

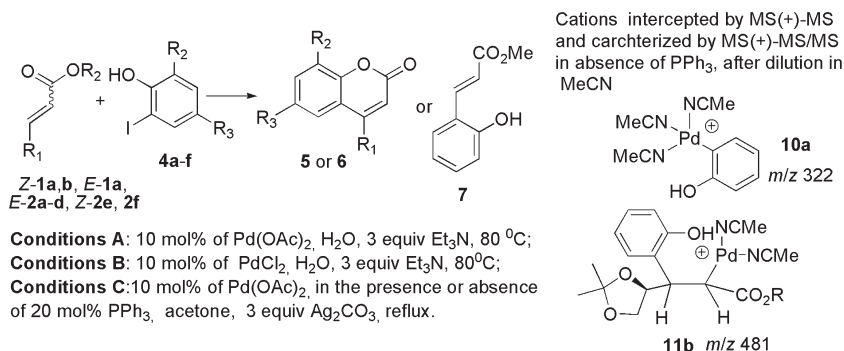
# Palladium-Catalyzed Tandem Heck-Lactonization from *o*-Iodophenols and Enoates: Synthesis of Coumarins and the Study of the Mechanism by Electrospray Ionization Mass Spectrometry

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Received June 5, 2010



The tandem Heck-lactonization reaction between enoates **Z-1a,b**, **E-1a**, **E-2a-d**, **Z-2e**, **2f**, and *o*-iodophenols (**4a–f**) was studied in the presence of substoichiometric amounts of Pd(OAc)<sub>2</sub> or PdCl<sub>2</sub>, under experimental conditions favoring the cationic mechanism (conditions A, B, and C), leading to coumarins **5a–f** and **6a–e**. Moderate to excellent yields were obtained under aqueous conditions (conditions A and B). Using electrospray ionization for transferring ions directly from solution to the gas phase, and mass spectrometry for structural assignments, key cationic palladium intermediates have been successfully intercepted and structurally characterized for the first time for this type of reaction.

## Introduction

The arylation of olefins, discovered by Heck and Mizoroki, is one of the most important palladium-catalyzed carbon–carbon coupling reactions.<sup>1</sup> Aryl- and heteroaryl-palladium

intermediates can be generated in situ from the corresponding aryl and heteroaryl iodides, bromides, triflates, diazonium salts, or even chlorides in the presence of Pd reagents, whereas nonconjugated olefins, olefins conjugated with both electron withdrawing groups or electron donating groups, as well as styrenes, can be used as acceptors of aryl-palladium species.<sup>2</sup> Intramolecular Heck reactions are also powerful tools in

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(1) (a) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518–5526. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. (c) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320–2322. (d) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7. (e) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379–2411. (f) Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Eds.; Wiley-VCH: New York, 1998; pp 231–269. (g) Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963.

(2) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771–11835. (c) Knowles, J. P.; Whiting, A. *Org. Biomol. Chem.* **2007**, *5*, 31–44. (d) Negishi, E., Ed.; *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons: New York, 2002. (e) Brase, S.; de Meijere, A. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: New York, 1998; pp 99–166.

organic synthesis.<sup>3</sup> Several functional groups are tolerated in the structure of these intermediates and this feature has facilitated the use of the Heck reaction to synthesize a variety of highly functionalized carbon skeletons.<sup>4</sup> Enantioselective Heck reactions in the presence of chiral ligands leading to products in high enantiomeric excess have also been described.<sup>5</sup>

When aryl palladium intermediates are substituted at the *ortho*-position by hydroxyl or amine groups, they react with olefins by tandem or domino reactions leading to heterocyclics. For example, dihydrobenzofurans are formed in oxa-Heck reactions by oxyarylation of chromenes,<sup>6</sup> dihydronaphthalenes, enol ethers, and other olefins with *o*-iodophenols, whereas dihydrobenzopyrrolidines are obtained by aza-Heck reactions by azaarylation of dihydronaphthalene by *o*-iodoaniline.<sup>7</sup>

Coumarins display many biological activities such as anticoagulant, antioxidant, antiproliferative, and anti-HIV,<sup>8</sup> and can also be used as intermediates in the synthesis of cumestans and benzofurans.<sup>9</sup> Several years ago, Heck et al.<sup>10</sup> failed to prepare coumarins by the reaction between enoates and *o*-iodophenols. However, lactams were successfully prepared from enoates and *o*-iodoaniline under the same conditions.<sup>10</sup> More recently, coumarins were obtained by the tandem Heck-lactonization reaction involving enoates or cinnamates and *o*-halophenols, as reported by

Battistuzzi et al.,<sup>11</sup> Ulgueri et al.,<sup>12</sup> Fernandes et al.,<sup>13</sup> and Giguère et al.<sup>14</sup> To gain further knowledge into the scope of the tandem Heck-lactonization under the conditions previously studied by us,<sup>13</sup> we report here results from the reaction of enoates **Z-1a,b**, **E-1a**, **E-2a–d**, **Z-2e**, and **2f** with *o*-iodophenols (**4a–f**)<sup>15</sup> as Figure 1 summarizes. From electrospray ionization mass spectrometry (ESI-MS) monitoring, a mechanistic rationalization is proposed for the tandem Heck-lactonization reactions accomplished under conditions favoring the cationic mechanism (use of Ag<sub>2</sub>CO<sub>3</sub> as base or water as solvent). An intramolecular Heck reaction from enoates **3** leading to coumarins or aurones is also evaluated (Figure 1).

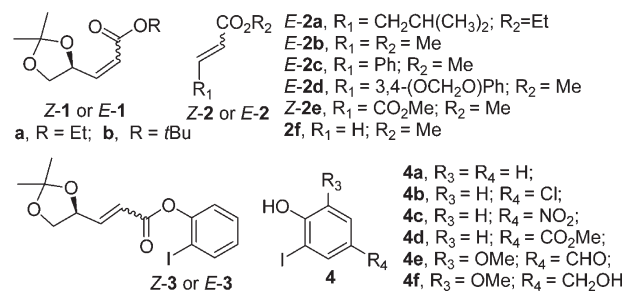
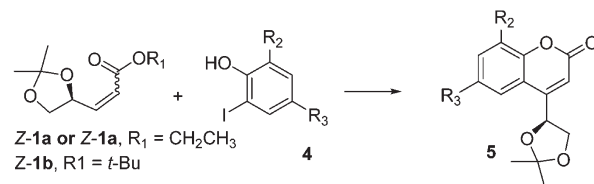


FIGURE 1. Enoates (**1–3**) and *o*-iodophenols (**4a–f**) used in this work.

## Results

In recent studies by our research group, the tandem Heck-lactonization reaction between enoates **E-1**, **Z-1**, **E-2b** and *o*-iodophenols **4a–d** leading to the corresponding coumarins (Scheme 1) was investigated under several conditions and three procedures were selected as the more efficient: condition A, condition B, and condition C (Table 1).<sup>16</sup> In this paper we extend the scope of this reaction including in our study new conjugated esters (**Z-1b**, **E-2a**, **E-2c**, **E-2d**, and **E-2e**) and *o*-iodophenols (**4e,f**). These new results are presented in Table 1 along with those previously obtained, which were included for comparative purposes.<sup>13</sup>

### SCHEME 1. Reaction of **Z-1a** and **Z-1b** with *o*-Iodophenols **4a–f**



For **4** and **5**:

**a**, **R**<sub>2</sub> = H; **R**<sub>3</sub> = H; **b**, **R**<sub>2</sub> = H; **R**<sub>3</sub> = Cl; **c**, **R**<sub>2</sub> = H; **R**<sub>3</sub> = NO<sub>2</sub>; **d**, **R**<sub>2</sub> = H; **R**<sub>3</sub> = CO<sub>2</sub>Me; **e**, **R**<sub>2</sub> = OMe; **R**<sub>3</sub> = CHO; **f**, **R**<sub>2</sub> = OMe; **R**<sub>3</sub> = CH<sub>2</sub>OH

(13) Fernandes, T. A.; Carvalho, R. C. C.; Gonçalves, T. M. D.; da Silva, A. J. M.; Costa, P. R. R. *Tetrahedron Lett.* **2008**, *49*, 3322–3325.

(14) Giguère, D.; Patnam, R.; Juárez-Ruiz, J. M.; Neault, M.; Roy, R. *Tetrahedron Lett.* **2009**, *50*, 4254–4257.

(15) Enoates **E-1** and **Z-1**, and *o*-iodophenols **4a–f** were prepared as previously described: (a) Costa, J. S.; Dias, A. G.; Anholetto, A. L.; Monteiro, M. D.; Patrocínio, V. L.; Costa, P. R. R. *J. Org. Chem.* **1997**, *62*, 4002–4006. (b) da Frota, L. C. R. M.; Canavez, R. C. P.; Gomes, S. L. S.; Costa, P. R. R.; da Silva, A. J. M. *J. Braz. Chem. Soc.* **2009**, *20*, 1916–1920.

(16) (a) Botella, L.; Nájera, C. *J. Org. Chem.* **2005**, *70*, 4360–4369. (b) Buarque, C. D.; Pinto, V. D.; Vaz, B. G.; Eberlin, M. N.; da Silva, A. J. M.; Costa, P. R. R. *J. Organomet. Chem.* **2010**, *695*, 2062–2067.

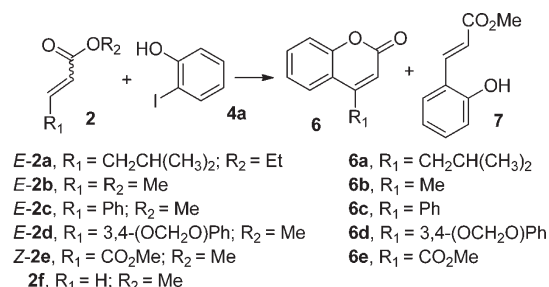
- (3) (a) Rizzi, E.; Dallavalle, S.; Merlini, L.; Beretta, G. L.; Pratesi, G.; Zunino, F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4313–4316. (b) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499. (c) Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447–455. (d) McDermott, M. C.; Stephenson, G. R.; Hughes, D. L.; Walkington, A. J. *Org. Lett.* **2006**, *8*, 2917–2920. (e) Link, J. T.; Overman, L. E. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Eds.; Wiley-VCH: New York, 1998; pp 231–269; (f) Overman, L. E. *Pure Appl. Chem.* **1994**, *66*, 1423–1430. (g) Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (4) (a) Geng, X.; Miller, M. L.; Lin, S.; Ojima, I. *Org. Lett.* **2003**, *5*, 3733–3736. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680. (5) (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516. (c) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7393. (d) Tietze, L.; Raschke, T. *Synlett* **1995**, 597–598. (e) Ozawa, F.; Kobatake, Y.; Hayashi, T. *Tetrahedron Lett.* **1993**, *34*, 2505–2508. (f) Loiseleur, O.; Hayashi, M.; Schmees, N.; Pfaltz, A. *Synthesis* **1997**, 1338–1345. (g) Honzawa, S.; Mizutani, T.; Shibasaki, M. *Tetrahedron Lett.* **1999**, *40*, 311–314. (6) (a) Larock, R. C. U.S. Pat. Appl. No. 767,794, **1998**. (b) Kiss, L.; Kurtán, T.; Antus, S.; Brunner, H. *Arkivoc* **2003**, 69–76. (c) Sant'Anna, S. S.; Evangelista, E. A.; Alves, R. B.; Raslan, D. S. *Chem. Nat. Compd.* **2005**, *41*, 385–387. (d) Kerti, G.; Kurtán, T.; Antus, S. *Arkivoc* **2009**, 103–110. (e) Horino, H.; Inoue, N. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3210. (f) Horino, H.; Arai, M.; Inoue, N. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1683–1686. (7) Emrich, D. E.; Larock, R. C. *J. Organomet. Chem.* **2004**, *689*, 3756–3766. (8) (a) Wardrop, D.; Keeling, D. *Br. J. Haematol.* **2008**, *141*, 757–763. (b) Narváez-Mastache, J. M.; Novillo, F.; Delgado, G. *Phytochemistry* **2008**, *69*, 451–456. (c) Musa, M. A.; Cooperwood, J. S.; Khan, M. O. F. *Curr. Med. Chem.* **2008**, *15*, 2664–2679. (d) Chiang, C. C.; Mouscadet, J. F.; Tsai, H. J.; Liu, C. T.; Hsu, L. Y. *Chem. Pharm. Bull.* **2007**, *55*, 1740–1743. (e) Kostova, I.; Raleva, S.; Genova, P.; Argirova, R. *Bioinorg. Chem. Appl.* **2006**, 68274. (9) (a) Chang, C. F.; Yang, L. Y.; Chang, S. W.; Fang, Y. T.; Lee, Y. J. *Tetrahedron* **2008**, *64*, 3661–3666. (b) Lee, Y. R.; Suk, J. Y.; Kim, B. S. *Org. Lett.* **2000**, *2*, 1387–1389. (c) Jin, Y. L.; Kim, S.; Kim, Y. S.; Kim, S. A.; Kim, H. S. *Tetrahedron Lett.* **2008**, *49*, 6835–6837. (d) Yamashita, M.; Inaba, T.; Nagahama, M.; Shimizu, T.; Kosaka, S.; Kawasaki, I.; Ohta, S. *Org. Biomol. Chem.* **2005**, *3*, 2296–2304. (e) Yamashita, M.; Yadav, N. D.; Sawaki, T.; Takao, I.; Kawasaki, I.; Sugimoto, Y.; Miyatake, A.; Murai, K.; Takahara, A.; Kurume, A.; Ohta, S. *J. Org. Chem.* **2007**, *72*, 5697–5703. (10) Cortese, N. A.; Ziegler, C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2952–2958. (11) Battistuzzi, G.; Cacchi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308–312. (12) Ulgheri, F.; Marchetti, M.; Piccolo, O. *J. Org. Chem.* **2007**, *72*, 6056–6059.

**TABLE 1.** New Conditions and Yields for Reactions Shown in Scheme 1

entry	4	olefin	product	condition <sup>a</sup>	yield (%)
1	4a	Z-1a	5a	A	73 <sup>b</sup>
2	4a	Z-1a	5a	B	84 <sup>b</sup>
3	4a	Z-1a	5a	C	68
4	4a	Z-1b	5a	A	56
5	4a	Z-1b	5a	C	42
6	4a	E-1a	5a	B	7
7	4b	Z-1a	5b	A	78
8	4b	Z-1a	5b	B	90
10	4b	Z-1a	5b	C	23
10	4c	Z-1a	5c	A	59
11	4c	Z-1a	5c	B	51
12	4c	Z-1a	5c	C	68
13	4d	Z-1a	5d	A	50
14	4d	Z-1a	5d	C	52
15	4e	Z-1a	5e	A	31
16	4e	Z-1a	5e	C	traces
17	4f	Z-1a	5f	A	53
18	4f	Z-1a	5f	C	

<sup>a</sup>Condition A: 10 mol % of Pd(OAc)<sub>2</sub>, H<sub>2</sub>O, Et<sub>3</sub>N, 80 °C, 40 h. Condition B: 10 mol % of PdCl<sub>2</sub>, H<sub>2</sub>O, Et<sub>3</sub>N, 80 °C, 40 h. Condition C: 10 mol % of Pd(OAc)<sub>2</sub>, acetone, 3 equiv of Ag<sub>2</sub>CO<sub>3</sub>, 20 mol % of PPh<sub>3</sub>, 70 °C, 40 h. <sup>b</sup>1 mol % was used in these cases.

Enoate Z-1a reacted with 4a leading to coumarin 5a in good yields under conditions A and B, even in the presence of 1 mol % of the catalyst (entries 1 and 2). A lower yield was obtained under conditions C (entry 3) and poor yields were observed when the amount of catalyst was reduced to 5 mol % (data not shown). Enoate Z-1b was also allowed to react with 4a under condition B, leading to coumarin 5a (entry 4), but the yield was reduced to 56% (entry 4) probably due to the presence of the bulky *t*Bu ester group, which could hamper the lactonization step. A poor yield was obtained in condition C (entry 5). In contrast, only 7% of 5a was formed in the reaction of E-1 with 4a in condition B (entry 6). Enoate Z-1a also reacted with *p*-chloro-*o*-iodophenol (4b) leading to coumarin 5b in good yields under conditions A and B (entries 7 and 8), but in this case the yield dropped to 23% under condition C (entry 9). For the reactions of Z-1 with 4c,d, moderate to good yields were obtained in conditions A, B, and C (entries 11–14). In the case of *o*-iodophenols 4e,f, coumarins 5e and 5f were obtained in moderated yields, only in condition A (entries 15–18).

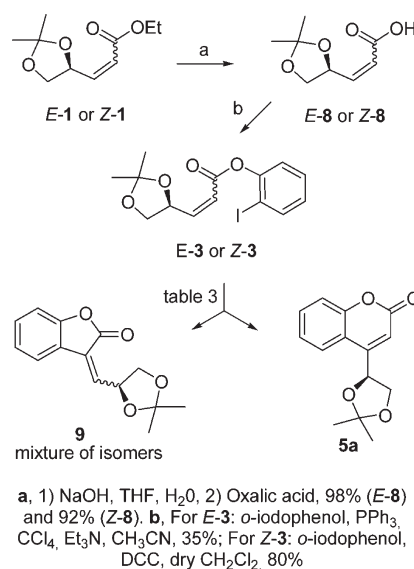
**SCHEME 2.** Reactions of *o*-Iodophenol (4a) with Olefins E-2a–d, Z-2e, and 2f

To further investigate the scope of this interesting reaction, enoates E-2a–d, Z-2e, and 2f were allowed to react with 4a (Scheme 2, Table 2). In contrast with enoate E-1a, E-2a led to coumarin 6a in reasonable yield in condition B (entry 1), but only 12% was obtained in condition C (entry 2). Coumarin 6b could be obtained in reasonable yield in conditions A and C (entries 3 and 4). Cinnamates E-2c did not react with 4a in

**TABLE 2.** Conditions and Yields for Scheme 2

entry	4	olefin	product	condition <sup>a</sup>	yield (%)
1	4a	E-2a	6a	B	55
2	4a	E-2a	6a	C	12
3	4a	E-2b	6b	A	44
4	4a	E-2b	6b	C	63
5	4a	E-2c	6c	B	66
6	4a	E-2c	6c	C	
7	4a	E-2d	6d	B	68
8	4a	Z-2e	6e	B	18
9	4a	2f	7	C	17
10	4a	2f	7	D	100

<sup>a</sup>Condition A: 10 mol % of Pd(OAc)<sub>2</sub>, H<sub>2</sub>O, 3 equiv of Et<sub>3</sub>N, 80 °C, 40 h. Condition B: 10 mol % of PdCl<sub>2</sub>, H<sub>2</sub>O, 3 equiv of Et<sub>3</sub>N, 80 °C, 40 h. Condition C: 10 mol % of Pd(OAc)<sub>2</sub>, 20 mol % of PPh<sub>3</sub>, acetone, 3 equiv of Ag<sub>2</sub>CO<sub>3</sub>, 70 °C, 40 h. Condition D: 10 mol % of Pd(OAc)<sub>2</sub>, MeCN, 3 equiv of Et<sub>3</sub>N, 70 °C, 40 h.

**SCHEME 3.** Synthesis of E-3 and Z-3 and Their Intramolecular Heck Reactions

condition C (entry 6) but 66% yield of arylcoumarin 6c was obtained under condition B (entry 5). Arylcoumarin 6d could also be obtained by reaction of Z-1a with 4a (entry 7). Despite the Z-geometry, however, Z-2e furnished 6e in reduced yield (entry 8). Methylacrylate (2f), in contrast, afforded the cinnamate 7 in low yield under condition C while under classical Heck conditions 7 can be obtained in quantitative yields (entries 9 and 10).<sup>13</sup>

To confirm that Z enoates are more reactive in oxaarylation reactions than E enoates, a competitive reaction was carried out with a 2:1 mixture of E-2a and Z-2a. Via NMR monitoring (not shown), we were able to observe that Z-2a was consumed much faster than E-2a.

When the reactions between Z-1a and 4a–f were interrupted before completion under conditions A, B, or C, unreacted Z-1a was isolated without loss of its optical purity, as shown by its [α] value.

Finally, we investigated the intramolecular Heck reaction using enoates E-3 and Z-3 as substrates, which were prepared respectively from E-1a and Z-1a (Scheme 3). The ester groups of E-1a and Z-1a were hydrolyzed in basic medium leading to E-8 and Z-8,<sup>17</sup> respectively, and these acids were

(17) Fernandes, T. A.; Master Thesis, NPPN-UFRJ, 2008.

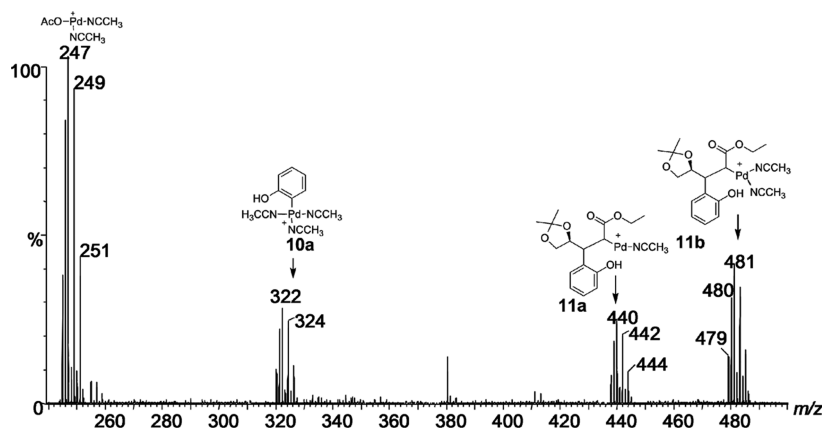


FIGURE 2. ESI(+)-MS of the reaction solution of **Z-1** with **4a** (condition B, in the absence of  $\text{PPh}_3$ :acetone,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$ ).

TABLE 3. Conditions and Yields for Scheme 3

entry	olefin	condition <sup>a</sup>	product	yield (%)
1	<i>E</i> - <b>3</b>	C	<b>8</b>	45
2	<i>E</i> - <b>3</b>	B	<b>5a</b>	traces
3	<i>Z</i> - <b>3</b>	C	<b>8</b>	32
4	<i>Z</i> - <b>3</b>	B	<b>5a</b>	29

<sup>a</sup>Condition C: 10 mol % of  $\text{Pd}(\text{OAc})_2$ , 20 mol % of  $\text{PPh}_3$ , acetone, 3 equiv of  $\text{Ag}_2\text{CO}_3$ , 70 °C, 40 h. Condition B: 10 mol % of  $\text{PdCl}_2$ ,  $\text{H}_2\text{O}$ , 3 equiv of  $\text{Et}_3\text{N}$ , 80 °C, 40 h.

allowed to react with *o*-iodophenol (**4a**) in the presence of a mixture of  $\text{PPh}_3$ ,  $\text{CCl}_4$ , and  $\text{Et}_3\text{N}$  (*E*-**7**)<sup>18</sup> or DCC (*Z*-**7**),<sup>19</sup> leading to the respective *E*-**3** and *Z*-**3**.<sup>20</sup>

In intramolecular Heck reactions, preference for the *exo*-cyclization is usual even when the electronic effects favor the *endo*-approach, mainly forming five-membered-ring compounds.<sup>21</sup> For example, Rizzi et al.<sup>3a</sup> recently reported that the ester obtained from *o*-iodophenol and *p*-methoxy cinnamate cyclized to the corresponding aurone in the presence of  $\text{Pd}(\text{OAc})_2$  whereas Ashimori et al.<sup>22</sup> showed that the amide formed from  $\alpha$ -methyl-*Z*-crotonate and *o*-iodoaniline furnished an indole derivative in the presence of  $\text{Pd}_2(\text{dba})_3$ . In our study, as expected, *E*-**3** led to aurone **9** (mixture of isomers, 1/1) in acetone in the presence of  $\text{Pd}(\text{OAc})_2$  and  $\text{Ag}_2\text{CO}_3$  (condition B), whereas in the presence of  $\text{PdCl}_2$  and  $\text{Et}_3\text{N}$  in  $\text{H}_2\text{O}$  (condition D) only traces of coumarin **5a** were found (Scheme 3, Table 3, entries 1 and 2). From *Z*-**3**, both aurone **9** and coumarin **5a** were obtained in moderate yield, depending on the reaction conditions employed (entries 3 and 4). It has been described that aqueous media must exert influence on the regioselectivity of intramolecular reactions.<sup>2a</sup>

## Discussion

For Heck-lactonization, enoate *Z*-**1a** proved to be more reactive than its *E*-isomer, leading to coumarin **5a** in better yields under all reaction conditions studied. The *Z*-double bond is less sterically hindered, which may allow a better

accommodation of the incoming arylpalladium species in the transition state of the cyclopalladation step. Among *E*-enoates, however, the reactivity depended on the  $\beta$ -substituent. In *E*-**2a** and *E*-**2b**,  $\text{C}_\beta$  is substituted by a  $\text{CH}_2\text{CH}(\text{Me})_2$  and a  $\text{CH}_3$  group, respectively, and their double bonds are therefore less sterically hindered than that in *E*-**1a**, for which the carbon attached at the double bond is disubstituted. This reduced hindering could explain why *E*-**2a** and *E*-**2b** are more reactive than *E*-**1a**. In cinnamates *E*-**2c** and *E*-**2d**, the planar aryl groups do not afford an important steric hindrance at the double bond carbons and, additionally, these electron donating groups may facilitate the reaction through electronic effects. However, the electron poor olefin *Z*-**2e** led to **6e** in poor yield.

Since better yields of coumarins were obtained under conditions favoring the cationic mechanism (conditions A, B, and C), these reactions were monitored by ESI-MS, which has been shown to provide continuous snapshots of the changing composition of reaction solutions of major organic reactions.<sup>23</sup>

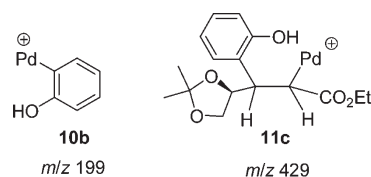


FIGURE 3. Proposed cationic palladium intermediates formed in the reaction of *Z*-**1a** with **4a** in acetone, under condition C, in the absence of  $\text{PPh}_3$ .

**Heck-Lactonization-Pd(II) Intermediates.** The reaction of *Z*-**1** with **4a** (condition C, in the absence of  $\text{PPh}_3$ :acetone,  $\text{Pd}(\text{OAc})_2$ ,  $\text{Ag}_2\text{CO}_3$ ) was monitored via direct infusion ESI-MS and its tandem version (ESI-MS/MS) in the positive ion mode. Samples were diluted in MeCN before recording the spectra.

(18) Hashimoto, S.; Furukawa, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2227–2228.

(19) Lemieux, R. P.; Schuster, G. B. *J. Org. Chem.* **1993**, *58*, 100–110.

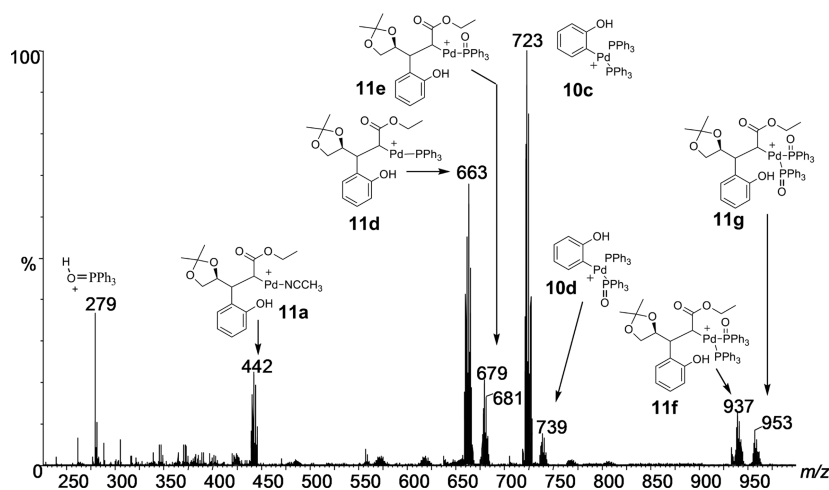
(20) Several conditions were tried before to find an optimal synthetic procedure to synthesize esters *E*-**9** and *Z*-**9**.

(21) Baldwin, J. E. *J. Chem. Soc., Chem Commun.* **1976**, 734–736.

(22) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488–6499.

(23) (a) Amarante, G. W.; Milagre, H. M. S.; Vaz, B. G.; Ferreira, B. R. V.; Eberlin, M. N.; Coelho, F. *J. Org. Chem.* **2009**, *74*, 3031–3037. (b) Stefani, H. A.; Pena, J. M.; Gueogjian, K.; Petragnani, N.; Vaz, B. G.; Eberlin, M. N. *Tetrahedron Lett.* **2009**, *50*, 5589–5595. (c) Orth, E. S.; Brandao, T. A. S.; Milagre, H. M. S.; Eberlin, M. N.; Nome, F. *J. Am. Chem. Soc.* **2008**, *130*, 2436–2437. (d) Raminelli, C.; Precht, M. H. G.; Santos, L. S.; Eberlin, M. N.; Comasseto, J. V. *Organometallics* **2004**, *23*, 3990–3996. (e) Santos, L. S.; Rosso, G. B.; Pilli, R. A.; Eberlin, M. N. *J. Org. Chem.* **2007**, *72*, 5809–5812. (f) Santos, L. S. *Eur. J. Org. Chem.* **2008**, 235–253. (g) de Vries, J. G. *Dalton Trans.* **2006**, 421–429. (h) Svennebring, A.; Sjöberg, P. J. R.; Larhed, M.; Nilsson, P. *Tetrahedron* **2008**, *64*, 1808–1812.





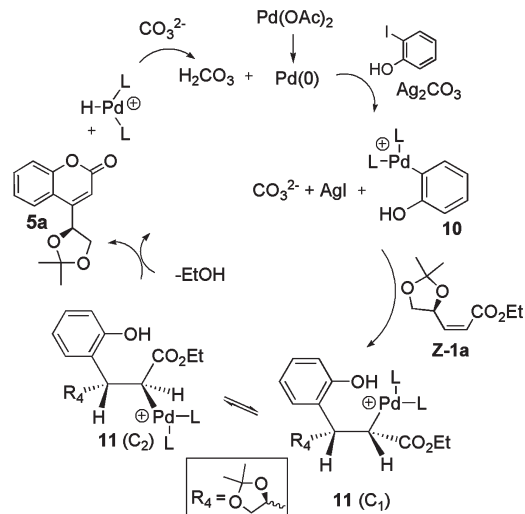
**FIGURE 4.** Cationic palladium intermediates in the reaction of **Z-1** with **4a** (condition C in the presence of  $\text{PPh}_3$ ; acetone,  $\text{Pd}(\text{OAc})_2$ ,  $\text{Ag}_2\text{CO}_3$ , intercepted as MeCN adducts).

Interestingly, ESI(+)-MS was able to provide the first mechanistic detail for the reaction of **Z-1a** with **4a** (Figure 2) by intercepting a series of key cationic  $\text{Pd}(\text{II})^+$  intermediates: (a) **10a** of  $m/z$  322, which results from oxidative addition of  $\text{Pd}[0]$  to **4a** and triple-complexation with MeCN, and (b) **11a** of  $m/z$  440 and **11b** of  $m/z$  481 originated from carbopalladation of **Z-1a** and mono- and dicomplexation with MeCN. The proposed structures of **10a** and **11b** are corroborated by their characteristic Pd multi-isotopic patterns and by ESI-MS/MS (see the Supporting Information). Cation **11b**, as expected, dissociates by two consecutive losses of MeCN to form **11a** of  $m/z$  440 and **11c** of  $m/z$  399 or by the loss of the reactant olefin to form  $\text{H-Pd}(\text{MeCN})_2^+$  of  $m/z$  189, which in turn loses MeCN to form  $\text{H-Pd}(\text{MeCN})^+$  of  $m/z$  148. (Figure S1, Supporting Information). The intervention of the **10b** and **11c** (Figure 3) in the actual reaction media likely occurs via stabilization by chelating agents (other than MeCN) present in the reaction solution, such as the acetone solvent.

In the reaction carried out in the presence of  $\text{PPh}_3$ , analogous cationic  $\text{Pd}(\text{II})^+$  intermediates now mainly coordinated to  $\text{PPh}_3$  (and  $\text{O}=\text{PPh}_3$ ) were also intercepted (Figure 4). Cation **10c** of  $m/z$  723, also originated from the oxidative addition of  $\text{Pd}(0)$  to **4a**, is analogous to **10a** and corresponds to coordination to two  $\text{PPh}_3$  ligands. Cation **11d** of  $m/z$  663 originates from regioselective carbopalladation of the double bond of **Z-1a** by **10c** (or an analogous species), strongly suggesting that the lactonization step occurs after the carbopalladation step. Note that **11** (see Scheme 4) was intercepted in Figure 4 in a variety of coordinated forms: **11a**, **11d**, **11e**, **11f**, and **11g**. The  $\text{O}=\text{PPh}_3$  ligand likely originated from  $\text{PPh}_3$  oxidation by air, which occurs even when these reactions are run under dry argon.<sup>24</sup>

The intervention of cationic palladium intermediates in Heck reaction with  $\text{ArI}$  as substrates has been suggested when halide scavengers such as  $\text{Ag}_2\text{CO}_3$  are used.<sup>2</sup> For the

**SCHEME 4.** Mechanistic View for the Reaction of **4a** with **Z-1a** Based on the ESI(+)-MS/MS Data



Heck–Matsuda reaction, using tellurides<sup>25</sup> or diazonium salts<sup>26</sup> as substrates instead of aryl iodides, and for oxyarylation reactions with *o*-iodophenols,<sup>27</sup> the major cationic palladium species were also detected and characterized by ESI-MS/MS. Therefore, ESI(+)-MS/MS is shown herein to also be able to intercept and characterize major cationic intermediates in Heck-lactonization reactions, further establishing in detail the mechanism of this reaction.

Our next goal was to monitor the tandem Heck-lactonization between **Z-1a** and **4a** in water in the presence of  $\text{PdCl}_2$  and  $\text{Et}_3\text{N}$ . The aim was to verify whether cationic intermediates could also be intercepted and characterized by ESI-MS/MS under these conditions. With use of  $\text{Et}_3\text{N}$ , the major cationic species detected from the aqueous reaction solutions was the protonated base  $\text{Et}_3\text{NH}^+$ . When  $\text{Et}_3\text{N}$

(24) (a) Kong, K. C.; Cheng, C. H. *J. Am. Chem. Soc.* **1991**, *113*, 6313–6315. (b) Herrmann, W. A.; Brossmer, C.; Ofele, K.; Beller, M.; Fischer, H. *J. Mol. Catal.* **1995**, 133–146. (c) Sakamoto, M.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **1995**, 1101–1102. (d) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576–8581. (e) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *J. Am. Chem. Soc.* **1997**, *119*, 12441–12453.

(25) Stefani, H. A.; Pena, J. M.; Guegjian, K.; Petragiani, N.; Vaz, B. G.; Eberlin, M. N. *Tetrahedron Lett.* **2009**, *50*, 5589–5595.

(26) Sabino, A. A.; Machado, A. H. L.; Correia, C. R. D.; Eberlin, M. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 2514–2518.

(27) Buarque, C. D.; Pinho, V. D.; Vaz, B. G.; Eberlin, M. N.; da Silva, A. J. M.; Costa, P. R. R. *J. Organomet. Chem.* **2010**, *695*, 2062–2067.

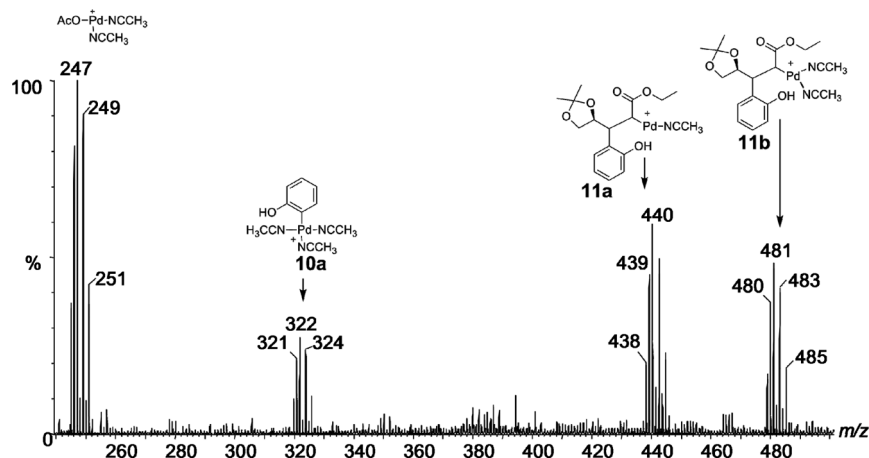
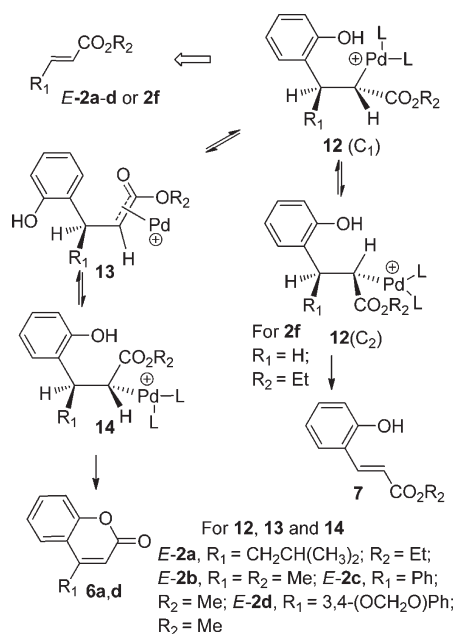


FIGURE 5. ESI(+)-MS of the reaction solution of the reaction of **Z-1** with **4a** in  $\text{H}_2\text{O}$  in the presence of 10 mol % of  $\text{PdCl}_2$  and  $\text{NaOH}$ .

SCHEME 5. The Different Reaction Pathways for the Reaction of **4a** with Either *E-2a–d* or **2f**



was replaced by  $\text{NaOH}$ , however, the same set of cationic intermediates intercepted in reactions with acetone/ $\text{Ag}_2\text{CO}_3$  (Figure 4) could also be intercepted in water, after dilution with  $\text{MeCN}$  (Figure 5). Although these conditions are not useful for preparative purposes (ester hydrolysis is expected) these results strongly suggest the participation of cationic palladium species **10b** and **11c** (Figure 3) as intermediates in the oxyarylation of **Z-1a** by **4a** under conditions A and B.

On the basis of the key information provided by ESI(+)-MS(/MS) monitoring, oxyarylation reactions accomplished in the presence of  $\text{Ag}_2\text{CO}_3$  (conditions C) or with water as solvent (conditions A and B) can be rationalized to proceed via a cationic mechanism, as Scheme 4 proposes for the reaction between **4a** and **Z-1a** in condition C. The reaction proceeds as follows: oxidative insertion of  $\text{Pd}(0)$  to **4a** in the presence of  $\text{Ag}_2\text{CO}_3$  leads to **10**, and regioselective carbopalladation of the double bond in **Z-1a** by **10** leads to **11** (conformer C1, *cis*-addition), which is in equilibrium with

conformer C2. The C2 conformer has the required steric relationships to undergo a *cis*-elimination of  $\text{HPd}^+$  and lactonization, leading to coumarin **5a**. The base present in the reaction medium ( $\text{CO}_3^{2-}$ ) regenerates  $\text{Pd}(0)$  thus restarting the catalytic cycle. A similar rationalization can be proposed for the reactions in water.

On the basis of the mechanism of Scheme 4, we can rationalize the formation of either **6** or **7** from enoates *E-2a–d* and **2f** (Scheme 5). When methyl acrylate **2f** was used in reaction with **4a**, intermediate **12a** (conformer C1,  $\text{R}_4 = \text{H}$ ), formed by *syn*-carbopalladation, is in equilibrium with C2, and after the elimination step leads to cinnamate **7** (Scheme 5). In intermediates **12b,c**, conformer C1,  $\text{R}_4 = \text{Me}$  or *i*Bu, formed from substituted enoates *E-2a–d* is, however, more stable than conformer C2 (steric interactions between  $\text{R}_4$  and  $\text{CO}_2\text{Et}$ ) and this conformer isomerizes to **14** via a palladium enolate **13**, which after the elimination step leads to coumarins **6a,b**. Precedents for epimerization of organopalladium intermediates in which the palladium is attached to the  $\alpha$ -position of aromatic rings and carbonyl groups are known.<sup>28</sup>

## Conclusions

The general scope of the Heck-lactonization involving *E*- and *Z*-enoates was investigated. It was shown that this reaction is sensitive to steric hindrance around the double bond in the enoates. The intervention of cationic palladium intermediates was evidenced by ESI(+)-MS(/MS) for reactions in the presence of  $\text{Ag}_2\text{CO}_3$  or with  $\text{H}_2\text{O}$  as solvent. A series of coumarins disubstituted at the 6- and 4-positions could be obtained in one step from enoates **Z-1a**, *E-2a–d*, and **Z-2e** via a tandem Heck-lactonization reaction under eco-friendly conditions employing water and avoiding the use of silver salts and phosphines.

## Experimental Section

**General Procedures.**  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were acquired at 200, 400, or 500 MHz for proton and 50 or 100 MHz for

(28) (a) Takahashi, T.; Jinbo, Y.; Kitamura, K.; Tsuji, J. *Tetrahedron Lett.* **1984**, 25, 5921–5924. (b) Ludwig, M.; Strömberg, S.; Svessos, M.; Akermark, B. *Organometallics* **1999**, 18, 970–975. (c) Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, 114, 6858–6863. (d) Kuwano, R. *Synthesis* **2009**, 1049–1061.

carbon nuclei in  $\text{CDCl}_3$  or  $\text{CH}_3\text{OD}$ . All reagents were used without purification. All MS experiments were performed on a hybrid quadrupole time-of-flight mass spectrometer (Q-TOF). For typical electrospray ionization (ESI) conditions, the Teflon-sealed microsyringe was put in a pump that delivered the reagent solution into the ESI source at a flow rate of  $10 \mu\text{L min}^{-1}$ . ESI and the mass spectrometer were operated in the positive ion mode. Main conditions were capillary voltage, 3500 eV; cone voltage, 35 eV; source temperature,  $100^\circ\text{C}$ ; and desolvation temperature,  $100^\circ\text{C}$ . The cationic species were subjected to collision-induced dissociation (CID) with argon by using collision energies ranging from 5 to 45 eV.

**General Procedure for the Synthesis of Coumarins.**<sup>29</sup> A mixture of *o*-iodophenols (1 equiv), enoate (3 equiv), palladium salt (1–10 mol %), phosphine ligand (in some cases was not used), and base was heated in the selected solvent for the indicated temperature and time under nitrogen atmosphere. Then, the reaction mixture was partitioned between ethyl acetate and brine and the organic layer was filtered in diatomaceous earth, dried over anhydrous sodium sulfate, and evaporated. The resulting oil was purified by flash chromatography leading to the coumarins in the indicated yield. The products obtained were characterized by  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and mass spectrometry (high resolution).

**(S)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2H-chromen-2-one (5a).** Compound **5a** was obtained as a yellow solid after purification by flash chromatography (EtOAc–hexane 1:9):  $\alpha_{\text{D}} +107$  (*c* 1.0,  $\text{CHCl}_3$ ); mp  $132\text{--}135^\circ\text{C}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.55 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1 H), 7.46–7.23 (m, 3 H), 6.72 (d, *J* = 1.2 Hz, 1 H), 5.39 (dt, *J* = 1.2, 7.0 Hz, 1 H), 4.59 (dd, *J* = 7.2, 8.3 Hz, 1 H), 3.80 (dd, *J* = 6.9, 8.3 Hz, 1 H), 1.57 (s, 3 H), 1.53 (s, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  160.5, 153.5, 153.3, 131.7, 124.2, 123.1, 117.3, 117.0, 111.5, 110.4, 73.0, 69.3, 25.9, 25.1. HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{15}\text{O}_4$  [*M* + *H*] 247.0970, found 247.0965.

**(S)-6-Chloro-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-2H-chromen-2-one (5b).** Compound **5b** was obtained as a white solid after purification by flash chromatography (EtOAc–hexane 1:19):  $\alpha_{\text{D}} +96.9$  (*c* 1.0,  $\text{CHCl}_3$ ); mp  $129\text{--}130^\circ\text{C}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  7.50 (dd, *J* = 2.3, 8.8 Hz, 1 H), 7.38 (d, *J* = 2.3 Hz, 1 H), 7.32 (d, *J* = 8.8 Hz, 1 H), 6.73 (d, *J* = 1.2 Hz, 1 H), 5.31 (dt, *J* = 1.2, 6.9 Hz, 1 H), 4.59 (dd, *J* = 7.2, 8.4 Hz, 1 H), 3.81 (dd, *J* = 6.7, 8.4 Hz, 1 H), 1.57 (s, 3 H), 1.53 (s, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  159.9, 152.3, 152.0, 131.7, 129.7, 122.9, 118.8, 118.3, 112.8, 110.7, 72.9, 69.2, 26.0, 25.1; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{14}\text{ClO}_4$  [*M* + *H*] 281.0581, found 281.0575.

**(S)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-6-nitro-2H-chromen-2-one (5c).** Compound **5c** was obtained as a white solid after purification by flash chromatography (EtOAc–hexane 1:9):  $\alpha_{\text{D}} +109.6$  (*c* 1.0,  $\text{CHCl}_3$ ); mp  $154\text{--}156^\circ\text{C}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  8.50–8.36 (m, 2 H), 7.52 (d, *J* = 9.2 Hz, 1 H), 6.82 (s, 1 H), 5.41 (t, *J* = 6.8 Hz, 1 H), 4.72–4.59 (m, 1 H), 3.93–3.81 (m, 1 H), 1.61 (s, 3 H), 1.56 (s, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  158.8, 157.2, 152.5, 143.7, 126.5, 119.8, 118.5, 117.3, 113.9, 111.1, 73.0, 69.0, 25.9, 24.9; HRMS (ESI) calcd for  $\text{C}_{14}\text{H}_{14}\text{NO}_6$  [*M* + *H*] 292.0821, found 292.0815.

**(S)-Methyl 4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-oxo-2H-chromene-6-carboxylate (5d).** Compound **5d** was obtained as a yellow solid after purification by flash chromatography (EtOAc–hexane 1:9):  $\alpha_{\text{D}} +88.9$  (*c* 1.0,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (dd, *J* = 1.8, 8.8 Hz, 1 H), 8.13 (s, 1 H), 7.42 (d,

*J* = 8.4 Hz, 1 H), 6.76 (s, 1 H), 5.42 (t, *J* = 7.0 Hz, 1 H), 4.75–4.54 (m, 1 H), 3.97 (s, 3 H), 3.92–3.69 (m, 1 H), 1.59 (s, 3 H), 1.55 (s, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  165.4, 159.8, 156.4, 153.2, 132.7, 126.2, 125.4, 117.6, 117.0, 112.4, 110.7, 73.0, 69.3, 52.5, 25.9, 25.2; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{17}\text{O}_6$  [*M* + *H*] 305.1025, found 305.1019.

**(S)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-8-methoxy-2-oxo-2H-chromene-6-carbaldehyde (5e).** Compound **5e** was obtained as a pale solid after purification by flash chromatography (EtOAc–hexane 2:8):  $\alpha_{\text{D}} +73.3$  (*c* 1.0,  $\text{CHCl}_3$ ); mp  $194\text{--}196^\circ\text{C}$ ;  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  9.99 (s, 1 H), 7.60 (d, *J* = 1.5 Hz, 1 H), 7.51 (d, *J* = 1.5 Hz, 1 H), 6.80 (d, *J* = 1.2 Hz, 1 H), 5.41 (dt, *J* = 1.3, 6.9 Hz, 1 H), 4.63 (dd, *J* = 8.3, 7.1 Hz, 1 H), 4.05 (s, 3 H), 3.83 (dd, *J* = 8.4, 6.7 Hz, 1 H), 1.59 (s, 3 H), 1.55 (s, 3 H);  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  189.9, 159.0, 153.2, 148.6, 147.7, 132.3, 118.4, 117.9, 112.9, 111.5, 110.9, 73.1, 69.3, 56.4, 26.0, 25.1; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{17}\text{O}_6$  [*M* + *H*] 305.1025, found 305.1019.

**(S)-4-(2,2-Dimethyl-1,3-dioxolan-4-yl)-6-(hydroxymethyl)-8-methoxy-2H-chromen-2-one (5f).** Compound **5f** was obtained as a pale solid after purification by flash chromatography (EtOAc–hexane 1:1):  $\alpha_{\text{D}} +66.9$  (*c* 1.0,  $\text{CHCl}_3$ ); mp  $139\text{--}141^\circ\text{C}$ ;  $^1\text{H}$  NMR (200 MHz, MeOD)  $\delta$  7.23 (s, 1 H), 7.07 (s, 1 H), 6.57 (d, *J* = 1.3 Hz, 1 H), 5.52–5.37 (m, 1 H), 4.84 (s, 2 H), 4.74–4.56 (m, 2 H), 3.94 (s, 3 H), 3.74 (dd, *J* = 8.4, 6.6 Hz, 1 H), 1.54 (s, 3 H), 1.50 (s, 3 H);  $^{13}\text{C}$  NMR (50 MHz, MeOD)  $\delta$  162.7, 156.9, 148.9, 143.7, 140.0, 118.8, 113.9, 113.8, 111.8, 111.7, 74.6, 70.7, 64.5, 56.8, 26.5, 25.5; HRMS (ESI) calcd for  $\text{C}_{16}\text{H}_{19}\text{O}_6$  [*M* + *H*] 307.1182, found 307, 1174.

**Acknowledgment.** We acknowledge the Rio de Janeiro State Science Foundation (FAPERJ) and the Brazilian National Science Council (CNPq) for financial support. P.R.R.C. and M.N.E. thank CNPq, T.A.F. thanks FAPERJ and CAPES, and B.G.V. thanks FAPESP for research fellowships.

**Supporting Information Available:** ESI(+)-MS/MS of *m/z* 322 “fished” from the reaction solution containing **Z-1**, **4a**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$  in acetone diluted with MeCN (p S1); ESI(+)-MS/MS of *m/z* 481 “fished” from the reaction solution containing **Z-1**, **4a**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$ ,  $\text{PPh}_3$  in acetone diluted with MeCN (p S2); ESI(+)-MS/MS of *m/z* 661 “fished” from the reaction solution containing **Z-1**, **4a**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$ ,  $\text{PPh}_3$  in acetone diluted with MeCN (p S3); ESI(+)-MS/MS of *m/z* 677 “fished” from the reaction solution containing **Z-1**, **4a**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$ ,  $\text{PPh}_3$  in acetone diluted with MeCN (p S4); ESI(+)-MS/MS of *m/z* 939 “fished” from the reaction solution containing **Z-1**, **4a**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$ ,  $\text{PPh}_3$  in acetone diluted with MeCN (p S5); ESI(+)-MS/MS of *m/z* 957 “fished” from the reaction solution containing **Z-1**, **4a**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$ ,  $\text{PPh}_3$  in acetone diluted with MeCN (p S6); ESI(+)-MS/MS of *m/z* 723 “fished” from the reaction solution containing **Z-1**, **4a**,  $\text{Pd}(\text{OAc})_2$ , and  $\text{Ag}_2\text{CO}_3$ ,  $\text{PPh}_3$  in acetone diluted with MeCN (p S7);  $^1\text{H}$  NMR of **5a** (p S8); APT of **5a** (p S9); high resolution mass of **5a** (p S10);  $^1\text{H}$  NMR of **5b** (p S11); APT of **5b** (p S12); high resolution mass of **5b** (p S13);  $^1\text{H}$  NMR of **5c** (p S14); APT of **5c** (p S15); high resolution mass of **5c** (p S16);  $^1\text{H}$  NMR of **5d** (p S17); APT of **5d** (Figure S18); high resolution mass of **5d** (p S19);  $^1\text{H}$  NMR of **5e** (p S20); APT of **5e** (p S21); high resolution mass of **5e** (p S22);  $^1\text{H}$  NMR of **5f** (p S23); APT of **5f** (p S24); high resolution mass of **5f** (p S25);  $^1\text{H}$  NMR of **6a** (p S26); APT of **6a** (p S27);  $^1\text{H}$  NMR of **6b** (p S28);  $^1\text{H}$  NMR of **6c** (p S29);  $^1\text{H}$  NMR of **6d** (p S30); high resolution mass of **6d** (p S31);  $^1\text{H}$  NMR of **6e** (p S32); and high resolution mass of **6e** (p S33). This material is available free of charge via the Internet at <http://pubs.acs.org>.

(29) (a) Nagesam, M.; Raju, M. S. *Indian J. Heterocycl. Chem.* **1994**, *4*, 27–32. (b) Boland, G. M.; Donnelly, D. M. X.; Finet, J. P.; Rea, M. D. *J. Chem. Soc., Perkin Trans. 1* **1996**, *21*, 2591–2597. (c) Donnelly, D. M. X.; Finet, J. P.; Guiry, P. J.; Hutchinson, R. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, *10*, 2851–2852. (d) Ramazani, A.; Yousefi, L.; Souldozi, A.; Noshiranzadeh, N. *Asian J. Chem.* **2007**, *19*, 1595–1596.