JOC Article

Unexpected Pd-Catalyzed Coupling, Propargyl−Allenyl Isomerization and Alder−Ene Reaction: Facile Synthesis of Some Not Readily Available 2,3-Dihydrofuran Derivatives

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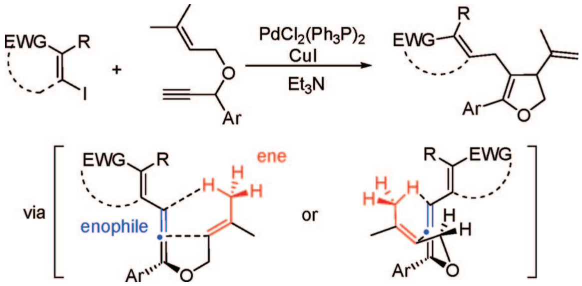

An interesting sequential reaction involving Pd-catalyzed coupling, propargyl−allenyl isomerization, and Alder−ene cycloaddition is reported, providing a facile synthesis of some not readily available 2,3-dihydrofurans from electron-deficient vinyl or aromatic halides and 1-aryl-prop-2-ynyl 3′-methylbut-2′-enyl ethers.

Introduction

The synthesis of various cyclic compounds by efficient formation of carbon−carbon bonds is a highly desired activity in organic synthesis.[1] Sequential reaction represents one of the most powerful tools for the rapid construction of complex molecular skeletons via a process that often features multibonds and stereocenters formed in a single stroke with high efficiency.[2,3] Müller et al. have pioneered Sonogashira coupling−isomerization sequential reactions for the synthesis of a variety of useful compounds including chalcones, pyrazolines, pyrroles, fluorescent spirocycles, and some other pharmaceutically interesting heterocycles.[4] Previously, we also developed a useful palladium-catalyzed sequential reaction utilizing an intramolecular [4 + 2] cyclization involving an allene intermediate as a key step, providing a facile and stereoselective synthesis of structurally complex polycyclic scaffolds,[5a] and very recently an efficient method to produce a variety of structurally diverse dihydroisobenzofuran derivatives based on this line was reported

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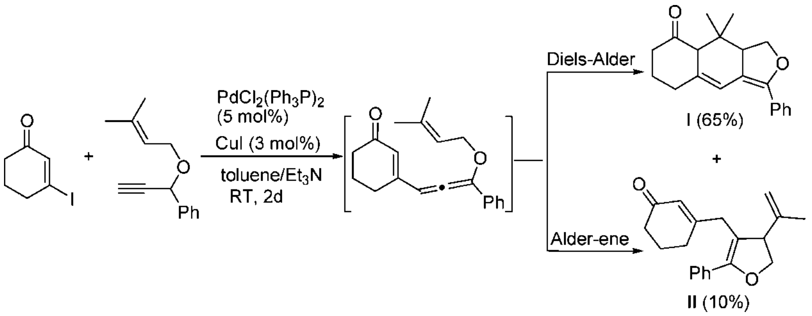
10.1021/jo900440u CCC: $40.75

SCHEME 1



SCHEME 2

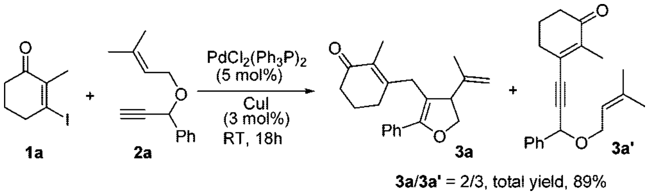
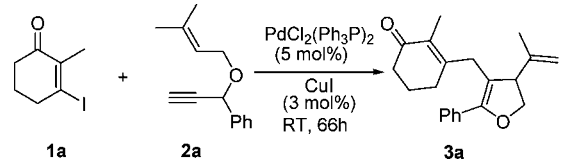


TABLE 1. Solvent and Base Effects on the Pd-Catalyzed Coupling, Propargyl−Allenyl Isomerization, and Alder−Ene Reaction

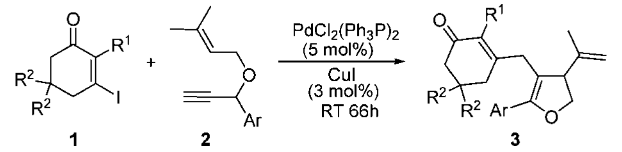


entry	solvent	base[a]	yield of **3a**[b]
1	toluene	Et_3N	79
2	THF	Et_3N	76
3	MeCN	Et_3N	75
4	toluene	Et_2NH	*c*
5	toluene	pyrrolidine	*c*
6	toluene	*i*-Pr_2NH	*c*

[a] Reactions were carried out using **1a** (0.25 mmol), **2a** (0.3 mmol), 5 mol % [PdCl$_2$(PPh$_3$)$_2$], and 3 mol % of CuI in 1.8 mL of solvent and 0.6 mL of amine at room temperature. [b] Isolated yields. [c] No identified product was obtained.

as well.[5b] During the course of our systematic investigation on the scope of these reactions, it was surprising but also interesting to observe that the reaction of 3-iodocyclohex-2-enone and 1-phenylprop-2-ynyl 3′-methylbut-2′-enyl ether led to a mixture of Diels−Alder-type product **I** in 65% yield together with **II** in 10% yield (Scheme 1).[5a] The formation of 2,3-dihydrofuran **II** was presumed to be a result of the competitive Alder−ene reaction of the in situ generated allene intermediate. This reaction would be an alternative way to access some structurally interesting 2,3-dihydrofurans and may be useful as dihydrofuran is a very important unit in many potentially useful natural products. [6,7] As a matter of fact, further investigation demonstrated that this pathway could preferentially occur by delicately tuning the substrates. In this paper, we wish to report our results on this cascade Pd-catalyzed coupling, propargyl−allenyl isomerization, and Alder−ene reaction, leading to some not readily available 2,3-dihydrofuran derivatives.

TABLE 2. Pd-Catalyzed Coupling, Propargyl−Allenyl Isomerization, and Alder−Ene Reaction To Yield 2,3-Dihydrofurans 3[a]



entry	**1** (R^1, R^2)	**2** (Ar)	**3**, yield[b] (%)
1	**1a** (CH_3, H)	**2a** (Ph)	**3a**, 79
2	**1a**	**2b** (*p*-$CH_3C_6H_4$)	**3b**, 75
3[c]	**1a**	**2c** (*p*-ClC_6H_4)	**3c**, 77
4	**1a**	**2d** (*m*-BrC_6H_4)	**3d**, 80
5	**1a**	**2e** (*p*-FC_6H_4)	**3e**, 83
6	**1b** (allyl, H)	**2a**	**3f**, 79
7	**1b**	**2b**	**3g**, 78
8	**1b**	**2c**	**3h**, 80
9	**1b**	**2e**	**3i**, 83
10	**1c** (3-methylbut-2-enyl, CH_3)	**2b**	**3j**, 65[c]
11	**1c**	**2e**	**3k**,63[c]

[a] Unless otherwise noted, the reaction was carried out using **1** (0.25 mmol) and **2** (0.3 mmol) in the presence of 5 mol % PdCl$_2$(PPh$_3$)$_2$ and 3 mol % of CuI in 1.8 mL of toluene and 0.6 mL of Et$_3$N at room temperature. [b] Isolated yields. [c] Unidentified byproducts observed.

Results and Discussion

When our efforts turned to the reaction of 3-iodo-2-methylcyclohex-2-enone **1a** and 1-phenylprop-2-ynyl 3′-methylbut-2′-enyl ether **2a** in the presence of a catalytic amount of Pd(PPh$_3$)$_2$Cl$_2$ and CuI at room temperature for 18 h in toluene,[8] we found that the reaction gave an inseparable mixture of the ene-type product **3a** together with the Sonogashira coupling product **3a′**, and no Diels−Alder product was formed (Scheme 2). Prolonging the reaction time to 66 h ultimately led to the full conversion of **3a′** into the final product **3a**, which was determined by ^{1}HNMR analysis of the crude product (Table 1, entry 1). The reaction could be carried out in solvents such as THF and MeCN with good yields (Table 1, entries 2 and 3). However, the reaction was very sensitive to the amine bases

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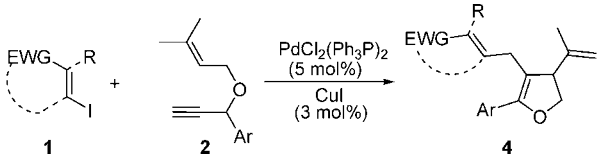
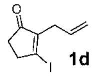
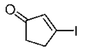
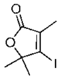
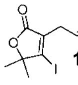
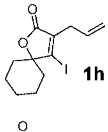
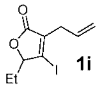
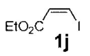
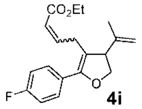
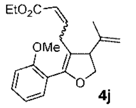
TABLE 3. Pd-Catalyzed Coupling, Propargyl−Allenyl Isomerization, and Alder−Ene Reaction To Yield 2,3-Dihydrofurans 4[a]

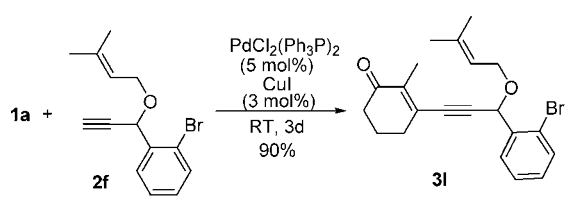


Entry	1	2	4	Time (h)	Yield[b] (%)
1	 **1d**	**2e**	**4a**	66	81
2[c]	 **1e**	**2a**	**4b**	48	63
3[c]	**1e**	**2c**	**4c**	48	65
4	 **1f**	**2a**	**4d**	66	78
5	 **1g**	**2a**	**4e**	66	76
6	**1g**	**2e**	**4f**	66	79
7	 **1h**	**2a**	**4g**	66	80
8	 **1i**	**2a**	**4h**	66	75[d]
9	 **1j**	**2e**	 **4i** (Z: E = 22: 78)[e]	96	65
10	**1j**	**2g**	 **4j** (Z: E = 29:71)[e]	18	39[f]

[a] Unless otherwise noted, the reaction was carried out using **1** (0.25 mmol) and **2** (0.3 mmol) in the presence of 5 mol % $PdCl_2(PPh_3)_2$ and 3 mol % of CuI in 1.8 mL of toluene and 0.6 mL of Et_3N at room temperature. [b] Isolated yields. [c] Small amount of Diels−Alder product was observed. [d] Obtained as diastereoisomers. [e] Ratio of *Z*/*E* isomers was deduced from ^{1}H NMR analysis; see Supporting Information. [f] Reaction was carried out at 100 °C.

employed. Diethylamine, pyrrolidine, and diisopropylamine, which are frequently employed in Sonogashira coupling reactions, were found to be incompatible in this reaction (Table 1, entries 4−6).

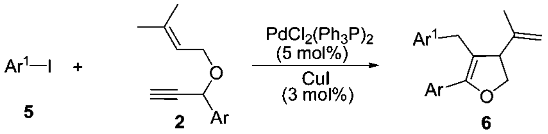
Under the established conditions, we examined the scope of the reaction. As indicated in Table 2, a variety of propargyl allyl ethers **2** could be applied to produce the corresponding products in good yields. Ar could be a *meta*- or *para*-substituted phenyl group either with an electron-donating or electron-withdrawing group incorporated. The presence of a substituent on the *ortho* position of the benzene ring of the propargyl allyl ether affected the reaction negatively. For example, when Ar = *o*-BrC_6H_4, the reaction failed to afford the expected product and only the coupled product **3l** was isolated (eq 1). When an allyl group was introduced to the 2-position of the 3-iodocyclohex-2-enone, i.e., **1b**, **1c**, the reaction proceeded smoothly to afford the expected products (Table 2, entries 6−11).

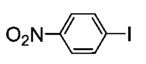
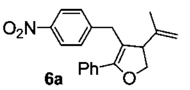
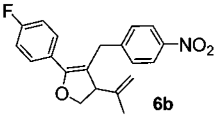
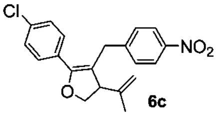
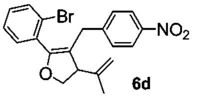
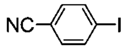
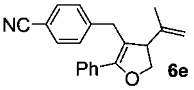
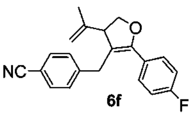
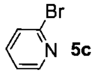
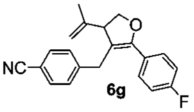
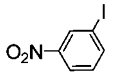
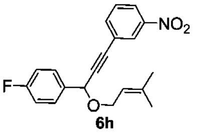


(1)

With these encouraging results, we further investigated the reaction scope by employing a variety of other electron-

TABLE 4. **Pd-Catalyzed Coupling, Propargyl−Allenyl Isomerization, and Alder−Ene Reaction To Yield 2,3-Dihydrofurans 6**[a]



Entry	5	2	6	Time (h)	Yield[b] (%)
1	 **5a**	**2a**	 **6a**	76	61
2	**5a**	**2e**	 **6b**	76	65
3	**5a**	**2c**	 **6c**	76	61
4[c]	**5a**	**2f**	 **6d**	72	51
5[c]	 **5b**	**2a**	 **6e**	48	69
6[c]	**5b**	**2e**	 **6f**	48	71
7	 **5c**	**2e**	 **6g**	76	48
8	 **5d**	**2e**	 **6h**	72	91

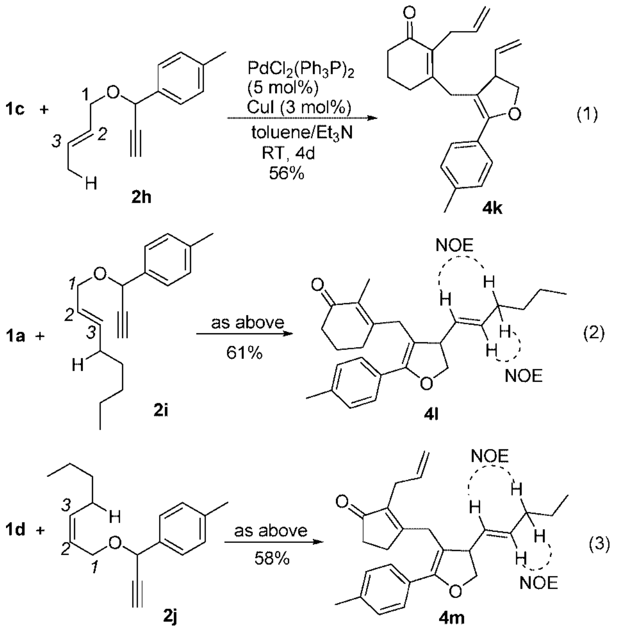
[a] Unless otherwise noted, the reaction was carried out using **5** (0.25 mmol) and **2** (0.3 mmol) in the presence of 5 mol % $PdCl_2(PPh_3)_2$ and 3 mol % of CuI in 1.8 mL of THF and 0.6 mL of Et_3N at 40 °C. [b] Isolated yields. [c] Reaction was carried out in toluene at 80 °C.

deficient vinyl iodides (Table 3). The reaction proceeded smoothly at room temperature to afford the corresponding 2,3-dihydrofuran **4a** in good yields when 2-allyl-3-iodocyclopent-2-enone **1d** was employed (Table 3, entry 1). Similar results were observed for 2-substituted 3-iodobutenolides **1f**, **1g**, **1h**, and **1i** (Table 3, entries 4−8). When (*Z*)-ethyl 3-iodoacrylate **1j** was employed to react with 1-aryl-prop-2-ynyl 3′-methylbut-2′-enyl ethers **2e** and **2g**, respectively, however, we obtained the products **4i** and **4j** both as a mixture of the *Z*/*E* isomers (Table 3, entries 9 and 10). The isomerization of the double bonds may be explained by the possibility that the resulted **Z-4i** and **Z-4j** are quite instable and easily transform to their *E*-isomers as a result of the intramolecular steric repulsive effect between the ester group and the dihydrofuran moiety. In addition, it is also interesting to find that the reaction preferentially produced the Alder−ene products **4b** and **4c**[9] in 63% and 65% yields, respectively, when 3-iodocyclopent-2-enone was employed (Table 3, entries 2 and 3).[10]

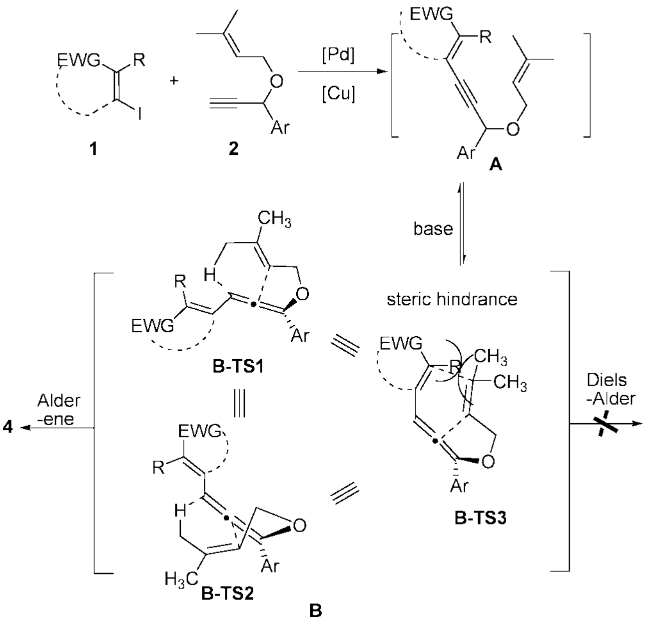
Furthermore, this sequential reaction also could be extended to electron-deficient aromatic or heteroaromatic halides including 1-iodo-4-nitrobenzene **5a**, 4-iodobenzonitrile **5b**, and 2-bromopyridine **5c**, producing the corresponding 2,3-dihydrofuran derivatives in moderate to good yields (Table 4, entries 1−7).

When only a single methyl or long-chain alkyl group such as *n*-pentyl was introduced at the 3-position of the alkene moiety of the propargyl allyl ether, i.e., **2h** or **2i**, the corresponding product **4k** or **4l** was also formed, implying that the subsequent

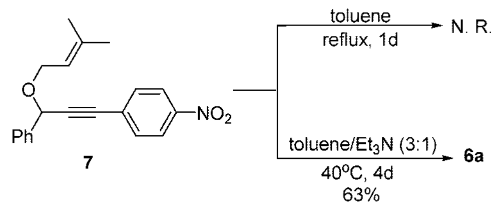
SCHEME 3



SCHEME 4. Proposed Mechanism for the Reaction



SCHEME 5



Alder–ene reaction is still favored even with only one alkyl group bearing hydrogens to be shifted (Scheme 3, eqs 1 and 2). Further experiments demonstrate that the reaction proceeded smoothly as well to furnish the desired 2,3-dihydrofuran **4m** for 2-allyl-3-iodocyclopent-2-enone **1d** and ether **2j** in which the *n*-butyl group was introduced at the 3-position of the alkene moiety in a *cis*-fashion (Scheme 3, eq 3). The structures of these compounds were determined by spectroscopic analysis, and the stereochemistry of **4l** and **4m** was further established by the NOESY analysis.

As depicted in Scheme 4, this reaction can be rationalized by a consecutive process involving a Pd-catalyzed coupling reaction between the electron-deficient vinyl or aromatic iodide and the propargyl allyl ether to produce the enyne intermediate **A**, base-promoted propargyl–allenyl isomerization to give the ene-allene intermediate **B**,[11] and the final Alder–ene cyclization to afford the 2,3-dihydrofuran derivatives via two possible transition states **B-TS1** (typically for the formation of **4k** and **4l**) and **B-TS2** (typically for **4m**). Accordingly, the following should be noted: (1) The formation of the allene intermediate is crucial for the subsequent Alder–ene reaction since controlled experiments show that the treatment of the enyne **7** in the presence of excessive triethyl amine at 40 °C for 4 d ultimately gave **6a** in 63% yield, but direct heating of **7** even under reflux for 24 h in toluene did not result in any product **6a** (Scheme 5). (2) The reason that the ene-allene intermediate **B** favors an Alder–ene reaction to conclude the sequence rather than an intramolecular Diels–Alder reaction may be attributed to the steric repulsive interaction in the transition state **B-TS3** for the [4 + 2] cycloaddition, which makes this pathway disfavored (Scheme 4). (3) The Alder–ene reactions of ene-allenes and yne-allenes remain understudied, and only limited examples either employing high temperature[12] or with the assistance of transition metal complexes[13] have been reported. Therefore, our observation on this mild reaction may be of considerable interest.

Conclusion

In conclusion, we have disclosed an interesting sequential reaction in which the in situ generated ene-allene intermediates could proceed via an Alder–ene reaction under very mild conditions to produce some not readily available 2,3-dihydrofuran derivatives. As demonstrated, a variety of electron-deficient vinyl or aromatic halides and 1-aryl-prop-2-ynyl allyl ethers can be employed in this reaction. We proposed a plausible mechanism involving two possible transition states for the final Alder–ene cyclization to rationalize the obtained results. It should be noted that the in situ generated ene-allene intermediate favors an Alder–ene reaction to conclude the sequence rather than the Diels–Alder reaction probably as a result of the steric hindrance of the transition state for the [4 + 2] cycloaddition. Further efforts in this area are currently underway.

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(9) X-ray crystal data for compound **4c**: $C_{19}H_{19}ClO_2$; MW = 314.79; orthorhombic, space group *Fdd*2; $a = 31.869(5)$, $b = 36.630(6)$, $c = 5.7018(10)$ Å; $\alpha = 90.00°$, $\beta = 90.00°$, $\mu = 90.00°$, $V = 6656(2)$ Å^3, $T = 293$ (2) K, $Z = 16$, $\rho_{\text{calcd}} = 1.257$ Mg/m^3, $\mu = 0.234$ mm^{-1}, $\mu = 0.71073$ Å; F(000) 2656, independent reflections ($R_{\text{int}} = 0.1093$), 9507 reflections collected; refinement method, full-matrix least-squares refinement on F2; goodness-of-fit on $F_2 = 0.822$; final *R* indices [$I > 2\sigma(I)$] $R_1 = 0.0523$, $wR_2 = 0.1136$.

(10) For the reaction of 3-iodocyclohex-2-enone and **2a**, see Scheme 1.

(11) For review on *O*-substituted allenes, see: Krause, N.; Hashmi, A. S. K. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, Germany, 2004; Vol. 1, Chapters 1 and 8.

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Experimental Section

Typical Procedure for the Synthesis of 2,3-Dihydrofurans. An oven-dried Schlenk tube containing a Teflon-coated stir bar was charged with $PdCl_2(PPh_3)_2$ (8.5 mg, 5 mol %), CuI (1.5 mg, 3 mol %), and 3-iodocyclohex-2-enone **1a** (59 mg, 0.25 mmol). The Schlenk tube was sealed and then evacuated and backfilled with N_2 (3 cycles). A solution of propargyl allyl ether **2a** (60 mg, 0.3 mmol) in 1.8 mL of toluene and 0.6 mL of Et_3N was subsequently injected to the Schlenk tube. The reaction mixture was stirred at rt for 66 h. After the reaction was completed (monitored by TLC), the mixture was quenched with diluted HCl and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and removal of the solvent in vacuo, the residues were purified with flash chromatography (silica, petroleum ether/ethyl acetate 8:1 v/v) to afford **3a** (61 mg, 79%). ^{1}H NMR (400M, $CDCl_3$): δ 7.50 (d, $J = 8.0$ Hz, 2H), 7.40−7.36 (m, 3H), 4.85 (s, 1H), 4.78 (s, 1H), 4.47−4.42 (m, 1H), 4.24−4.20 (m, 1H), 3.49−3.45 (m, 1H), 3.29 (d, $J = 15.6$ Hz, 1H), 3.13 (d, $J = 15.6$ Hz, 1H), 2.40−2.31 (m, 3H), 2.21−2.16 (m, 1H), 1.90−1.85 (m, 2H), 1.75 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100M, $CDCl_3$): δ 199.7, 156.7, 152.4, 144.9, 131.9, 131.2, 128.6, 128.3, 127.5, 112.9, 107.9, 72.6, 54.4, 37.8, 30.7, 30.0, 22.4, 18.5, 11.0. IR (neat): 2937, 1661, 1445, 1377, 1354, 1068. EIMS *m*/*z* (%): 308 (M^+, 35), 186 (70), 105 (100). HRMS: calcd for $C_{21}H_{24}O_2$, 308.1776; found, 308.1773.

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Supporting Information Available: General experimental procedures; spectroscopic data for **3a**−**3l**, **4a**−**4m**, **6a**−**6h**, and **7**; crystallographic characterization data of **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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