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Synthesis of 6-oxacyclopropa[*a*]indene derivatives starting from Baylis–Hillman adducts via Pd-mediated C(sp^3)–H activation

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Abstract

We prepared novel 1-phenyl-1,6a-dihydro-6-oxacyclopropa[*a*]indene-1a-carboxylic acid derivatives starting from the Baylis–Hillman adducts via the palladium-mediated domino carbopalladation involving activation of C(sp^3)–H bond.

Keywords: Baylis–Hillman adducts; 6-Oxacyclopropa[*a*]indene; Activation of C(sp^3)–H bond; Palladium

Recently we reported the synthesis of novel pentacyclic compounds from enamide derivatives of Baylis–Hillman adducts via the consecutive carbopalladation and the final β-elimination processes.[1] In the synthesis, second carbopalladation occurred successively due to the absence of β-hydrogen atom in the intermediate formed by the first carbopalladation.[1] During the studies we imagined that we could synthesize 6-oxacyclopropa[*a*]indene skeleton[2,3] from the reaction of **1a** by the activation of C(sp^3)–H bond of the intermediate (**I**),[4] as depicted in Scheme 1.

From the literature survey we imagined a few possibilities such as (i) formation of eight-membered ring via aryl–aryl coupling,[5] (ii) formation of polycyclic compound (shown in Scheme 1) via 1,4-palladium migration,[6] and (iii) most probably the formation of cyclopropane ring via C(sp^3)–H activation.[4] Although activation of C–H bond of arenes has been studied extensively[5] only a few reports have been reported on C(sp^3)–H bond activation by palladium(0)-catalysis.[4] However, the examples are growing rapidly and we actually found very similar observations of Liron and Knochel during our investigation on the activation of C(sp^3)–H bond.[4b]

Thus, we prepared starting material **1a** from the Baylis–Hillman acetate and 2-bromophenol,[7] and examined the reaction of **1a** under a few typical conditions. As summarized in Table 1, we obtained compounds **2a** and **3a** in moderate yields under the conditions comprising $Pd(OAc)_2$/TBAB/K_2CO_3/DMF (entries 1 and 2). In all cases we observed variable amounts of compound **4a**[8] (maximum 23% in entry 7). Best results were obtained when we subjected **1a** under the conditions of entry 2 at higher temperature (110 °C) in short time (40 min). We obtained two diastereomers **2a** and **3a** in 55% and 22% yields, respectively, under the optimized conditions.

The structures of compounds **2a** and **3a** were assigned by their ^{1}H NMR, ^{13}C NMR, IR, and mass data and by comparison with the spectroscopic data of reported compounds having similar structure.[2,3,9] In ^{1}H NMR spectrum of **2a**, two protons at 1- and 6a-positions appeared at 2.43 and 5.54 ppm with coupling constant of 3.3 Hz. The same protons of compound **3a** appeared at 3.25 and 5.31 ppm with coupling constant $J = 6.0$ Hz. The stereochemistry of **2a** and **3a** was confirmed by NOE experiments (Fig. 1). The plausible reaction mechanism is depicted in Scheme 1, which involved the key intermediate (**I**) and the four-membered palladacycle intermediate (**II**). Highly encouraged by the successful results and the importance of 1-phenyl-1,6a-dihydro-6-oxacyclopropa[*a*]indene-1a-carboxylic

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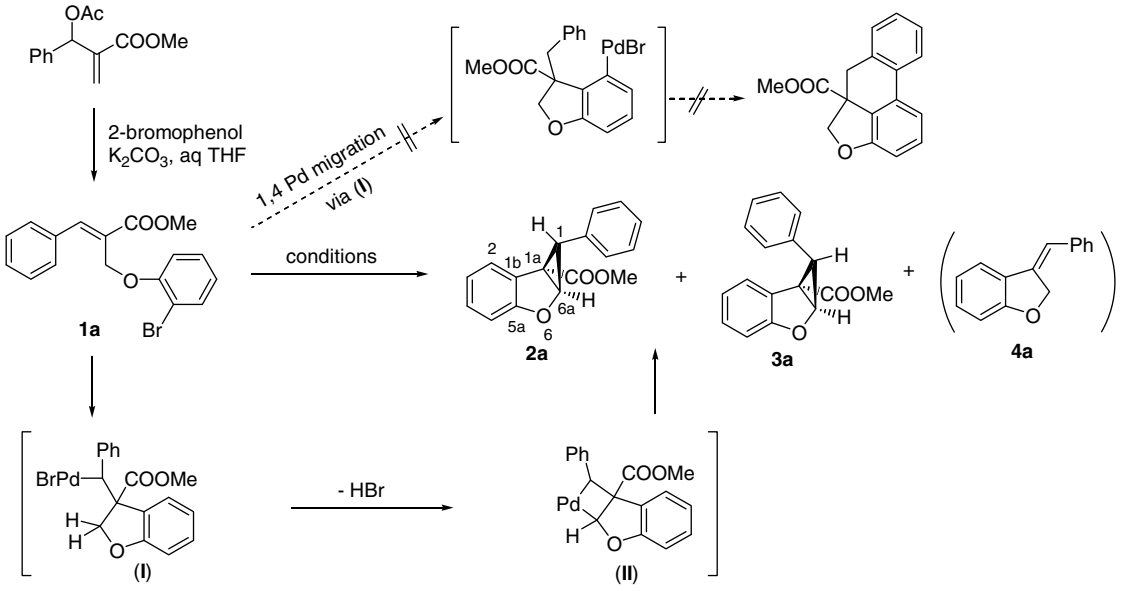


Scheme 1.

Table 1
Optimization of reaction conditions with compound **1a**

Entry	Conditions	Time	**2a** + **3a**[a] (%)	**4a**[a] (%)
1	$Pd(OAc)_2$ (10 mol %), K_2CO_3 (2.0 equiv), TBAB (1.0 equiv), DMF, 80 °C	8 h	55	<5
2	$Pd(OAc)_2$ (10 mol %), K_2CO_3 (2.0 equiv), TBAB (1.0 equiv), DMF, 110 °C	40 min	77	<5
3	$Pd(OAc)_2$ (10 mol %), K_2CO_3 (2.0 equiv), TBAB (1.0 equiv), CH_3CN, reflux	20 h	44	13
4	$Pd(OAc)_2$ (10 mol %), K_2CO_3 (2.0 equiv), PPh_3 (1.0 equiv), DMF, 110 °C	30 min	28	7
5	$Pd(OAc)_2$ (10 mol %), Et_3N (2.0 equiv), TBAB (1.0 equiv), DMF, 80 °C	15 h	<5	11
6	$Pd(OAc)_2$ (10 mol %), Cs_2CO_3 (2.0 equiv), TBAB (1.0 equiv), DMF, 110 °C	30 min	21	<5
7	$Pd(OAc)_2$ (10 mol %), Na_2CO_3 (2.0 equiv), TBAB (1.0 equiv), DMF, 110 °C	3 h	<5	23
8	$Pd(OAc)_2$ (10 mol %), $KHCO_3$ (2.0 equiv), TBAB (1.0 equiv), DMF, 110 °C	1 h	8	7

[a] Isolated yield.

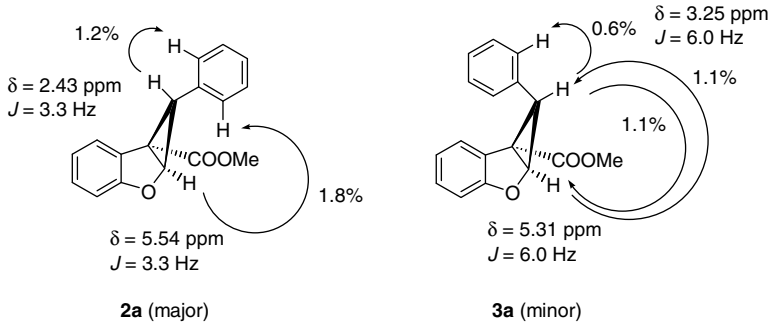
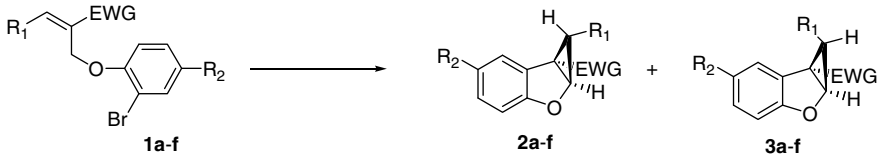


Fig. 1. NOE results of compound **2a** and **3a**.

acid derivatives,[2,3] we examined the generality and the results are summarized in Table 2.[9]

Compounds **2a**–**e** were isolated as the major products (40–57%) and **3a**–**e** as the minor (14–23%). However, the ratio was inverted for substrate **1f** with much lower combined yields of **2f** and **3f** (entry 6). The reason is not clear at this stage. In order to check the possibility for the synthesis of the corresponding nitrogen analog, compound **6** was prepared from 2-bromoaniline by successive tosylation and the reaction with Baylis–Hillman acetate (Scheme 2). The reaction of **6** under the same conditions produced compounds **7** (19%) and **8** (21%). We did not observe the formation of expected cyclopropane derivatives in appreciable amounts. The formation of compound **7** must be the result of reductive Heck type reaction caused by the solvent DMF,[10] and the formation of compound **8** can be regarded similarly as the formation of compound **4a** in Scheme 1.[8,11]

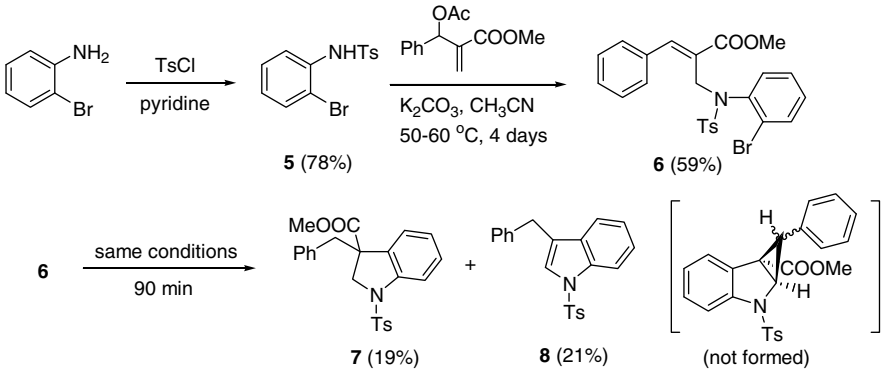
Table 2
Synthesis of tricyclic compounds **2** and **3**[a]



a: R_1 = Ph, R_2 = H, EWG = COOMe
b: R_1 = Ph, R_2 = H, EWG = COOEt
c: R_1 = Ph, R_2 = Me, EWG = COOMe
d: R_1 = 4-MeC_6H_4, R_2 = H, EWG = COOMe
e: R_1 = 4-MeC_6H_4, R_2 = Me, EWG = COOMe
f: R_1 = 2-naphthyl, R_2 = H, EWG = COOMe

Entry	Substrate	Products (%)	
1	**1a**	**2a** (55)	**3a** (22)
2	**1b**	**2b** (52)	**3b** (14)[b]
3	**1c**	**2c** (57)	**3c** (23)
4	**1d**	**2d** (40)	**3d** (23)
5	**1e**	**2e** (40)	**3e** (20)
6	**1f**	**2f** (13)	**3f** (26)

[a] Conditions: $Pd(OAc)_2$ (10 mol %), K_2CO_3 (2.0 equiv), *n*-Bu_4NBr (1.0 equiv), DMF, 100–110 °C, 40 min (80 min for entries 3 and 6).
[b] Trace amounts of inseparable impurity were contaminated.



Scheme 2.

In summary, we prepared novel 1-phenyl-1,6a-dihydro-6-oxacyclopropa[*a*]indene-1a-carboxylic acid derivatives starting from the modified Baylis–Hillman adducts via the palladium-mediated domino carbopalladation involving activation of C(sp^3)–H bond.

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8. Sasaki, K.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 411–414. The mechanism for the formation of compound **4a** could be a β-carbon elimination from intermediate **I**, followed by decarboxylation. The formation of compound **8** could also be regarded similarly. Further studies on the mechanism are currently underway.
9. *Typical procedure for the synthesis of* **2a** *and* **3a**: A stirred mixture of **1a** (174 mg, 0.5 mmol), $Pd(OAc)_2$ (11 mg, 10 mol %), K_2CO_3 (138 mg, 1.0 mmol), *n*-Bu_4NBr (161 mg, 0.5 mmol) in DMF (2.0 mL) was heated to 110 °C for 40 min under nitrogen atmosphere. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 25:1) we obtained **2a** (74 mg, 55%) and **3a** (30 mg, 22%) as colorless oils. Other compounds were synthesized similarly and the spectroscopic data of selected compounds **2a**, **3a**, **2e**, **3e**, and **7** are as follows.

Compound **2a**: 55%; colorless oil; IR (film) 1734, 1475, 1460, 1228, 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.43 (d, $J = 3.3$ Hz, 1H), 3.50 (s, 3H), 5.54 (d, $J = 3.3$ Hz, 1H), 6.91 (d, $J = 8.1$ Hz, 1H), 7.00 (t, $J = 7.5$ Hz, 1H), 7.20 (t, $J = 8.1$ Hz, 1H), 7.24–7.35 (m, 5H), 7.83 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.44, 41.64, 51.75, 69.35, 110.78, 121.07, 125.03, 127.39, 128.00, 128.16, 128.32, 128.80, 133.10, 159.30, 167.48; ESIMS *m*/*z* 267 (M^++1). Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.44; H, 5.23.

Compound **3a**: 22%; colorless oil; IR (film) 1726, 1477, 1460, 1236, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.25 (d, $J = 6.0$ Hz, 1H), 3.87 (s, 3H), 5.31 (d, $J = 6.0$ Hz, 1H), 6.54 (d, $J = 8.1$ Hz, 1H), 6.83 (t, $J = 7.5$ Hz, 1H), 6.94 (t, $J = 7.8$ Hz, 1H), 7.03–7.28 (m, 5H), 7.62 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.95, 39.44, 52.49, 70.83, 109.68, 120.96, 126.50, 126.90, 127.78, 127.87, 128.03, 128.49, 130.61, 159.52, 170.64; ESIMS *m*/*z* 267 (M^++1). Anal. Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.79; H, 5.21.

Compound **2e**: 40%; yellow oil; IR (film) 1730, 1483, 1236, 1147 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.32 (s, 3H), 2.36 (s, 3H), 2.38 (d, $J = 3.3$ Hz, 1H), 3.52 (s, 3H), 5.48 (d, $J = 3.3$ Hz, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 6.98 (d, $J = 8.1$ Hz, 1H), 7.07–7.18 (m, 4H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.89, 21.12, 36.48, 41.59, 51.73, 69.54, 110.26, 125.42, 128.01, 128.49, 128.62, 129.01, 130.08, 130.45, 137.00, 157.24, 167.64; ESIMS *m*/*z* 295 (M^++1). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.73; H, 5.98.

Compound **3e**: 20%; yellow oil; IR (film) 1728, 1483, 1277, 1240, 1209 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.17 (s, 3H), 2.25 (s, 3H), 3.17 (d, $J = 6.0$ Hz, 1H), 3.85 (s, 3H), 5.26 (d, $J = 6.0$ Hz, 1H), 6.44 (d, $J = 8.4$ Hz, 1H), 6.74 (d, $J = 8.1$ Hz, 1H), 6.85–7.10 (m, 4H), 7.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.92, 21.07, 28.93, 39.49, 52.41. 71.20, 109.13, 123.36, 126.82, 127.79, 128.35, 128.53, 130.16, 130.28, 136.38, 157.76, 170.84; ESIMS *m*/*z* 295 (M^++1). Anal. Calcd for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.36; H, 6.41.

Compound **7**: 19%; colorless oil; IR (film) 1734, 1477, 1358, 1167, 1092 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H), 2.87 (d, $J = 13.5$ Hz, 1H), 3.30 (d, $J = 13.5$ Hz, 1H), 3.62 (s, 3H), 3.98 (d, $J = 11.4$ Hz, 1H), 4.23 (d, $J = 11.4$ Hz, 1H), 6.92–6.95 (m, 2H), 7.02 (t, $J = 7.5$ Hz, 1H), 7.21–7.30 (m, 6H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.63 (d, $J = 7.8$ Hz, 1H), 7.68 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.52, 44.36, 52.51, 55.54, 55.65, 114.25, 123.45, 125.41, 127.18, 127.38, 128.47, 129.40, 129.61, 129.66, 132.19, 133.96, 135.68, 141.26, 144.17, 172.29; ESIMS *m*/*z* 422 (M^++1). Anal. Calcd for $C_{24}H_{23}NO_4S$: C, 68.39; H, 5.50; N, 3.32. Found: C, 68.27; H, 5.38; N, 3.26.

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