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Highly Chemoselective Palladium-Catalyzed Cross-Trimerization between Alkyne and Alkenes Leading to 1,3,5-Trienes or 1,2,4,5-Tetrasubstituted Benzenes with Dioxygen

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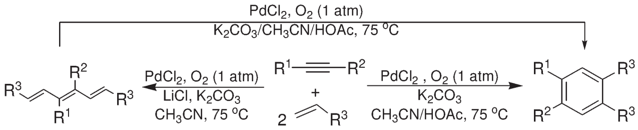

A palladium-catalyzed 1:2 linear/cyclic cross-trimerization of alkyne with alkenes using molecular oxygen as the sole oxidant has been reported for the first time. A series of 1,3,5-trienes and 1,2,4,5-tetrasubstituted benzenes are obtained with high chemoselectivity respectively and mechanisms of these reactions are proposed based on some controlled examination.

Palladium-catalyzed processes for carbon−carbon bond formation have proven to be a powerful and useful tool for the construction of natural products and complicated compounds.[1] Although classic reactions such as Sonogashira,[2] Suzuki,[3] Stille,[4] and Heck cross-coupling[5] have been developed and widely used in organic synthesis, from the viewpoint of green chemistry, it is necessary to develop more atom economic and environmental benign methodologies to construct C−C bonds. To address this issue, a lot of effort has been made to achieve the sequential reaction system with molecular oxygen as oxidant. However, it still remains a challenge to combine various factors of green chemistry with Pd-catalyzed coupling reactions.

Chloropalladation of alkynes is well-recognized to be one of the most efficient and atom economic methods for the construction of both the carbon−carbon and carbon−halide bonds.[6] Among its application, a majority of research was concerned about the capture of σ-vinylpalladium intermediate with alkynes, alkenes, allyl halides, and carbon monoxide in which taking alkenes to carry out a tandem Heck cross-coupling has been proven to be an extremely important and convenient method for the synthesis of 1-chloro-1,3-tetradiene.[7] However, in all these systems, the activation of the C−Cl σ-bond in vinyl chloride received little attention, which were inert in the presence of the oxidant like cupric salts, BQ, and etc., probably due to the efficient oxidation of Pd(0) to Pd(II). However, a weaker oxidant may allow a smaller TON of Pd(0) oxidation, thus sustaining Pd(0) for another Heck catalytic cycle (Scheme 1). In this context, oxygen was found to be a perfect candidate for its medium oxidation ability toward Pd(0).[8] Moreover, the use of oxygen may eliminate the byproducts from traditional oxidants in a Pd catalytic system such as superfluous Cu(II) salts, Ag(I) salts, and phenyliodine(III) diacetate. On the basis of our interest in oxygen and chloropalladation chemistry on triple bonds,[9] we herein disclose a highly chemoselective palladium-catalyzed oxidative cross-trimerization of one alkyne with two alkenes to 1,3,5-trienes or 1,2,4,5-tetrasubstituted benzenes which both are very useful in the field of pharmaceutical and materials chemistry.[10]

In an initial attempt, ethyl phenylpropiolate (**1a**) was used as a model compound for the reaction with methyl acrylate (**2a**) to screen the reaction conditions (see the Supporting Information). Under the optimal conditions (10 mol % $PdCl_2$, 120 mol % LiCl, 150 mol % K_2CO_3 in acetonitrile at 75 °C for 18 h under 1 atm O_2) the cross-trimerization of **1a**

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[1] For selected reviews on C−C bond formation, see: (a) Corbet, J.; Mignani, G. *Chem. Rev.* **2006**, *106*, 2651–2710. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285–2310.

[2] For reviews on Sonogashira cross-coupling, see: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922. (b) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979–2018.

[3] For reviews on Suzuki cross-coupling, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.

[4] For a selected review on Stille cross-coupling, see: Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359–1469.

[5] For reviews on Heck cross-coupling, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009–3066. (b) Dounay, A. B.; Oyerman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (c) Alsonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771–11835.

[6] For a review on chloropalladation, see: Lu, X. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 2, pp 2267−2288.

[7] For selected examples, see: (a) Ma, S.; Lu, X. *J. Org. Chem.* **1991**, *56*, 5120–5125. (b) Zhu, G.; Lu, X. *Organometallics* **1995**, *14*, 4899–4904. (c) Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* **2003**, *5*, 4429–4432. (d) Huang, X. C.; Wang, F.; Liang, Y.; Li, J. H. *Org. Lett.* **2009**, *11*, 1139–1142. (e) Li, Y.; Jardine, K.; Tan, R.; Song, D.; Dong, V. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 9690–9692. (f) Yin, G.; Liu, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 5442–5445.

[8] For reviews on oxygen, see: (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (b) Punniyamurthy, T.; Velusamy, S.; Lqbal, J. *Chem. Rev.* **2005**, *105*, 2329. For selected recent palladium-catalyzed examples, see: (c) Shi, Z. Z.; Zhang, C.; Li, S.; Pan, D. L.; Ding, S. T.; Cui, Y. X.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572–4576. (d) Aouf, C.; Thiery, E.; Bras, J. L.; Muzart, J. *Org. Lett.* **2009**, *11*, 4096–4099. (e) Stahl, S. S. *Science* **2005**, *309*, 1824–1826. (f) Li, B.; Tian, S.; Fang, Z.; Shi, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115–1118. (g) Wang, D.; Wasa, M.; Giri, R.; Yu, J. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191.

[9] (a) Huang, J. M.; Zhou, L.; Jiang, H. F. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945–1949. (b) Wang, A.; Jiang, H. F. *J. Am. Chem. Soc.* **2008**, *130*, 5030–5031. (c) Wang, A.; Jiang, H. H.; Chen, H. J. *J. Am. Chem. Soc.* **2009**, *131*, 3846–3847. (d) Wang, A.; Jiang, H. F. *J. Org. Chem.* **2010**, *75*, 2321–2326. (e) Shen, Y. X.; Jiang, H. F.; Chen, Z. W. *J. Org. Chem.* **2010**, *75*, 1321–1324. (f) Jiang, H. F.; Liu, X. H.; Zhou, L. *Chem.—Eur. J.* **2008**, *14*, 11305–11309.

[10] (a) Gobbi, L.; Seiler, P.; Diederich, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 674–677. (b) Horiguchi, H.; Hirano, K.; Satoh, T.; Miura, M. *Adv. Synth. Catal.* **2009**, *351*, 1431–1436. (c) Saltiel, J.; Papadimitriou, D.; Krishna, T. S. R.; Huang, Z.; Krishnamoorthy, G.; Laohhasurayotin, S.; Clark, R. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 8082–8085. (d) Thirsk, C.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 999–1023.

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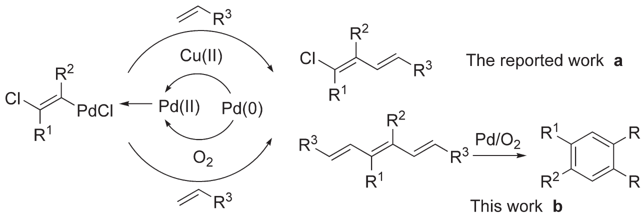
SCHEME 1. **(a) Direct Chloropalladation of Alkyne and Heck Cross-Coupling with One Alkene with Pd/Cu(II) and (b) Cross-Trimerization of One Alkyne with Two Alkenes to 1,3,5-Triene or 1,2,4,5-Tetrasubstituted Benzene by One Pot with Pd/O$_2$**

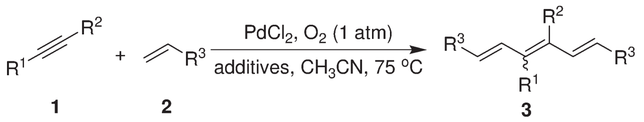


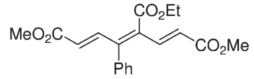
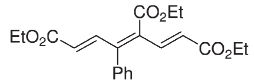
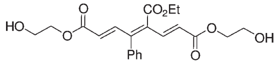
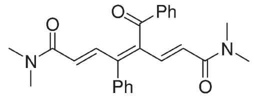
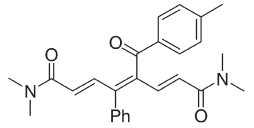
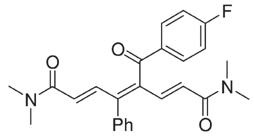
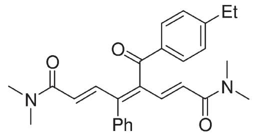
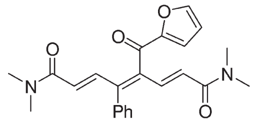
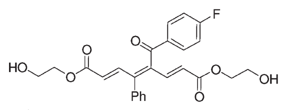
(0.5 mmol) with **2a** (1.25 mmol) gave the corresponding product linear *E*-**3aa** in 90% yield (Table 1, entry 1). The structure of **3aa** was determined by ^{1}H NMR, ^{13}C NMR, MS, and NOE. Treated with the same conditions, **1a** could react with ethyl acrylate and water solvable 2-hydroxyethyl acrylate very well (Table 1, entries 2 and 3). Only the *E* isomer of **3ac** was obtained as polar acrylates were used. When the reaction was run with aromatic ynones, the corresponding 1,3,5-trienes **3bd**−**3fd** were also obtained in high yields (Table 1, entries 4−8). Interestingly, the electronic effect of the substituted group on the aromatic ring did not affect the reactivity and selectivity of the reaction. When ynone **1g** was employed, the reaction system was complex due to the byproduct derived from the Heck cross-coupling of 4-bromobenzene with the acrylate (Table 1, entry 9). Additionally, ynone **1d** could react with **2c** in good yield (Table 1, entry 10). Surprisingly, to the alkynes with double electron-withdrawing groups such as diethyl but-2-ynedioate (**1h**) and dimethyl but-2-ynedioate (**1i**), few linear products were obtained but with good yields of tetrasubstituted benzenes.

Stimulated by the cycloproducts of alkynes with double electron-withdrawing groups and in view of the special structure of these trienes, we speculated that other 1,3,5-trienes could be cyclized too. To our delight, the benzene ring (**4aa**) under consideration was obtained when **3aa** was treated at higher temperature under typical conditions. Encouraged by this result and the comparability of the linear cross-trimerization's conditions, we tried to carry out the cyclotrimerization in one pot. After screening different catalysts, additives, solvents, and temperature, the reaction of **1a** with **2a** afforded **4aa** in high yield in the presence of PdCl$_2$ (10 mol %) and K$_2$CO$_3$ (40 mol %) in CH$_3$CN (2 mL) and CH$_3$COOH (0.3 mL) under 1 atm of O$_2$. With the optimum reaction condition in hand, we then investigated the scope of this transformation by different alkynes and alkenes (Table 2). In the scope of alkynes, substrates **1h**−**i** bearing two electron-withdrawing groups (Table 2, entries 2 and 3) are more efficient than their analogues with only one electron-withdrawing group (Table 2, entry 1) in this cyclization upon comparison of their respective product yields and reaction temperature. This cyclization is also very suitable for other acrylates with alterations of their substituents with ethyl, *n*-hexyl, water solvable 2-hydroxyethyl, and long-chain alkyl (Table 2, entries 5−8). Interestingly, styrene which was usually inert in chloropalladation was also efficient in this system (Table 2, entry 9). However, in the case of 1-hexylene (**2h**), the considered benzene ring, even the linear 1,3,5-triene was not detected because of the easy trimerization of **2h** itself (Table 2, entry 10).[11]

To better understand this methodology, we executed some other examinations for the potential mechanism (Scheme 2).

TABLE 1. **Pd-Catalyzed Linear Cross-Trimerization between Alkynes and Alkenes to 1,3,5-Trienes with Oxygen**[a]



Entry	Alkyne R^1; R^2	Alkene R^3	Product (yield, the ratio of *E*-3/*Z*-3)[b]
1	**1a** Ph; CO$_2$Et	**2a** CO$_2$Me	 **3aa** (90%, 94/6)
2	**1a**	**2b** CO$_2$Et	 **3ab** (81%, 85/15)
3	**1a**	**2c** CO$_2$CH$_2$CH$_2$OH	 **3ac** (76%, 100/0)
4	**1b** PhCO; Ph	**2d** CON(CH$_3$)$_2$	 **3bd** (89%, 100/0)
5	**1c** 4-CH$_3$C$_6$H$_4$CO; Ph	**2d**	 **3cd** (85%, 100/0)
6	**1d** 4-FC$_6$H$_4$CO; Ph	**2d**	 **3dd** (90%, 100/0)
7	**1e** 4-EtC$_6$H$_5$CO; Ph	**2d**	 **3ed** (82 %, 100/0)
8	**1f** 2-Furyl; Ph	**2d**	 **3fd** (91%, 100/0)
9[c]	**1g** 4-BrC$_6$H$_4$CO; Ph	**2d**	-
10	**1d** 4-FC$_6$H$_4$CO; Ph	**2c**	 **3dc** (85%, 99/1)

[a] All the reactions of **1** (0.5 mmol) with **2** (2.5 equiv) were carried out in the presence of PdCl$_2$ (10 mol %), LiCl (1.2 equiv), and K$_2$CO$_3$ (1.5 equiv) in CH$_3$CN (4 mL) under 1 atm of oxygen at 75 °C for 18 h. [b] Isolated yield. And the ratio of *E*/*Z* was determined by ^{1}H NMR. [c] Without designed product.

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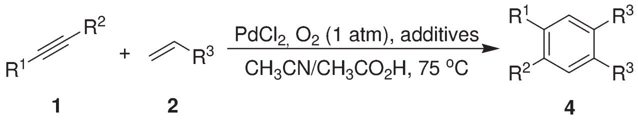
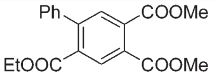
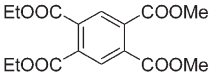
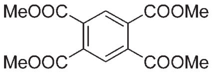
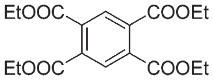
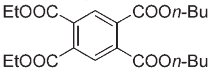
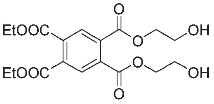
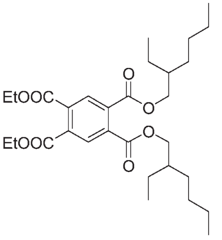
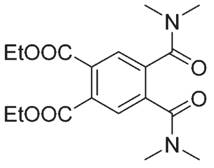
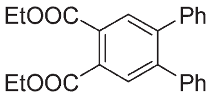
[11] Jiang, H. F.; Shen, Y. X.; Wang, Z. Y. *Tetrahedron Lett.* **2007**, *48*, 7542–7545.

TABLE 2. Pd-Catalyzed Cross-Cyclotrimerization between Alkynes and Alkenes to 1,2,4,5-Tetrasubstituted Benzenes with Oxygen[a]

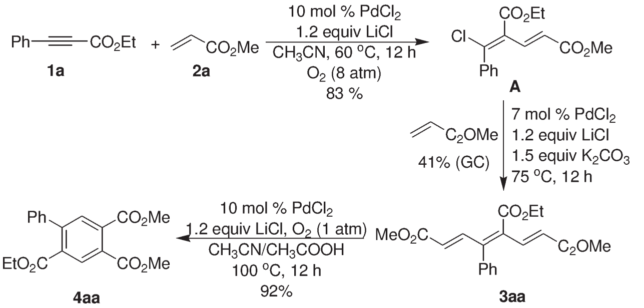


Entry	Alkyne R^1; R^2	Alkene R^3	Product (yield) [b]
1[c]	**1a** Ph; CO_2Et	**2a** CO_2Me	 **4aa** (80%)
2	**1h** CO_2Et; CO_2Et	**2a**	 4ha (89%)
3	**1i** CO_2Me; CO_2Me	**2a**	 **4ia** (86%)
4	**1h** CO_2Et; CO_2Et	**2b** CO_2Et	 **4hb** (90%)
5	**1h**	**2e** CO_2n-Bu	 **4he** (87%)
6	**1h**	**2c** $CO_2CH_2CH_2OH$	 **4hc** (65%)
7	**1h**	**2f** CO_2(2-Ethyl)hexyl	 **4hf** (78%)
8	**1h**	**2d** $CON(CH_3)_2$	 **4hd** (94%)
9	**1h**	**2g** Ph	 **4hg** (71%)

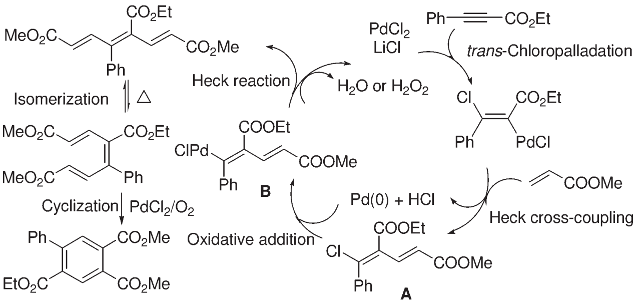
[a] All reactions of **1** (0.5 mmol) with **2** (2.5 equiv) were performed in a mixture of CH_3CN (4 mL) and CH_3COOH (0.3 mL) in the presence of $PdCl_2$ (10 mol %) and K_2CO_3 (40 mol %) under 1 atm of oxygen at 75 °C for 24 h, unless otherwise noted. [b] Isolated yield. [c] At 100 °C for 24 h.

By analyzing the results from GC-MS, we found as a trace byproduct chloro-substituted 1,3-diene (**A**), which may be a intermediate. Prompted by this detection, we carried out a chloropalladation/Heck cross-coupling using **1a** and **2a** with the system of $PdCl_2$ (10 mol %), LiCl (1.2 equiv), CH_3CN (2 mL), and oxygen (8 atm). And chloro-substituted 1,3-diene (**A**) was obtained in the yield of 83% after 12 h. Then, **A** was treated with **2a** under the terms of linear cross-trimerization without oxygen to obtain **3aa** in GC yield of 41%. As we assume, **3aa** was transferred into the corresponding benzene ring **4aa** under the condition of cross-cyclotrimerization. On the basis of the above experimentations, we propose the mechanism of these transformations may come by the combination of three steps: (1) *trans*-chloro-palladation of alkyne and a Heck cross-coupling with alkene to chloro-substituted 1,3-diene, (2) another Heck cross-coupling with alkene through a β-H elimination to 1,3,5-trienes,[12] and (3) isomerization of (1*E*,3*E*,5*E*)-trienes to (1*E*,3*Z*,5*E*)-trienes with higher temperature[13] and then palladium-catalyzed cyclization of trienes to afford benzenes. In the above three steps, oxygen was needed by steps 1 and 3, which can oxidize Pd(0) to Pd(II) (Scheme 3).

SCHEME 2. Controlled Examinations for the Mechanism



SCHEME 3. The Possible Reaction Mechanism



In summary, we have carried out a palladium-catalyzed 1:2 linear/cyclic cross-trimerization of alkyne with alkenes taking molecular oxygen as the sole oxidant for the first time. The reaction proceeds efficiently and a series of 1,3,5-trienes and 1,2,4,5-tetrasubstituted benzenes have been synthesized in good yields through this green and atom-economic route by one pot. Otherwise, mechanisms of these reactions are proposed based on some controlled examinations. Future work will focus on expanding the scope, exploring mechanisms all-around, and applying the method to the field of natural products.

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[12] For selected examples on σ-vinylhalorine activation catalyzed by palladium, see: (a) Hua, R.; Tanaka, M. *New J. Chem.* **2001**, *25*, 179–184. (b) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770–8779. (c) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271.

[13] For some examples on the *Z*/*E* isomerization of alkene, see: (a) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627–4629. (b) Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2009**, *74*, 7094–7099.

Experimental Section

Typical Procedure for the Synthesis of (1*E*,3*E*,5*E*)-3-Ethyl-1,6-dimethyl 4-Phenylhexa-1,3,5-triene-1,3,6-tricarboxylate (3aa). To a 25 mL round-bottomed flask with condensator were added $PdCl_2$ (8.8 mg, 10 mol %), LiCl (25 mg, 1.2 equiv), K_2CO_3 (105 mg, 1.5 equiv), and ethyl phenylpropiolate (**1a**) (87 mg, 0.5 mmol). Then, the flask was purged with O_2 three times, followed by addition of methyl acrylate (**2a**) (107 mg, 1.25 mmol) and CH_3CN (3 mL). The formed mixture was gradually heated from rt to 75 °C under O_2 (1 atm kept with a balloon) and stirred for 18 h as monitored by TLC. The solution was then cooled to rt, diluted with ethyl acetate (30 mL), washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by TLC on silica gel to afford colorless oil **3aa**, whose structure was determined by ^1H NMR, ^{13}C NMR, MS, and NOE and compared with literature data. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 12 Hz, 1H), 7.40−7.42 (m, 3H), 7.12−7.14 (m, 2H), 7.06 (d, J = 16 Hz, 1H), 5.98 (d, J = 16 Hz, 1H), 5.61 (d, J = 16 Hz, 1H), 4.44 (q, J = 8 Hz, 2H), 3.67 (d, J = 16 Hz, 6H), 1.42 (t, J = 8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 166, 144.6, 141.6, 137.8, 135.9, 133.8, 129.1, 128.5, 128.3, 126.4, 122.6, 61.6, 51.3, 51.2, 13.8; MS (EI, 70 eV) *m*/*z* (%) 344 (M^+, 1), 285 (30), 253 (19), 239 (50), 180 (30), 151, (44), 77 (8), 58 (18), 27 (100). Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.23; H, 5.88.

Typical Procedure for the Synthesis of [1,1′-Biphenyl]-2,4,5-tricarboxylic Acid, 2-Ethyl-4,5-dimethyl Ester (4aa). To a 25 mL round-bottomed flask with condensator were added $PdCl_2$ (8.8 mg, 10 mol %), K_2CO_3 (28 mg, 40 mol %), and ethyl phenylpropiolate (**1a**) (87 mg, 0.5 mmol). Then, the flask was purged with O_2 three times, followed by the addition of methyl acrylate (107 mg, 1.25 mmol), CH_3CN (3 mL), and CH_3COOH (0.3 mL). The formed mixture was gradually heated from rt to the corresponding temperature under O_2 (1 atm kept with a balloon) and stirred for 18 h as monitored by TLC. The solution was then cooled to rt, diluted with ethyl acetate (30 mL), washed with H_2O (3 × 10 mL), dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude product was purified by TLC on silica gel to afford colorless oil **4aa**. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.23 (s, 1H), 7.69 (s, 1H), 7.39−7.42 (m, 3H), 7.30−7.33 (m, 2H), 4.13 (q, J = 6.6 Hz, 2H), 3.93 (s, 3H), 3.95 (s, 3H), 1.02 (t, J = 5.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 167.1, 166.6, 145.4, 133.3, 130.9, 130.7, 129.7, 128.2, 128.2, 128.2, 128.1, 61.5, 52.9, 52.8, 13.6; MS (EI, 70 eV) *m*/*z* (%) 342 (M^+, 20), 311(30), 297 (35), 283 (20), 152 (35), 77 (5), 28 (100). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.71; H, 5.29.

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Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.