JOC Article

Oxidative Coupling of Benzenes with α,β-Unsaturated Aldehydes by the $Pd(OAc)_2$/Molybdovanadophosphoric Acid/O_2 System

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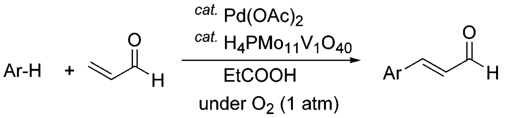
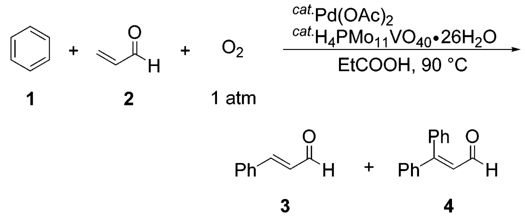


The oxidative coupling reaction of benzene with an α,β-unsaturated aldehyde was examined by the combined catalytic system of $Pd(OAc)_2$ with molybdovanadophosphoric acid (HPMoV) under atmospheric dioxygen. Thus, the reaction of benzene with acrolein under dioxygen (1 atm) by the use of catalytic amounts of $Pd(OAc)_2$ and $H_4PMo_{11}VO_{40}\cdot 26H_2O$ in the presence of dibenzoylmethane as a ligand in propionic acid at 90 °C for 1.5 h afforded cinnamaldehyde in 59% yield and β-phenylcinnamaldehyde in 5% yield. This catalytic system was extended to the direct oxidative coupling through the C−H bond activation of various arenes with acrolein and methacrolein.

Result and Discussion

The arylation of olefins represented by the Heck−Mizoroki reaction is an important synthetic tool for constructing C−C bonds, and the reaction is carried out between various aryl halides and substituted alkenes, especially electron-deficient alkenes having −COOR and −CN groups. However, there have been only a few reports on the coupling reaction of aryl halides with α,β-unsaturated aldehydes such as acrolein. The first trial of arylation with acrolein was made by using diarylmercury compounds and $LiPdCl_3$ as the arylating combination.[1] Jeffery reported the Pd-catalyzed coupling reaction of phenyl, *m*-tolyl, and *p*-chlorophenyl iodides with acrolein in the presence of Bu_4NCl.[2] To avoid the polymerization problem of aldehydes, acrolein dimethyl acetal, a synthetic equivalent of acrolein, is used instead of acrolein, and the reaction with bromobenzene by $Pd(OAc)_2$ in the presence of a tri-*o*-tolylphosphine ligand and triethylamine as a base is reported to give a mixture of cinnamaldehyde dimethyl acetal (56%) and methyl 3-phenylpropionate (39%).[3] Quite recently, Cacchi et al. showed the Pd-catalyzed coupling of aryl iodides and bromides with acrolein diethyl acetal, leading to the corresponding cinnamaldehydes in good yields.[4] It is reported that dimethyl(phenyl)silanol reacts with acrolein in the presence of a stoichiometric amount of $Pd(OAc)_2$ to form cinnamaldehyde.[5] To our best knowledge, however, there is no report so far on the Pd-catalyzed direct coupling of benzene with acrolein. Therefore, it is very interesting to examine the oxidative coupling of benzene with acrolein. Recently, we have successfully carried out the Heck−Mizoroki reaction through the direct C−H bond activation of benzenes with acrylates by the use of $Pd(OAc)_2$ combined with molybdovanadophosphoric acid (HPMoV) under air.[6] In this paper, we report the first direct oxidative coupling reaction of benzene (**1**) with acrolein (**2**), leading to cinnamaldehyde (**3**) and β-phenylcinnamaldehyde (**4**) by the $Pd(OAc)_2$/HPMoV/O_2 system (eq 1), although the coupling is not fully successful owing to the difficulty in suppressing the polymerization of **2**.



(1)

The representative results for the coupling reaction between **1** and **2** using the $Pd(OAc)_2$/HPMoV/O_2 system

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(1) Heck, R. F. *J. Am. Chem. Soc.* **1968**, *90*, 5518.

(2) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

(3) Zebovitz, T. C.; Heck, R. F. *J. Org. Chem.* **1977**, *42*, 3907.

(4) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777.

(5) Hirabayashi, K.; And, J.; Kawashima, J.; Nishihara, Y.; Mori, A.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1409.

(6) (a) Yokota, T.; Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2003**, *125*, 1476. (b) Tani, M.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2004**, *69*, 1221.

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TABLE 1. Oxidative Coupling of 1 with 2 by the $Pd(OAc)_2/H_4PMo_{11}VO_{40}\cdot 26H_2O/O_2$ System under Various Conditions[a]

run	ligand	time/h	conv/%	yield/% 3	yield/% 4
1	DBM	1.5	94	59	5
2	DBM	2	96	45	18
3	DBM	3	97	17	40
4	DBM	1	61	26	0
5[b]	DBM	1.5	95	53	6
6		1.5	76	33	0
7	BA	1.5	92	52	6
8	AA	1.5	85	48	1
9	AA	2	96	54	8
10[c]	AA	2	74	3	0
11[d]	AA	2	82	44	2
12[e]		2	72	5	5
13[f]	DBM	1.5	93	52	5

[a] Benzene (**1**) (30 mmol) was reacted with acrolein (**2**) (1.5 mmol) by $Pd(OAc)_2$ (0.1 mmol), $H_4PMo_{11}VO_{40}\cdot 26H_2O$ (45.2 mg. ca. 0.02 mmol), Na_2CO_3 (0.05 mmol), and ligand (0.1 mmol) under O_2 (1 atm) in EtCOOH (5 mL) at 90 °C. [b] **1** (20 mmol) was used. [c] In the absence of Na_2CO_3. [d] NaOAc (0.08 mmol) was used instead of Na_2CO_3. [e] $Pd(acac)_2$ was used instead of $Pd(OAc)_2$. [f] In the presence of BHT (0.05 mmol).

are shown in Table 1. To suppress the polymerization of **2**, the reaction was carried out using excess benzene (**1**) with respect to **2**. From the practical synthetic viewpoint, it is important for **1** of low boiling point to be easily recovered from the reaction mixture. Thus, the reaction of **1** (30 mmol) with **2** (1.5 mmol) in the presence of $Pd(OAc)_2$ (0.1 mmol), $H_4PMo_{11}VO_{40}\cdot 26H_2O$ (45.2 mg, ca. 0.02 mmol), Na_2CO_3 (0.05 mmol), and dibenzoylmethane (DBM) (0.1 mmol) under O_2 (1 atm) in propionic acid (5 mL) at 90 °C for 1.5 h afforded **3** in 59% yield along with **4** (5%) formed by the further coupling of the resulting **3** with **1** (run 1). In the present reaction, the yield of cinnamic acid, a further oxidation product of **3**, was found to be less than 2%. Because of the easy polymerization of **2**, the desired coupling product **3** was difficult to obtain in high yield. But it is important to note that the direct oxidative coupling of **1** with **2**, leading to **3**, was first performed by the $Pd(OAc)_2$/HPMoV/O_2 system. When the reaction was prolonged to 3 h, dicoupling product **4** became a major product rather than **3** (run 3). The yield of **3** was found to become maximum in the reaction for 1.5 h (run 4). The amount of **1** was reduced to 20 mmol, but the result was almost the same as that of the reaction using 30 mmol of **1** (run 5). The reaction lacking a DBM ligand resulted in a slight decrease of the yield of **3** (run 6). Thus, the effect of several ligands on the present coupling reaction was examined. The use of benzoylacetone (BA) led to a result similar to that of DBM (run 7). The use of acetylacetone (AA) instead of DBM needed a longer reaction time (runs 8 and 9). The reaction in the absence of Na_2CO_3 resulted in a considerable decrease of the selectivity in the coupling product **3**, and several unidentified products (probably oligomers of **2**) were formed (run 10). A similar effect was observed when NaOAc was added to the catalytic solution (run 11). It was found that the base inhibited the polymerization of **2**. When $Pd(acac)_2$ was employed in place of $Pd(OAc)_2$, **3** was formed in poor selectivity (run 12). To suppress the polymerization of **2**, the reaction was examined in the presence of a radical inhibitor such as 2,6-di-*tert*-butyl-4-methylphenol (BHT), but the result was almost the same as that in the absence of BHT (run 13). This fact shows that **2** is not polymerized through a radical process.

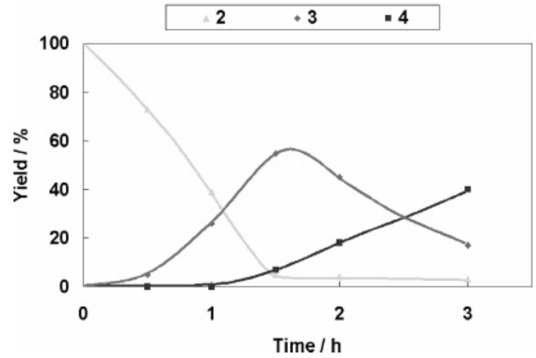


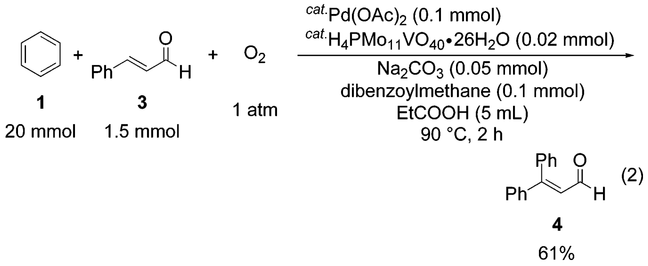
FIGURE 1. Time-dependence curves of the coupling reaction of **1** with **2**.

TABLE 2. Oxidative Coupling of 1 with 2 by $Pd(OAc)_2$ Combined with Several HPAs[a]

run	HPA	conv/%	yield/% 3	yield/% 4
1	$H_4PMo_{11}VO_{40}\cdot 26H_2O$	94	59	5
2	$H_5PMo_{10}V_2O_{40}\cdot 28H_2O$	92	54	6
3	$H_6PMo_9V_3O_{40}\cdot 30H_2O$	93	47	6
4	$H_7PMo_8V_4O_{40}\cdot 28H_2O$	80	35	1
5	$H_5PW_{10}V_2O_{40}\cdot 27H_2O$	28	0	0
6	$H_3PMo_{12}O_{40}\cdot 30H_2O$	66	24	0

[a] Benzene (**1**) was reacted with acrolein (**2**) under the same conditions as run 1 in Table 1 except for HPA.

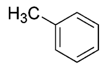
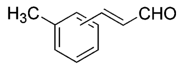
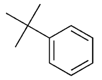
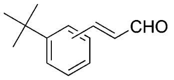
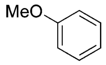
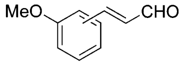
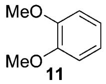
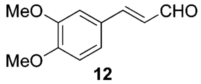
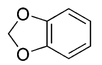
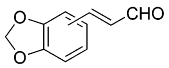
Figure 1 shows the time-dependence curves for the coupling products **3** and **4** in the reaction of **1** with **2**. Although **2** was immediately consumed when the reaction started, a short induction period was observed till the formation of coupling product **3**. The coupling product **3** was attained maximum after 1.5 h, and gradually decreased because of further coupling with **1**, leading to dicoupling product **4**. An independent reaction of **3** with **1** under these conditions produced **4** in fair yield (61%) (eq 2).



(2)

Table 2 shows the coupling reaction of **1** with **2** by the combination of $Pd(OAc)_2$ with several heteropoly acids (HPAs). The reaction by the combined catalyst of $Pd(OAc)_2$ with $H_5PMo_{10}V_2O_{40}\cdot 28H_2O$ gave **3** and **4** in 54% and 6% yield, respectively (run 2). The employment of $H_6PMo_9V_3O_{40}\cdot 30H_2O$ and $H_7PMo_8V_4O_{40}\cdot 28H_2O$ as HPMoV brought about a slight decrease of coupling products **3** and **4** (runs 3 and 4). However, vanadotungstphosphoric acid ($H_5PW_{10}V_2O_{40}\cdot 27H_2O$) did not catalyze the coupling reaction at all (run 5). $H_3PMo_{12}O_{40}\cdot 30H_2O$ not containing a vanadium atom was found to be less efficient than HPMoV (run 6).

TABLE 3. Oxidative Coupling of Substituted Benzenes (Ar−H) with 2 by the Pd(OAc)$_2$/H$_4$PMo$_{11}$VO$_{40}$·26H$_2$O/O$_2$ System[a]

Run	Ar-H	Method	Conv. / %	Products	(Yield / %)
1	 **5**	A	95	 **6**	59 (13:44:43)[b]
2	**5**	B	97	**6**	60 (14:41:45)[b]
3	 **7**	A	91	 **8**	54 (0:56:44)[b]
4	**7**	B	97	**8**	59 (0:54:46)[b]
5	 **9**	C	93	 **10**	45 (17:10:73)[b]
6	 **11**	C	>99	 **12**	47[c]
7	 **13**	C	>99	 **14a**, **14b**	45 (45:55)[d]

[a] Method A: The reaction was carried out by the same method as run 1 in Table 1. Method B: The reaction was carried out by the same method as run 9 in Table 1. Method C: The method is the same as method B, except using Ar−H (10 mmol) for 1 h. [b] Ratio of *ortho* to *meta* to *para* isomers. [c] 2,3-Dimethoxycinnamaldehyde was in 2% yield. [d] Ratio of 2,3-methylenedioxycinnamaldehyde (**14a**) to 3,4-methylenedioxycinnamaldehyde (**14b**).

On the basis of these results, several substituted benzenes were reacted with **2** under varying conditions (Table 3). The reaction of toluene (**5**) with **2** afforded a mixture of structural isomers **6** (*ortho*:*meta*:*para* = 13:44:43) in 59% yield along with small amounts of dicoupling products (run 1). An almost similar result was obtained when the reaction was carried out using AA in place of DBM (run 2). In the reaction with *tert*-butylbenzene (**7**), the *ortho* product was not detected because of its steric hindrance (runs 3 and 4). Anisole (**9**) coupled with **2** to give a mixture of the corresponding coupling products **10** (*ortho*:*meta*:*para* = 17:10:73) in 45% yield (run 5). The reaction of 1,2-dimethoxybenzene (**11**) with **2** proceeded in high regioselectivity to produce 3,4-dimethoxycinnamaldehyde (**12**) (47%), and the yield of 2,3-dimethoxycinnamaldehyde was found to be less than 2% (run 6). In contrast, the reaction of 1,2-methylenedioxybenzene (**13**) with **2** led to a 45:55 mixture of 2,3- and 3,4-methylenedioxycinnamaldehydes (**14a** and **14b**) in 45% yield (run 7).

The oxidative coupling of methacrolein (**15**) with **1** was examined (eq 3).

In this reaction, three isomeric coupling products consisting of **16a**, **16b**, and **16c** were obtained in 54% yield (**16a**:**16b**:**16c** = 65:6:29) and dicoupling product **17** was obtained in 7% yield. The formation of **16a**, **16b**, and **16c** can be rationally explained by reaction paths a and b, through phenylpalladium intermediate **II** formed by the insertion of phenylpalladium σ-complex **I** into **15** (Scheme 1).[7]

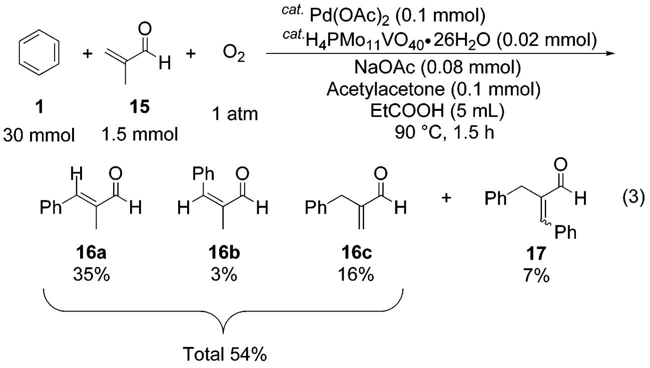
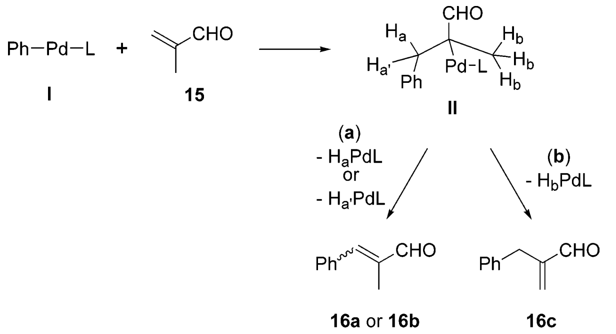


Table 4 shows the results of the oxidative coupling of substituted benzenes with **15**. In these reactions, monocoupling products were obtained as a mixture of structural isomers such as **16a**−**16c** along with small amounts of the corresponding dicoupling product **17** depicted in eq 3. The reaction of **15** with *tert*-butylbenzene (**7**) produced mainly four monocoupling products corresponding to **16** in 66% yield. Due to difficulty of the isolation of these products, the hydrogenation with H$_2$ (1 atm) catalyzed by Pd/C was performed. After the hydrogenation, *meta* and *para* products **18** were found to be formed (*meta*:*para* = 56:44) without formation of the *ortho* isomer (run 1). Similarly, the coupling reaction of **15** with cumene (**19**) followed by hydrogenation produced a regioisomeric mixture (*o*-**20**:*m*-**20**:*p*-**20** = 9:51:40) (run 2). *p*-Xylene (**21**) coupled with **15** to form a single coupling product which, after hydrogenation, produced **22** (run 3). In the reaction of anisole (**9**) with **15**, the corresponding monocoupling products consisting of *o*-**23**:*m*-**23**:*p*-**23** = 18:7:75 after the hydrogenation were obtained (run 4). 1,2-Methylenedioxybenzene (**13**) produced the corresponding monocoupling products which formed a 40:60 mixture of α-methyl-1,3-benzodioxole-4-propanal (**24a**) and α-methyl-1,3-benzodioxole-5-propanal (**24b**) by hydrogenation (run 5).

SCHEME 1



In conclusion, we have shown the first direct oxidative coupling of arenes with α,β-unsaturated aldehydes. Thus, the direct oxidative coupling of aromatic hydrocarbons with acrolein (**2**) could be performed by Pd(OAc)$_2$ combined with H$_4$PMo$_{11}$VO$_{40}$·26H$_2$O using dioxygen as the terminal oxidant to produce the corresponding coupling products in moderate yields. This synthetic method would

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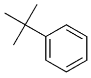
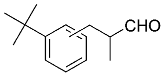
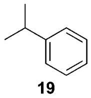
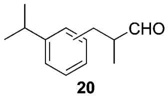
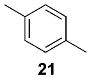
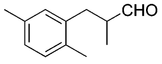
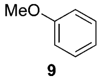
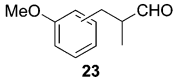
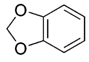
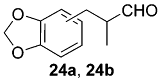
[7] Jia, C.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* **1999**, *1*, 2097.

TABLE 4. Oxidative Coupling of Substituted Benzenes with 15 by the $Pd(OAc)_2/H_4PMo_{11}VO_{40}\cdot 26H_2O/O_2$ System[a]

Run	Ar-H	Method	Conv. / %	Hydrogenated Product[b]	Yield / %[c]
1	 **7**	D	95	 **18**	66 (0:56:44)[d]
2	 **19**	D	88	 **20**	63 (9:51:40)[d]
3	 **21**	E	79	 **22**	52
4	 **9**	F	68	 **23**	46 (18:7:75)[d]
5	 **13**	G	72	 **24a**, **24b**	51 (40:60)[e]

[a] Method D: The reaction was carried out under the same conditions as eq 3. Method E: Ar−H (20 mmol), EtCOOH (4 mL), 3 h. Method F: Ar−H (10 mmol), EtCOOH (4 mL), 70 °C, 4 h. Method G: The method is the same as method F, except for 3 h. [b] The structure of the coupling products was identified after hydrogenation of the resulting mixture by H_2 (1 atm) on Pd/C. [c] The yields are given for regioisomeric mixtures of the monocoupling products corresponding to **16**. [d] Ratio of *ortho* to *meta* to *para* isomers. [e] Ratio of α-methyl-1,3-benzodioxole-4-propanal (**24a**) to α-methyl-1,3-benzodioxole-5-propanal (**24b**).

provide an alternative route to a variety of cinnamaldehyde derivatives.

Experimental Section

Procedure for Oxidative Coupling of 1 with 2. A solution of $Pd(OAc)_2$ (0.1 mmol), $H_4PMo_{11}V_1O_{40}\cdot 26H_2O$ (45.2 mg, ca. 0.02 mmol), Na_2CO_3 (0.05 mmol), dibenzoylmethane (0.1 mmol), **1** (30 mmol), and **2** (1.5 mmol) in propionic acid (5 mL) was placed in a round-bottom flask (30 mL) equipped with a balloon filled with O_2, and the mixture was allowed to react under stirring at 90 °C for 1.5 h. After the reaction, the reaction mixture was diluted with ethyl acetate and extracted with the saturated sodium hydrogen carbonate solution. The organic layer was dried over $MgSO_4$ and concentrated by using a rotary vacuum evaporator. The residue was purified by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 95:5) to give the oxidative coupling products. Yields were determined by GLC analysis using dodecane as internal standard. The products were characterized by ^1H and ^{13}C NMR, GC−MS, and GC−IR. The yield of cinnamic acid was determined by LC analysis.

A Typical Procedure for Oxidative Coupling of 7 with 15. A solution of $Pd(OAc)_2$ (0.1 mmol), $H_4PMo_{11}V_1O_{40}\cdot 26H_2O$ (45.2 mg, ca. 0.02 mmol), NaOAc (0.08 mmol), acetylacetone (0.1 mmol), **7** (30 mmol), and **15** (1.5 mmol) in propionic acid (5 mL) was placed in a round-bottom flask (30 mL) equipped with a balloon filled with O_2, and the mixture was allowed to react under stirring at 90 °C for 2 h. After the reaction, the reaction mixture was diluted with ethyl acetate and extracted with the saturated sodium hydrogen carbonate solution. The organic layer was dried over $MgSO_4$ and concentrated by using a rotary vacuum evaporator. The crude products was reacted under H_2 (1 atm) in the presence of 5 wt % Pd/C (50 mg) in ethyl acetate (10 mL) at 40 °C for 8 h. The products were isolated by flash chromatography on silica gel (*n*-hexane/ethyl acetate, 95:5).

The products **18** and **20** were converted into the corresponding carboxylic acids **18′** and **20′** during the isolation process. **4**,[8] **6**,[4] *p*-**8**,[9] **10**,[4] **12**,[10] **14**,[11] **16**,[12] **17**,[13] *m*-**18**,[14] **20**,[15] **22**,[16] **23**,[17] and **24a**[17] are known compounds and have been reported previously. **3**, *m*- and *p*-**10**, *p*-**18**, *p*-**18′**, *p*-**20**, *p*-**20′**, and **24b** are commercially available.

Data for α-methyl-1,3-benzodioxole-4-propanal (24a): light yellow liquid; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (d, J = 6.71 Hz, 3 H), 2.57−2.79 (m, 2H), 2.98−3.05 (m, 1 H), 5.91 (s, 2 H), 6.62−6.62 (m, 3 H), 9.70 (s, 1 H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 13.3, 30.5, 46.5, 100.5, 106.9, 120.2, 121.4, 123.0, 145.5, 146.9, 204.0; IR (GC−IR) 726, 836, 942, 1061, 1171, 1250, 1351, 1460, 1743, 2706, 2880, 2939, 2979; MS *m/z* 77, 135, 164, 192; HRMS (EI) *m/z* calcd for $C_{11}H_{12}O_3$ $[M]^+$ 192.0786, found 192.0797.

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Supporting Information Available: ^1H and ^{13}C NMR, IR, MS, and HRMS spectral data of **4**, **6**, **8**, **12**, **14**, **16**, **17**, **18**, **18′**, **20**, **20′**, **22**, **23**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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