Formation of Coumarins by Palladium(II)-Catalyzed Reaction of Phenols with Ethyl Acrylates

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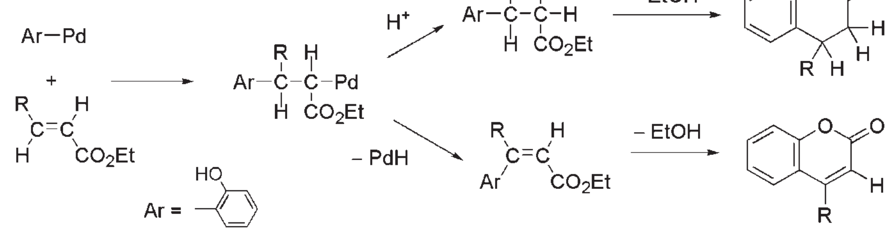
The reaction of phenols with ethyl acrylates in the presence of a $Pd(OAc)_2$ catalyst in trifluoroacetic acid did not yield dihydrocoumarins but gave coumarins, in contrast to the reaction of phenols with propiolates. The addition of $K_2S_2O_8$ as an oxidant increased the yield of coumarins. The reaction of several phenols with ethyl cinnamate, ethyl crotonate, or ethyl acrylate gave the corresponding coumarin derivatives in moderate to good yields. The coumarin formation competed with the oxidative coupling of electron-rich phenols, which reduced the product yield.

Activation or functionalization of C–H bonds is one of the most important reaction processes. The process is challenging since the C–H bonds of hydrocarbons are stable for most chemical transformations because of their relatively strong bonds. The reactions via C–H bond activation are noted as an environment-friendly process because such processes do not require toxic halogens for chemical transformations. One can reduce the reaction steps due to the direct use of hydrocarbons as the substrates instead of halogenated substrates that are usually used for synthetic reactions. Direct metalation of aromatic substrates can functionalize the C–H bond of aromatic hydrocarbons. To date, many reviews on aromatic C–H bond activation or functionalization have been reported.[1] If such reactions via C–H bond activation can proceed catalytically and perform functional transformations of simple or complex molecules, they become useful and straightforward processes for synthesis of valuable compounds and functional materials.

Recently, it has been found that hydroarylation of alkynes takes place in the presence of a palladium catalyst under mild conditions in trifluoroacetic acid (TFA).[2] This hydroarylation reaction efficiently proceeds intramolecularly to afford heterocycles, such as coumarins, quinolinones, and thiocoumarins.[2a,3] Interestingly, this reaction has been applied to direct synthesis of coumarins from phenols and propiolates.[4] The coumarin synthesis explains that an in situ-generated arylpalladium species adds to the triple bond of the propiolate to give an (2-arylvinyl)palladium intermediate, which is subject to protonation and cyclization.[2] In analogy with the coumarin synthesis from phenols and propiolates, it is expected that an (2-arylethyl)palladium intermediate is formed when an acrylate is employed instead of the propiolate in the Pd(II)-catalyzed reaction of phenols, as shown in Scheme 1. If the (2-arylethyl)palladium similarly undergoes the protonation followed by cyclization, a dihydrocoumarin may be formed. On the other hand, the elimination of "PdH" on the (2-arylethyl)palladium will give rise to ethyl cinnamates,[5] which undergo the cyclization to afford coumarins. Thus, we examined the reaction of phenols with acrylates in the presence of $Pd(OAc)_2$ to learn the behavior of the (2-arylethyl)palladium species in an acidic medium, TFA.

Results and Discussion

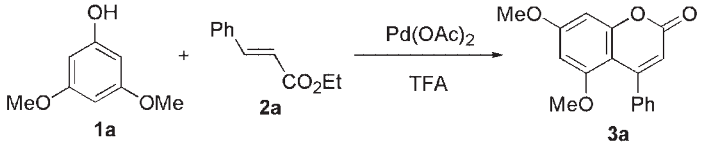
In order to find the difference of the reactivity between ethyl phenylpropiolate and ethyl cinnamate, reaction of 3,5-dimethoxyphenol (**1a**) with ethyl cinnamate (**2a**) was carried out in TFA in the presence of $Pd(OAc)_2$ (0.02 molar amount) at room temperature for 20 h. The product was 5,7-dimethoxy-4-phenylcoumarin (**3a**) but the yield was only 7% (Table 1, Entry 1). Most of **2a** was recovered unchanged. The elongation of the reaction time (70 h) improved the yield of **3a** up to 19% (Entries 2, 3). The reactions at 40 °C were not effective (Entries 4–6). No products were formed in the absence of $Pd(OAc)_2$ (Entry 4). We examined the reaction conditions to increase the yield of the product but the yield was less than 20%.



Scheme 1.

Published on the web March 11, 2005; DOI 10.1246/bcsj.78.468

Table 1. The Reaction of 3,5-Dimethoxyphenol with Ethyl Cinnamate[a)]



Entry	**1a**/mmol	**2a**/mmol	$Pd(OAc)_2$/mmol	Additive/mmol	Time/h	Yield/%[b)]
1	1	1	0.02	—	20	7
2	1	1	0.02	—	40	17
3	1	1	0.02	—	70	19
4	1	1	0	—	20[c)]	0
5	1	1	0.02	—	20[c)]	16
6	1	1	0.05	—	20[c)]	18
7	1	1	0.02	$Cu(OAc)_2$/0.5	40	24
8	1	1	0.02	OXONE[d)]/0.25	40	17
9	1	1	0.02	$K_2S_2O_8$/0.5	40	32
10	1	1	0.02	$K_2S_2O_8$/1	40	43
11	1	1	0.05	$K_2S_2O_8$/1	40	46
12	1	1	0.05	$K_2S_2O_8$/1	70	50
13	1	2	0.05	$K_2S_2O_8$/1	70	52
14	2	1	0.05	$K_2S_2O_8$/1	70	58

a) The reaction of **1a** with **2a** in TFA (1 mL) was carried out in the presence of $Pd(OAc)_2$ at room temperature. b) Isolated yields based on the least amount of the substrate. c) At 40 °C. d) $2KHSO_5–KHSO_4–K_2SO_3$.

The present reaction using cinnamate **2a** gave no 3,4-dihydro-5,7-dimethoxy-4-phenylcoumarin that was expected to be formed when the reaction proceeded in a similar manner to the reaction using ethyl phenylpropiolate. Therefore, this result suggests that the reaction using cinnamate **2a** predominantly takes place via elimination of "PdH" on the intermediate palladium species generated by addition of arylpalladium species to cinnamate **2a**. Since the in situ-generated palladium hydride species readily undergoes reductive transformation to Pd(0), the Pd(0) species is required to be re-oxidized to a Pd(II) species to maintain the catalytic cycle. Then, we examined the addition of oxidizing agents, such as $Cu(OAc)_2$, OXONE (Monopersulfate compound, $2KHSO_5–KHSO_4–K_2SO_4$), and $K_2S_2O_8$.

$Cu(OAc)_2$ was effective as the oxidizing agent but OXONE was not (Entries 7, 8). Among three oxidizing agents, $K_2S_2O_8$ was the best additive; it gave coumarin **3a** in 43% yield when 1 mmol of $K_2S_2O_8$ was added (Entries 7–10). The use of 0.05 mmol of $Pd(OAc)_2$ slightly increased the yield of **3a**. The best result (58% yield) was obtained when the reaction was carried out using **1a** (2 mmol), **2a** (1 mmol), $Pd(OAc)_2$ (0.05 mmol), $K_2S_2O_8$ (1 mmol), and TFA (1 mL) at room temperature for 70 h (Entry 14).

In order to examine the scope and limitations on the coumarin formation, we carried out the reaction of various phenols **1** with ethyl cinnamate (**2a**). The reaction of several phenols **1** with ethyl cinnamate **2a** in the presence of $Pd(OAc)_2$ and $K_2S_2O_8$ was carried out in TFA for 40 h. The results are given in Table 2.

The reaction of 3-methoxyphenol (**1b**) with ethyl cinnamate (**2a**) in the presence of $K_2S_2O_8$ gave 7-methoxy-4-phenylcoumarin (**3b**) in 75% yield. In addition to the methoxy-subsituted phenols, methyl-substituted phenols reacts with cinnamate **2a**. The reactions of 3,5-dimethylphenol (**1c**), 3,4-dimethylphenol (**1d**), and 3-methylphenol (**1e**) with cinnamate **2a** afforded 5,7-dimethyl-4-phenylcoumarin (**3c**), 6,7-dimethyl-4-phenylcoumarin (**3d**), and 7-methyl-4-phenylcoumarin (**3e**) in 46, 11, and 46% yields, respectively.

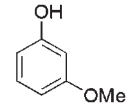
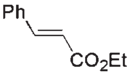
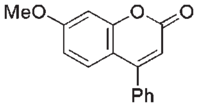
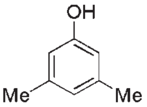
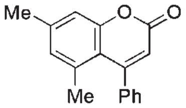
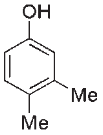
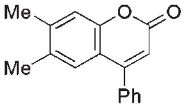
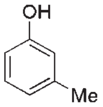
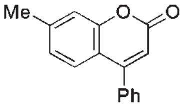
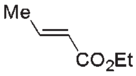
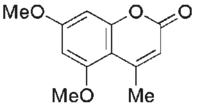
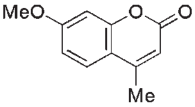
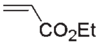
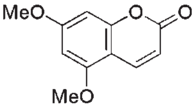
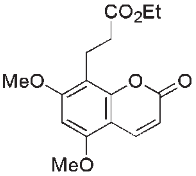
Furthermore, the reactions with ethyl crotonate (**2b**) and with ethyl acrylate (**2c**) were conducted. The reactions of ethyl crotonate (**2b**) with 3,5-dimethoxyphenol (**1a**) and with 3-methoxyphenol (**1b**) gave 5,7-dimethoxy-4-methylcoumarin (**4a**) and 7-methoxy-4-methylcoumarin (**4b**) in 25 and 32% yields, respectively. In the reaction of ethyl acrylate (**2c**) with 3,5-dimethoxyphenol (**1a**), 5,7-dimethoxycoumarin (**5**) and 8-[2-(ethoxycarbonyl)ethyl]-5,7-dimethoxycoumarin (**6**) were obtained in 40 and 6% yields, respectively. However, no coumarins were obtained when 4-methoxyphenol (**1f**), 3,4-methylenedioxyphenol (**1g**), and 2-naphthol (**1h**) were employed in this reaction. Particularly, the reactions using phenols **1g** and **1h** gave a complex mixture.

A possible mechanism for the formation of coumarins in the reaction of phenols with acrylates in the presence of $Pd(OAc)_2$ in TFA is shown in Scheme 2. The mildness of this reaction is attributable to an increased reactivity of $Pd(OAc)_2$ by replacing acetate with trifluoroacetate, compared with a Pd(II)-catalyzed reaction of aromatics with alkenes in acetic acid.[5] The reaction of an in situ-generated positive palladium species with a phenol followed by addition to an acrylate produces a phenol-substituted alkylpalladium species. Elimination of a palladium hydride takes place to give a phenol-subsitituted acrylate, which readily cyclizes intramolecularly to a coumarin.

On the other hand, the palladium hydride species undergoes reductive elimination to produce TFA and Pd(0), which is re-oxidized by $K_2S_2O_8$ in TFA to regenerate $Pd(OCOCF_3)_2$.[6]

In conclusion, we have demonstrated the coumarin formation in the Pd(II)-catalyzed reaction of phenols with acrylates in TFA. In contrast to the similar type of reactions with propio-

Table 2. Pd(II)-Catalyzed Reaction of Phenols with Acrylates[a)]

Phenol **1**	Acrylate **2**	Coumarin **3**	Yield/%[b)]
 **1b**	 **2a**	 **3b**	75
 **1c**	**2a**	 **3c**	46
 **1d**	**2a**	 **3d**	11
 **1e**	**2a**	 **3e**	46
1a	 **2b**	 **4a**	25
1b	**2b**	 **4b**	32
1a	 **2c**	 **5**	40
		 **6**	6

a) The reaction of **1** (1 mmol) with **2** (1 mmol) in TFA (1 mL) was carried out in the presence of $Pd(OAc)_2$ and $K_2S_2O_8$ (1 mmol) at room temperature for 40 h. b) Isolated yields.

lates, it is considered that an arylpalladium species undergoes addition to the double bond of an acrylate and the subsequent elimination of a palladium hydride instead of protonation by TFA. Therefore, the present reaction requires an oxidant to regenerate a palladium(II) species. The competition with the oxidative coupling of phenols takes place and reduces the yield of coumarins **3** when phenols are highly electron-rich.

Experimental

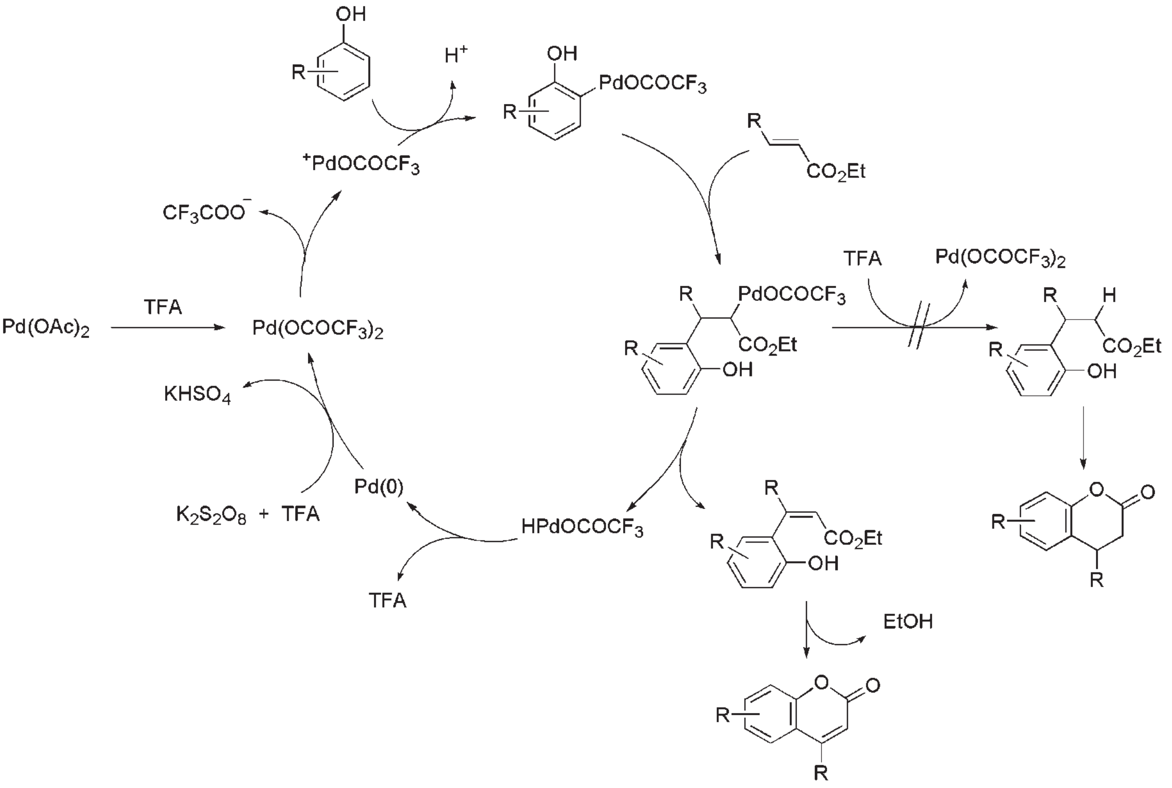
General. Melting points were measured with a Yanaco micromelting apparatus and are not corrected. ^{1}H NMR spectra were recorded on a JEOL AL 300 spectrometer (300 MHz); chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. ^{13}C NMR spectra were recorded on a JEOL AL 300 spectrometer (75 MHz); chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 77.00). Mass spectrum was recorded on a Shimadzu GCMS-QP5050A. Column chromatography was carried out on silica gel (Silica Gel 60, spherical, Kanto Chemical Co.).

Reaction of 3,5-Dimethoxyphenol with Ethyl Cinnamate in the Presence of $Pd(OAc)_2$ in TFA. Palladium acetate, 3,5-dimethoxyphenol, and ethyl cinnamate were placed in a test tube, sealed with a septum, and cooled in an ice/water bath. To a cold mixture was added TFA (1 mL) and then the mixture was stirred at room temperature for 20 h. The reaction mixture was neutralized with aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried with anhydrous Na_2SO_4, and concentrated. The product was separated by column chromatography on silica gel.

In the case of the reaction with an oxidant, TFA was added to a cold mixture of 3,5-dimethoxyphenol, ethyl cinnamate, $Pd(OAc)_2$, and an oxidant.

5,7-Dimethoxy-4-phenylcoumarin (3a).[4b] Mp 168–170 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42 (s, 3H, OMe), 3.87 (s, 3H, OMe), 6.00 (s, 1H, =CH), 6.23 (d, $J = 2.4$ Hz, 1H, ArH), 6.52 (d, $J = 2.4$ Hz, 1H, ArH), 7.23–7.29 (m, 2H, ArH), 7.34–7.38 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.36, 55.71, 93.61, 95.75, 103.55, 112.65, 127.07, 127.31, 127.84, 139.76, 155.63, 157.15, 158.23, 160.78, 163.36.

General Procedure for the Reaction of Phenols with Acrylates in the Presence of $Pd(OAc)_2$ in TFA. A phenol (1 mmol), an ethyl acrylate (1 mmol), $Pd(OAc)_2$ (0.05 mmol), and $K_2S_2O_8$ (1 mmol) were placed in a test tube, sealed with a septum, and



Scheme 2.

the mixture was cooled in an ice/water bath. To the cooled mixture was added TFA (1 mL) and then the mixture was stirred at room temperature for 40 h. The reaction mixture was neutralized with aqueous $NaHCO_3$, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, and concentrated. The product was isolated by column chromatography on silica gel with hexane and ethyl acetate as an eluent.

7-Methoxy-4-phenylcoumarin (3b).[4b] Mp 108 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H, OMe), 6.14 (s, 1H, =CH), 6.72 (dd, $J = 2.7$, 8.9 Hz, 1H, ArH), 6.82 (d, $J = 2.7$ Hz, 1H, ArH), 7.30 (d, $J = 8.9$ Hz, 1H, ArH), 7.34–7.38 (m, 2H, ArH), 7.42–7.45 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.75, 101.10, 111.85, 112.27, 112.51, 127.95, 128.34, 128.78, 129.54, 135.57, 155.77, 156.01, 161.15, 162.80.

5,7-Dimethyl-4-phenylcoumarin (3c).[4b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.71 (s, 3H, Me), 2.31 (s, 3H, Me), 6.09 (s, 1H, =CH), 6.75 (s, 1H, ArH), 7.00 (s, 1H, ArH), 7.18–7.21 (m, 2H, ArH), 7.34–7.38 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.16, 23.17, 115.37, 115.66, 115.98, 127.23, 128.44, 128.61, 129.39, 136.96, 139.48, 142.23, 155.08, 156.66, 160.35.

6,7-Dimethyl-4-phenylcoumarin (3d).[4b] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H, Me), 2.35 (s, 3H, Me), 6.28 (s, 1H, =CH), 7.18 (s, 1H, ArH), 7.20 (s, 1H, ArH), 7.42–7.47 (m, 2H, ArH), 7.50–7.54 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.31, 20.14, 114.14, 116.66, 117.85, 126.93, 128.40, 128.80, 129.50, 132.90, 135.62, 142.00, 152.63, 155.62, 161.24.

7-Methyl-4-phenylcoumarin (3e).[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H, Me), 6.22 (s, 1H, =CH), 6.96 (d, $J = 8.1$ Hz, 1H, ArH), 7.12 (s, 1H, ArH), 7.28 (d, $J = 8.1$ Hz, 1H, ArH), 7.33–7.38 (m, 2H, ArH), 7.41–7.45 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.54, 113.99, 116.52, 117.40, 125.30, 126.34, 128.36, 128.77, 129.55, 135.38, 143.14, 154.26, 155.62, 160.95.

5,7-Dimethoxy-4-methylcoumarin (4a).[4b] Mp 174 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H, Me), 3.78 (s, 3H, OMe), 3.79 (s, 3H, OMe), 5.88 (s, 1H, =CH), 6.22 (d, $J = 2.4$ Hz, 1H, ArH), 6.36 (d, $J = 2.4$ Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.03, 55.56, 55.61, 93.31, 95.28, 104.75, 111.22, 154.32, 156.86, 159.02, 160.91, 162.68.

7-Methoxy-4-methylcoumarin (4b).[7] Mp 155–158 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (d, $J = 0.9$ Hz, 3H, Me), 3.81 (s, 3H, OMe), 6.07 (d, $J = 0.9$ Hz, 1H, =CH), 6.75 (d, $J = 2.4$ Hz, 1H, ArH), 6.79 (dd, $J = 2.4$, 8.8 Hz, 1H, ArH), 7.43 (d, $J = 8.8$ Hz, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.53, 55.65, 100.79, 111.80, 112.10, 113.47, 125.45, 152.49, 155.19, 161.13, 162.58.

5,7-Dimethoxycoumarin (5).[4b] Mp 148–150 °C (CH_2Cl_2/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3H, OMe), 3.82 (s, 3H, OMe), 6.08 (d, $J = 9.5$ Hz, 1H, =CH), 6.21 (d, $J = 2.4$ Hz, 1H, ArH), 6.34 (d, $J = 2.4$ Hz, 1H, ArH), 7.89 (d, $J = 9.5$ Hz, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.69, 55.86, 92.77, 94.66, 103.88, 110.77, 138.60, 156.71, 156.90, 161.36, 163.64.

8-[2-(Ethoxycarbonyl)ethyl]-5,7-dimethoxycoumarin (6). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (t, $J = 7.2$ Hz, 3H, Me), 2.46 (t, $J = 8.0$ Hz, 2H, CH_2), 3.01 (t, $J = 8.0$ Hz, 2H, CH_2), 3.84 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.05 (q, $J = 7.2$ Hz, 2H, OCH_2), 6.06 (d, $J = 9.6$ Hz, 1H, =CH), 6.24 (s, 1H, ArH), 7.91 (d, $J = 9.6$ Hz, 1H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.19, 17.88, 33.53, 55.88, 55.92, 60.29, 90.21, 103.65, 108.59, 110.70, 138.83, 153.80, 155.66, 161.15, 161.53, 173.11; MS (EI) *m/e* 306 (M^+), 232 ($M^+ - HCO_2Et$), 219 ($M^+ - CH_2CO_2Et$). This compound contained a small amount of impurities that could not be separated out and removed.

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