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# Development of palladium(II)-catalyzed oxidative cyclization of olefinic keto and/or lactone esters

Ayaka Hibi, Masahiro Toyota *

*Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531, Japan*

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ABSTRACT

A highly efficient palladium-catalyzed oxidative cyclization of olefinic keto and/or lactone esters, which features a catalytic cyclization employing one atmosphere of oxygen as a reoxidizing agent, is developed.

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Recently, we developed a palladium-catalyzed cycloalkenylation, which has been successfully adapted to the stereoselective syntheses of polycyclic natural products (Scheme 1).[1,2]

In our efforts to expand the utility of this palladium-catalyzed cycloalkenylation, we undertook a concise synthesis of 6-oxatricyclo[6.3.0.0$^{1,5}$]undecane, which is the BCD ring system of ginkgolide C (Fig. 1).

Although ketene silyl acetal **1**[3] gave rise to desired tricyclic compound **2**[4] under palladium-catalyzed cycloalkenylation conditions, the yield was less than 11% probably due to the instability of ketene silyl acetal **1** (Scheme 2).[3]

To solve this problem, we recently developed a novel method to construct the aforementioned 6-oxatricyclo[6.3.0.0$^{1,5}$]undecane. Thus, desired compound **4** can be synthesized in good yield by palladium-promoted oxidative cyclization of olefinic lactone ester **3** (Scheme 3).[4] A related intermolecular reaction is reported,[5] however, this reaction can give the desired cyclization products under neutral reaction conditions.

However, to expand the utility of the cyclization, herein we report the preliminary results of our efforts to develop a catalytic version of this reaction in which olefinic keto and/or lactone esters are effectively converted into the corresponding cyclization products.

Requisite substrates were prepared as depicted in Scheme 4. Namely, lactone **5**[6] was treated with methyl chloroformate in the presence of lithium hexamethyldisilazide to afford lactone ester **6**[7] in 93% yield.

Table 1 summarizes the various reaction conditions on the conversion of olefinic lactone ester **6** to *exo*-olefin **7**.[7] Initially, **6** was treated with a stoichiometric amount of $Pd(OAc)_2$ in DMSO as a solvent, which gave desired product **7** in 28% isolated yield (entry 1). To convert this reaction into a catalytic process, numerous reac-


**Scheme 1.**

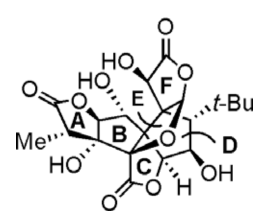
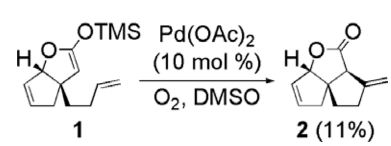
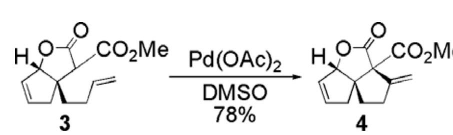



**Figure 1.**




**Scheme 2.**




**Scheme 3.**

* Corresponding author. Tel./fax: +81 72 254 9164.
*E-mail address:* toyota@c.s.osakafu-u.ac.jp (M. Toyota).

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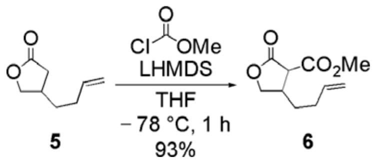
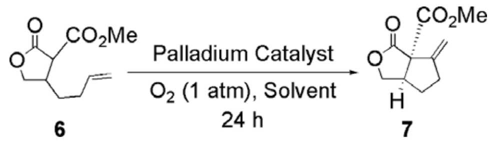


**Scheme 4.**

tion parameters, including the palladium catalyst, the amount of catalyst, temperature, and solvent, were evaluated (entries 2–14). Because DMSO was a suitable solvent for the palladium-catalyzed cycloalkenylation,[1a] the cyclization reaction was attempted using **6** in the presence of a catalytic amount of the palladium catalyst under one atmosphere of oxygen in DMSO (entries 2–11). Although employing $Pd(acac)_2$, $PdCl_2(MeCN)_2$, or $PdCl_2$ did not yield the

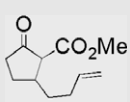
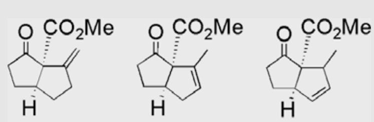
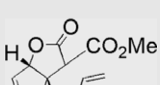
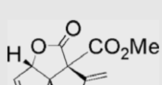
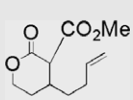
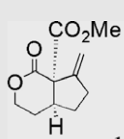
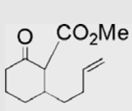
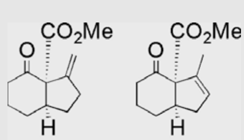
**Table 1**
Palladium-catalyzed cyclization of lactone ester **6**



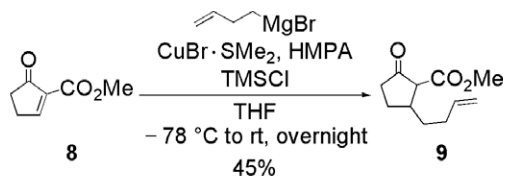
| Entry | Solvent | Catalyst | $Pd^{2+}$ (mol %) | Temperature (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1[a] | DMSO | $Pd(OAc)_2$ | 100 | rt | 28 |
| 2 | DMSO | $Pd(acac)_2$ | 10 | 45 | — |
| 3 | DMSO | $PdCl_2(MeCN)_2$ | 10 | 45 | — |
| 4 | DMSO | $PdCl_2$ | 10 | 45 | — |
| 5 | DMSO | $Pd(OCOCF_3)$ | 10 | 45 | 3 |
| 6 | DMSO | $Pd(OAc)_2$ | 10 | rt | 42 (56) |
| 7 | DMSO | $Pd(OAc)_2$ | 10 | 45 | 78 (81) |
| 8 | DMSO | $Pd(OAc)_2$ | 10 | 60 | 74 |
| 9 | DMSO | $Pd(OAc)_2$ | 5 | rt | 54 (84) |
| 10 | DMSO | $Pd(OAc)_2$ | 5 | 45 | 57 (79) |
| 11 | DMSO | $Pd(OAc)_2$ | 5 | 60 | 47 (70) |
| 12 | DMF | $Pd(OAc)_2$ | 10 | 45 | 33 (47) |
| 13 | THF | $Pd(OAc)_2$ | 10 | 45 | 15 (26) |
| 14 | MeCN | $Pd(OAc)_2$ | 10 | 45 | 23 (37) |

[a] Reaction was carried out under one atmosphere of argon.
[b] Values in parentheses refer to yield based upon recovered starting materials. rt = room temperature.

**Table 2**
Conversion of keto and/or lactone esters to five-membered ring

| Entry | Substrate | Temperature (°C) | Product[b] | Yield[a] (%) | | | |
|---|---|---|---|---|---|---|---|
| | | | | **10** | **11** | **12** | Cyclized products |
| 1 |  **9** | rt |  **10** **11** **12** | 43 (75) | 2 | 0 | 45 |
| 2 | | 45 | | 58 | 23 | 0 | 81 |
| 3 | | 60 | | 41 | 34 | 5 | 80 |
| 4 |  **3** | 45 |  **4** | | | 76 | |
| 5 | | 60 | | | | 84 | |
| 6 |  **13** | 45 |  **14** | | | 69 (82) | |
| 7 | | 60 | | | | 31 (50) | |
| | | | | **16** | **17** | | Cyclized products |
| 8 |  **15** | 45 |  **16** **17** | 38 (76) | 31 | | 69 |
| 9 | | 60 | | 17 (37) | 20 | | 37 |

[a] Values in parentheses refer to yield based upon recovered starting materials.
[b] Relative stereochemistry was established using NOE experiments employing cyclized products (Fig. 2).



**Scheme 5.**

cyclized product, 3% of **7** was isolated in the presence of 10 mol % of $Pd(OCOCF_3)_2$ (entry 5). On the other hand, when the reaction was conducted using $Pd(OAc)_2$ as the catalyst, the cyclization yield rose to 42% (entry 6). Moreover, heating the reaction mixture accelerated the cyclization, providing **7** in 78% yield (entry 7). Further increasing the temperature had a negligible effect on the yield (entry 8). When the reaction was carried out employing 5 mol % of $Pd(OAc)_2$, the yield of the cyclized product decreased (entries 9–11). Other solvents, such as DMF, THF, and MeCN, were unsuitable for this catalytic cyclization (entries 12–14). It was found that this catalytic cyclization proceeds smoothly under palladium-catalyzed cycloalkenylation conditions.

With the optimal reaction conditions in hand, we examined the effectiveness of this new methodology on the conversion of a variety of β-keto and/or lactone esters to the corresponding cyclized products. Table 2 summarizes the results.

Because the bicyclo[3.3.0]octane ring unit is found in important biologically active compounds,[8,2c] the catalytic reaction was initially adapted to synthesize that ring system. Compound **9**[7] was prepared from 2-carbomethoxycyclo-pent-2-enone **8**[9] via a 1,4-conjugate addition of the homoallyl group (Scheme 5).[10]

When the reaction was performed at room temperature with β-keto ester **9**, *exo*-olefin **10**[11] was isolated in 43% yield along with 2% of *endo*-isomer **11**[12] (entry 1). Increasing the reaction temperature to 45 °C increased the yield of **10**, but **11** was formed in 23% yield (entry 2). Further increasing the reaction temperature did not affect the yield of **10**, but isomer **12**[7] was generated in 5% yield (entry 3). When this catalytic cyclization was then subjected to bicyclic lactone ester **3** at 45 °C, desired cyclized product **4** was synthesized in 76% yield (entry 4). Heating of reaction mixture at 60 °C was the best condition, as **4** was obtained in 84% yield (entry 5). Substrate **13**[7], which was prepared in the same manner described in Scheme 4, was also suitable for this cyclization process, and led to **14**[7] as the sole product in 69% yield (entry 6). Cyclization at 60 °C decreased the yield of cyclized product **14** to 31% (entry 7). Only *exo*-isomer **14** was generated, when the reaction was conducted using **13** as the substrate. On the other hand, treating keto ester **15**[13] with $Pd(OAc)_2$ at 45 °C provided two cyclization products, *exo*-olefin **16**[7] (38%) and *endo*-isomer **17**[7] (31%). However, increasing the reaction temperature to 60 °C decreased the yield of cyclization products **16** and **17**. Through these experiments, substrates **13** and **15** turned out to be temperature sensitive.

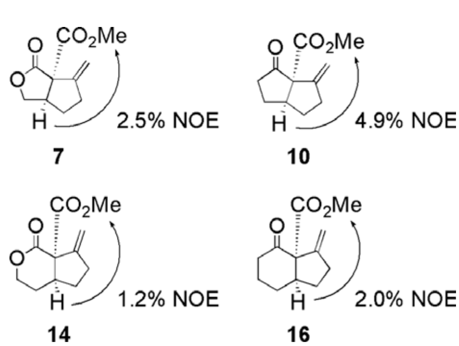



**Figure 2.**

Analyses of the $^1H$–$^1H$ COSY experiments of **7**, **10**, **14**, and **16** enabled all the protons of each compound to be assigned. Additionally, the relative stereochemistries were established on the basis of NOE correlations, as shown in Figure 2.

The carbomethoxy group at the angular position of tricyclic cyclization product **4** could be easily removed under the Krapcho reaction conditions without isomerization of the olefin.[4] Although Liu and co-workers have reported an efficient palladium-catalyzed methylene-cyclopentane annulation process,[14] the present protocol should be more effective due to its adaptability not only for various types of olefinic keto esters, but also for lactone esters.

## Acknowledgments

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7. *Data for new compounds*: Compound **6**: IR(KBr) 1782, 1739 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.56–1.74 (m, 2H), 2.05–2.11 (m, 1H), 3.00 (ddt, *J* = 16.4, 8.0, 8.0 Hz, 2H), 3.26 (d, *J* = 9.2 Hz, 1H), 3.81 (s, 3H), 3.92 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.52 (dd, *J* = 8.8, 8.0 Hz, 1H), 5.01–5.06 (m, 2H), 5.75 (ddt, *J* = 17.2, 10.4, 6.7 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 31.2, 31.7, 39.7, 52.5, 53.2, 72.1, 116.2, 136.8, 168.2, 172.0; LRMS *m/z* 198 ($M^+$), 143; HRMS calcd for $C_{10}H_{14}O_4$ ($M^+$) 198.0892, found 198.0887. Compound **7**: IR(KBr) 1778, 1744 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.63 (dddd, *J* = 12.8, 7.8, 7.7, 7.6 Hz, 1H), 2.15 (ddd, *J* = 13.0, 7.4, 7.0 Hz, 1H), 2.52–2.57 (m, 2H), 3.42 (dddd, *J* = 7.2, 7.2, 7.2, 4.0 Hz, 1H), 3.79 (s, 3H), 4.03 (dd, *J* = 9.2, 4.0 Hz, 1H), 4.46 (dd, *J* = 9.4, 7.4 Hz, 1H), 5.32 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.57 (dd, *J* = 2.2, 2.2 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 29.8, 33.5, 47.2, 53.5, 63.2, 70.5, 113.3, 145.8, 168.9, 173.0; LRMS *m/z* 196 ($M^+$), 152,120, 93, 77; HRMS calcd for $C_{10}H_{12}O_4$ ($M^+$) 196.0736, found 196.0732. Compound **9**: IR(KBr) 1758, 1730, 1641 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.41–1.56 (m, 2H), 1.63–1.72 (m, 1H), 2.01–2.45 (m, 5H), 2.53–2.64 (m, 1H), 2.84 (d, *J* = 10.8 Hz, 1H), 3.74 (s, 3H), 4.97 (ddd, *J* = 10.6, 1.2, 1.0 Hz, 1H), 5.02 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.79 (ddt, *J* = 17.2, 10.4, 6.7 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 27.3, 31.4, 34.2, 38.6, 41.0, 52.6, 61.9, 115.2, 137.9, 170.0, 211.8; LRMS *m/z* 196 ($M^+$), 109; HRMS calcd for $C_{11}H_{16}O_3$ ($M^+$) 196.1099, found 196.1095. Compound **12**: IR(KBr) 1749, 1732 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 7.2 Hz, 3H), 1.87–1.95 (m, 1H), 2.09–2.23 (m, 2H), 2.31–2.40 (m, 1H), 3.53–3.61 (m, 1H), 3.71 (s, 3H), 3.76–3.79 (m, 1H), 5.48 (ddd, *J* = 5.6, 2.4, 2.4 Hz, 1H), 5.58 (ddd, *J* = 5.6, 2.0, 2.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.3, 25.1, 38.5, 46.7, 52.7, 54.6, 67.1, 130.0, 136.2, 172.0, 213.8; LRMS *m/z* 194 ($M^+$), 84; HRMS calcd for $C_{11}H_{14}O_3$ ($M^+$) 194.0943, found 194.0939. Compound **13**: IR(KBr) 1747 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.36–1.45 (m, 1H), 1.50–1.64 (m, 2H), 2.01–2.20 (m, 3H), 2.41 (dddd, *J* = 14.2, 9.4, 9.4, 5.0 Hz, 1H), 3.26 (d, *J* = 9.6 Hz, 1H), 3.75 (s, 0.2H), 3.80 (s, 2.8H), 4.33 (ddd, *J* = 11.5, 10.0, 3.6 Hz, 1H), 4.41 (ddd, *J* = 11.6, 4.8, 4.8 Hz, 1H), 4.98–5.06 (m, 2H), 5.75 (ddt, *J* = 17.2, 10.4, 6.6 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 27.3, 30.5, 34.1, 34.5, 53.0, 54.3, 68.4, 115.7, 137.3, 167.5, 169.5; LRMS *m/z* 212 ($M^+$), 157; HRMS calcd for $C_{11}H_{16}O_4$ ($M^+$) 212.1049, found 212.1036. Compound **14**: IR(KBr) 1730 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.53 (dddd, *J* = 12.8, 7.8, 7.8, 6.4 Hz, 1H), 1.68 (dddd, *J* = 14.3, 10.2, 8.6, 4.0 Hz, 1H), 1.94–2.08 (m, 2H), 2.50–2.56 (m, 2H), 3.01 (ddd, *J* = 13.3, 8.7, 6.8 Hz, 1H), 3.77 (s, 3H), 4.24 (ddd, *J* = 11.4, 10.2, 3.0 Hz, 1H), 4.36 (ddd, *J* = 11.5, 4.8, 4.4 Hz, 1H), 5.32 (dd, *J* = 2.0, 2.0 Hz, 1H), 5.40 (dd, *J* = 2.0, 2.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 27.2, 30.3, 31.4, 42.9, 53.4, 63.7, 67.7, 113.6, 146.7, 168.3, 170.9; LRMS *m/z* 210 ($M^+$), 107; HRMS calcd for $C_{11}H_{14}O_4$ ($M^+$) 210.0892, found 210.0874. Compound **16**: IR(KBr) 1739, 1717 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 1.49–1.59 (m, 2H), 1.64–1.73 (m, 1H), 1.81–1.98 (m, 3H), 2.33–2.45 (m, 2H), 2.47–3.01 (m, 2H), 3.03 (ddd, *J* = 12.0, 8.4, 6.4 Hz, 1H), 3.75 (s, 3H), 4.96 (dd, *J* = 2.4, 2.4 Hz, 1H), 5.23 (dd, *J* = 2.2, 2.2 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 24.0, 26.2, 28.4, 30.0, 39.5, 47.9, 52.9, 72.1, 112.2, 148.1, 171.4, 206.2; LRMS *m/z* 208 ($M^+$), 176; HRMS calcd for $C_{12}H_{16}O_3$ ($M^+$) 208.1099,

found 208.1089. Compound **17**: IR(KBr) 1739, 1712 $cm^{-1}$; $^{1}H$ NMR (400 MHz, $CDCl_3$) $\delta$ 1.55–1.62 (m, 1H), 1.78 (dd, *J* = 3.6, 2.0 Hz, 3H), 2.06 (dddd, *J* = 16.4, 8.8, 4.8, 2.4 Hz, 1H), 2.24–2.31 (m, 2H), 2.41 (dddd, *J* = 16.8, 10.0, 4.4, 2.4 Hz, 1H), 2.45–2.53 (m, 1H), 3.13 (ddd, *J* = 11.6, 7.2, 6.0 Hz, 1H), 3.74 (s, 3H), 3.13 (ddd, *J* = 11.6, 7.2, 6.0 Hz, 1H), 3.74 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 15.5, 22.5, 27.8, 36.4, 40.3, 46.9, 52.6, 73.1, 129.6, 139.0, 172.7, 209.1; LRMS *m/z* 208 ($M^+$); HRMS calcd for $C_{12}H_{16}O_3$ ($M^+$) 208.1099, found 208.1089.
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