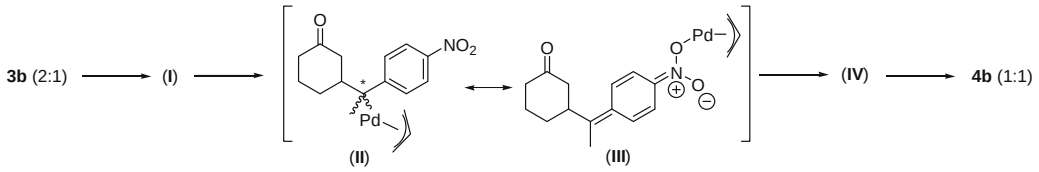


Entry	Substrates	Conditions	**3**[a] (%)	Conditions[b] (h)	**4** (%)
1	**1a** + **2a**	TBD (0.5 equiv), toluene, rt, 20 min	**3a** (84, 1:1)	1	**4a** (90)
2	**1a** + **2b**	TBD (0.5 equiv), toluene, rt, 20 min	**3b** (63, 2:1)	1	**4b** (86, 1:1)[a]
3	**1a** + **2c**	TBD (0.5 equiv), toluene, rt, 60 min	**3c** (65, 1:1)	1	**4c** (86)
4	**1a** + **2d**	TBAF (0.5 equiv), THF, rt, 20 min	**3d** (89, 1:1)	1	**4d** (90)
5	**1a** + **2e**	TBD (0.5 equiv), toluene, rt, 20 min	**3e** (76, 1:1)	6[c]	**4e** (75)
6	**1b** + **2a**	TBD (0.5 equiv), toluene, rt, 20 min	**3f** (83, 1:1)	1	**4f** (92)
7	**1b** + **2b**	TBD (0.8 equiv), toluene, rt, 20 min	**3g** (62, 1:1)	1	**4g** (84, 1:1)[a]
8	**1b** + **2c**	TBD (0.5 equiv), toluene, rt, 20 min	**3h** (68, 1:1)	3	**4h** (92)
9	**1b** + **2d**	TBAF (0.5 equiv), THF, rt, 20 min	**3i** (82, 1:1)	1	**4i** (95)
10	**1c** + **2a**	TBD (0.8 equiv), toluene, rt, 20 min	**3j** (82, 1:1)	1	**4j** (90)
11	**1d** + **2a**	TBD (0.5 equiv), toluene, rt, 20 min	**3k** (58, 1:1)[d]	1	**4k** (90)[e]

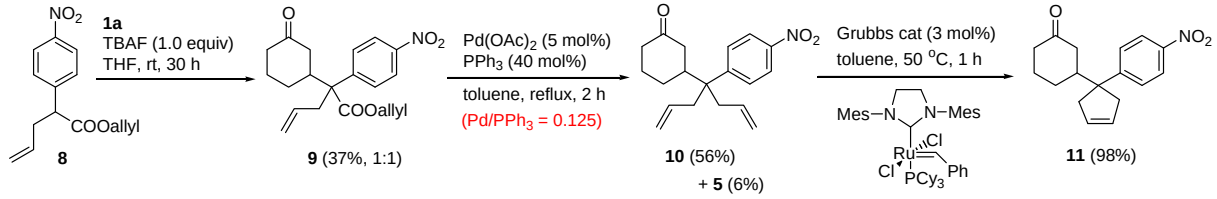
[a] Isolated yield and the *syn*/*anti* ratio was determined by ^{1}H NMR and is arbitrary.
[b] Conditions: $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), Et_3N (1.3 equiv), HCOOH (1.1 equiv), CH_3CN, reflux.
[c] DMF was used as solvent and the reaction was carried out at 80 °C.
[d] Two diastereomers (1:1) of trans form were the major and two diastereomers of cis form were mixed together (1:1), 5%.
[e] Single compound of trans form.



Scheme 2.



Scheme 3.



Scheme 4.

As a next trial, we examined the synthesis of spiro compound **11** via the RCM (ring-closing metathesis) reaction of **10** which was prepared by the Pd-mediated decarboxylative allylation of **9** (Scheme 4). Required starting material **9** was prepared by the Michael addition of **8** to **1a** in THF under the influence of TBAF (rt, 30 h) although the yield was low. The Pd-catalyzed decarboxylative allylation was carried out similarly (high loading of PPh_3), and compound **10** was isolated in 56% yield. Next RCM reaction of **10** was carried out with 3 mol % of second generation Grubbs catalyst (toluene, 50 °C, 1 h) to afford **11** in 98% yield.

In summary, we disclosed an efficient aralkylation method at the β-position of cycloalkenones via a sequential conjugate addition of allyl arylacetate and the following Pd-catalyzed decarboxylative protonation strategy. In addition, we demonstrated some interesting applications of this protocol including the synthesis of vinyl compound and spiro compound.

Acknowledgments

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8. *Typical experimental procedure for the synthesis of* **3a** *and* **4a**: A mixture of **1a** (96 mg, 1.0 mmol), **2a** (287 mg, 1.3 mmol), and TBD (70 mg, 0.5 mmol) in toluene (3 mL) was stirred at room temperature for 20 min. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc/CH_2Cl_2, 3:1:1) compound **3a** was obtained as a pale yellow solid, 266 mg (84% yield) as a *syn/anti* (1:1) mixture. A mixture of compound **3a** (160 mg, 0.5 mmol), Et_3N (66 mg, 0.65 mmol), HCOOH (25 mg, 0.55 mmol), $Pd(OAc)_2$ (6 mg, 5 mol %), and PPh_3 (13 mg, 10 mol %) in acetonitrile (2 mL) was heated

to reflux for 1 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 1:1) compound **4a** was obtained as colorless oil, 105 mg (90% yield). Other compounds were synthesized similarly and the selected spectroscopic data of **3a**, **4a**, **4k**, **5**, **7**, and **11** are as follows.

Compound **3a**: 84% yield (1:1 *syn*/*anti* mixture); pale yellow solid, mp 75–77 °C; IR (KBr) 1732, 1713, 1522, 1348, 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.17–1.30 (m, 1H), 1.47–2.64 (m, 8H), 3.57 (d, J = 10.2 Hz, 0.5H), 4.51–4.67 (m, 2H), 5.20–5.29 (m, 2H), 5.78–5.92 (m, 1H), 7.50 (d, J = 8.7 Hz, 2H 0.5), 7.54 (d, J = 8.7 Hz, 2H 0.5), 8.20 (d, J = 8.7 Hz, 2H 0.5), 8.21 (d, J = 8.7 Hz, 2H 0.5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2, 24.4, 28.4, 29.7, 40.9, 41.0, 41.7, 41.8, 45.0, 46.0, 57.4, 57.5, 65.9, 66.0, 119.0, 119.1, 123.8, 123.9, 129.3, 129.4, 131.2, 131.3, 143.4, 143.9, 147.5, 147.6, 171.0, 171.3, 209.2, 209.4; ESIMS m/z 318 (M^++1). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.55; H, 6.34; N, 4.17.

Compound **4a**: 90% yield; colorless oil; IR (film) 1712, 1604, 1517, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35–1.48 (m, 1H), 1.57–1.72 (m, 1H), 1.84–1.90 (m, 1H), 2.01–2.42 (m, 6H), 2.71 (dd, J = 13.5 Hz and 6.6 Hz, 1H), 2.78 (dd, J = 13.2 Hz and 6.6 Hz, 1H), 7.30 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.8, 30.8, 40.4, 41.2, 42.6, 47.5, 123.6, 129.8, 146.6, 147.2, 210.6; ESIMS m/z 234 (M^++1). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 67.08; H, 6.54; N, 6.31.

Compound **4k**: 90% yield; pale yellow solid, mp 52–54 °C; IR (KBr) 1740, 1517, 1347 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (d, J = 7.2 Hz, 3H), 1.40–2.50 (m, 6H), 2.70 (dd, J = 13.5 Hz and 8.7 Hz, 1H), 3.14 (dd, J = 13.5 Hz and 4.5 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 8.18 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.6, 26.9, 37.0, 40.4, 46.1, 49.9, 123.7, 129.7, 146.6, 147.6, 219.5; ESIMS m/z 234 (M^++1). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.77; H, 6.65; N, 5.81.

Compound **5**: 63% yield (major isomer in 9:1 mixture); pale yellow oil; IR (film) 1712, 1518, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13–1.69 (m, 3H), 1.83–2.46 (m, 6H), 2.54–2.80 (m, 3H), 4.89–4.98 (m, 2H), 5.43–5.57 (m, 1H) 7.28 (d, J = 8.4 Hz, 2H), 8.18 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.9, 28.7, 36.7, 41.2, 43.2, 46.4, 51.2, 117.3, 123.6, 129.3, 135.2, 146.7, 150.2, 210.6; ESIMS m/z 274 (M^++1). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.05; H, 7.34; N, 4.97.

Compound **7**: 53% yield; white solid, mp 91–93 °C; IR (KBr) 1712, 1596, 1516, 1345 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.51–1.80 (m, 2H), 1.95–2.13 (m, 2H), 2.28–2.58 (m, 4H), 2.97–3.05 (m, 1H), 5.25 (s, 1H), 5.37 (s, 1H), 7.46 (d, J = 9.0 Hz, 2H), 8.20 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.7, 30.3, 41.2, 42.4, 46.7, 115.2, 123.7, 127.5, 147.2, 148.2, 150.2, 210.4; ESIMS m/z 246 (M^++1). Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.82; H, 6.11; N, 5.57.

Compound **11**: 98% yield; colorless oil; IR (film) 1710, 1517, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18–1.72 (m, 3H), 1.91–2.36 (m, 6H), 2.81 (s, 4H), 5.72 (s, 2H), 7.38 (d, J = 9.0 Hz, 2H), 8.17 (d, J = 9.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.0, 26.7, 41.0, 41.7, 42.2, 44.0, 49.4, 53.8, 123.2, 128.4, 129.1, 146.1, 155.9, 211.3; ESIMS m/z 286 (M^++1). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.45; H, 6.89; N, 4.73.

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