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Synthesis of 2-Arylcycloalka-2,4-dienones Using Sulfone-Based Methodology

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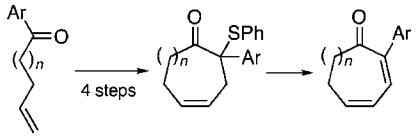


Addition of the anion derived from (phenylthiomethyl)phenyl sulfone to a selection of aryl ω-alkenyl ketones gives adducts that via a sequence of Lewis acid catalyzed rearrangement, α-allylation, and metathesis give rise to 2-thio-4-cycloalkenones. These in turn give cycloalkadienones upon oxidation and elimination. An attempt to develop a polymer-supported variant fails because of the reversibility of sulfone anion addition.

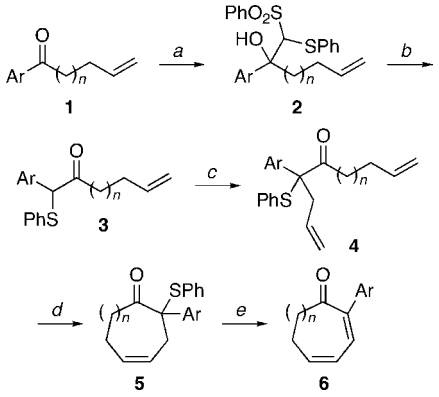
We have an ongoing interest in the adaptation of diverse synthetic methodologies to the solid state, including but not limited to rearrangement and cycloaddition chemistry, and with an emphasis on organometallic methodologies. Herein, we report the preparation of a small library of 2-arylcycloalka-2,4-dienone derivatives, using substrates derived from (phenylthiomethyl)-phenyl sulfone, which provides the potential for both convenient polymer linkage as well as Lewis acid promoted rearrangement chemistry (Scheme 1).

To obtain the necessary aryl ω-alkenyl ketones (**1a**−**g**), a selection of 3-aryl-3-ketoesters was prepared in ≥95% yields by Claisen condensations between diethyl carbonate and several substituted acetophenones.[1] Alkylation[2] and decarboxylation[3] gave ketones **1a**−**g** (Table 1).

We prepared (bromomethyl)phenyl sulfone from dibromomethane and sodium benzenesulfinate in refluxing DMF[4] and converted the sulfone into [(phenylthio)methyl]phenyl sulfone by treatment with sodium thiophenoxide in DMF.[5] Addition of the anion of [(phenylthio)methyl]phenyl sulfone anion to each of the ketones **1a**−**g** under Et_2AlCl catalysis gave the corresponding 1-(benzenesulfonyl)-2-aryl-1-(phenylthio)alken-2-ols **2a**−**g**.[6]

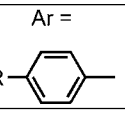
Each of these alcohols consisted, by ^1H NMR analysis, of a mixture of diastereomers, one of which in each case was a solid that was purified by recrystallization, while the other was either

SCHEME 1. Solution-Phase Synthesis of 2-Arylcycloalka-2,4-dienones 6[a]



[a] Reagents and conditions: (a) $PhSO_2CH(Li)SPh$, Et_2AlCl, THF, −78 °C, 4 h; (b) Et_2AlCl, CH_2Cl_2, hexane, various conditions; (c) LiOEt, EtOH, THF, 0 °C, 20 min, then $CH_2{=}CHCH_2Br$, 75 °C, 1 h; (d) $(CyP)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 70 °C, 48 h; (e) *m*-CPBA, CH_2Cl_2, −78 °C, 15 min, then CCl_4 60 °C, 18 h.

TABLE 1. Yields (%) of Intermediates and Final Products[a]

Ar = 	**1**	**2**	**3**	**4**	**5**	**6**
a, R = H, *n* = 1	78	65	55	83	42 (68)	87
b, R = Cl, *n* = 1	75	72	57	77	87	86
c, R = Br, *n* = 1	60	84	47	79	76	55 (67)
d, R = CH_3, *n* = 1	67	98	71	80	63 (74)	85
e, R = OCH_3, *n* = 1	72	92	81	88	69 (77)	67 (96)
f, R = H, *n* = 2	77	95	99	92	65 (85)	96
g, R = H, *n* = 3	77	99	84	95	<1	—

[a] Yields in parentheses are based upon recovered starting material (oxidized in the cases of **6c** and **6e**).

(1) (a) Nakano, J.; Katagiri, N.; Kato, T. *Chem. Pharm. Bull.* **1982**, *30*, 2590. (b) Iinuma, M.; Tanaka, T.; Hamada, K.; Mizuno, M.; Asai, F. *Chem. Pharm. Bull.* **1987**, *35*, 3909.

(2) (a) Queignec, R.; Kirschleger, B.; Lambert, F.; Aboutaj, M. *Synth. Commun.* **1988**, *18*, 1213. (b) Wang, E. S.; Choy, Y. M.; Wong, H. N. C. *Tetrahedron* **1996**, *52*, 12137. (c) Saint-Dizier, A. C.; Kilburn, J. D. *Tetrahedron Lett.* **2002**, *43*, 6201.

(3) (a) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *12*, 957. (b) Liotta, C. L.; Cook, F. L. *Tetrahedron Lett.* **1974**, *15*, 1095. (c) Krapcho, A. P.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Short, F. W. *Tetrahedron Lett.* **1974**, *15*, 1091. (d) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138. (e) Krapcho, A. P. *Synthesis* **1982**, *10*, 805, 893.

(4) (a) Makosza, M.; Golinski, J. *J. Org. Chem.* **1984**, *49*, 1488. (b) Bordwell, F. G.; Clemens, A. H.; Smith, D. E.; Begemann, J. *J. Org. Chem.* **1985**, *50*, 1151.

(5) (a) Bordwell, F. G.; Jarvis, B. B. *J. Org. Chem.* **1968**, *33*, 1182. (b) Langler, R. F.; Pincock, J. A. *Can. J. Chem.* **1977**, *55*, 2316. (c) Kay, D. G.; Langler, R. F.; Trenholm, J. E. *Can. J. Chem.* **1979**, *57*, 2185. (d) Durkin, K. A.; Langler, R. F.; Morrison, N. A. *Can. J. Chem.* **1988**, *66*, 3070.

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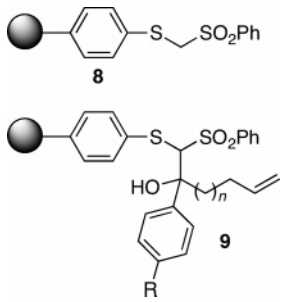
a solid or an oil that was isolated chromatographically. In the course of purifying **2a** we realized that these compounds slowly underwent retro-aldol-like reversion to the starting materials. Thus, complete separation and purification of each of the two diastereomers was not achieved in any of the cases. Nonetheless, good to excellent combined yields of diastereomers were obtained, especially in the cases of compounds **2c**−**g**, whose syntheses benefited from our prior experiences optimizing the procedure.

Treatment of the each of the isolated 1-(benzenesulfonyl)-2-aryl-1-(phenylthio)alken-2-ols **2a**−**g** with Et_2AlCl induced rearrangement to the corresponding 1-aryl-1-(phenylthio)alken-2-ones (**3a**−**g**)[6,7] in variable yields. We found that each case, although based upon Trost's general procedure, had to be individually optimized. The ketones **3a**−**g** were then regioselectively alkylated[8] with allyl bromide to give 4-aryl-4-(phenylthio)alkadien-5-ones **4a**−**g** in good to excellent yields. Finally, each of the alkylated ketones **4a**−**g** was treated with Grubbs' I catalyst for ring closing metathesis[9] to give the corresponding 2-aryl-2-(phenylthio)cycloalk-4-enone (**5a**−**g**). In a typical procedure, 10 mol % of catalyst solution was added to a 2−3 μM solution of ketone in CH_2Cl_2. After stirring at 50 °C for 24 h, another 10 mol % of catalyst solution was added and the cyclization allowed to proceed for another 24 h. Generation of the seven- and eight-membered ring enones (**5a**−**f**) proceeded satisfactorily. However, the synthesis of the nine-membered 2-phenyl-2-(phenylthio)cyclonon-4-enone (**5g**) gave only trace amounts under the same conditions. Using higher concentrations of substrate, higher molar ratios of catalyst, higher refluxing temperatures, and even microwave radiation failed to improve this result.

Oxidation of cycloalkenones **5a**−**f** with *m*-CPBA in dichloromethane at −78 °C gave the corresponding sulfoxides,[10] which were dehydrosulfenylated by reflux in CCl_4 overnight to give the final products, 2-arylcycloalka-2,4-dienones (**6a**−**f**), in good to excellent yields. The fully conjugated cycloalka-2,4-dienones **6a**−**f** display three ^{1}H NMR signals with an integration of one proton each at ca. δ 6.6−6.7 (H_2, d), at δ 6.1−6.2 (H_3, dt), and at δ 6.4−6.5 (H_4, ddt). NMR indicated that some of these dienones (**6b** and **6d** in particular) contained the deconjugated 2-arylcyclohepta-2,5-dienones, but in quantities too small to be isolated or purified.[11]

These solution-phase syntheses demonstrated gratifying versatility and diversity. We therefore attempted their adaptation to the solid phase. Following Fréchet's protocol,[12] we derivatized polystyrene/2% divinylbenzene beads with arylthiol functionality at a loading of 1.65 mmol/g.[13] Deprotonation to the arylthiolate and addition of (bromomethyl)phenyl sulfone gave the solid-supported [(arylthio)methyl]phenyl sulfone resin **8** (IR 1326 and 1151 cm^{-1}).[14,15] Unfortunately, deprotonation of this resin-bound sulfone followed by addition of excess aryl alkenyl ketone fails to produce polymer-bound alcohol **9**, no doubt a consequence of the reversibility of the latter process.



In conclusion, the use of [(phenylthio)methyl]phenyl sulfone has shown versatility in short solution-phase syntheses of several seven- and eight-membered 2-arylcycloalka-2,4-dienones. Adaptation to the solid phase was not successful.

Experimental Section

Representative Procedure:[6] 1-(Benzenesulfonyl)-2-(4-methoxyphenyl)-1-(phenylsulfanyl)hex-5-en-2-ol (2e). A hexane solution of *n*-BuLi (2.5 M, 24.0 mL, 60.0 mmol) was added dropwise to a solution of [(phenylsulfanyl)methyl]phenyl sulfone (14.2 g, 53.6 mmol) in THF (400 mL) at −78 °C. The mixture turned yellowish in color and was stirred for 30 min, whereupon a hexane solution of diethylaluminum chloride solution in hexane (1.0 M, 80.0 mL, 80.0 mmol) was added by syringe. After 5 min, a solution of 10.2 g of 1-(4-methoxyphenyl)pent-4-en-1-one[16] (**1e**) (53.6 mmol) in THF (50 mL) was added dropwise. After being stirred overnight at −78 °C, the reaction was quenched with 150 mL of

(6) (a) Breslow, R.; Mohacsi, E. *J. Am. Chem. Soc.* **1962**, *84*, 684. (b) Tanaka, K.; Matsui, S.; Kaji, A. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 3619. (c) Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1984**, *106*, 7260. (d) Trost, B. M.; Mikhail, G. K. *J. Am. Chem. Soc*. **1987**, *109*, 4124. (e) Nantz, M. H.; Radisson, X.; Fuchs, P. L. *Synth. Commun.* **1987**, *17*, 55. (f) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107. (g) Hewkin, C. T.; Jackson, R. F. W.; Clegg, W. *Tetrahedron Lett.* **1988**, *29*, 4889. (h) Bruckner, R.; Peiseler, B. *Tetrahedron Lett.* **1988**, 29, 5233. (i) Azadi-Ardakani, M.; Loftus, C. G.; Mjalli, A. M. M.; Newton, R. F.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 1709. (j) Hewkin, C. T.; Jackson, R. F. W.; Clegg, W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3091. (k) Montana, J. G.; Phillipson, N.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1994**, 2289. (l) Finch, H.; Mjalli, A. M. M.; Montana, J. G.; Roberts, S. M.; Taylor, R. J. K. *Tetrahedron* **1996**, *40*, 4925. (m) Toyooka, N.; Okumura, M.; Takahata, H. *J. Org. Chem*. **1999**, *64*, 2182.

(7) Phillipson, N.; Anson, M. S.; Montana, J. G.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2821.

(8) (a) Ozaki, Y.; Mochida, K.; Kim, S.-W. *J. Chem. Soc., Perkin Trans I* **1989**, 1219. (b) Imanishi, T.; Hirokawa, Y.; Yamashita, M.; Tanaka, T.; Miyashita, K.; Iwata, C. *Chem. Pharm. Bull.* **1993**, *41*, 31. (c) Kunz, U.; Krimm, S.; Fischer, T.; Kottke, T.; Stalke, D.; Christl, M. *Eur. J. Org. Chem*. **1998**, 2171. (d) Edwards, G. L.; Sinclair, D. J. *Tetrahedron Lett.* **1999**, *40*, 3933.

(9) (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606. (b) Schuster, M.; Pernerstorfer, J.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1979. (c) Dias, E. L.; Nguyen, S.-B. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887. (d) Peters, J.-U.; Blechert, S. *Synlett* **1997**, 348. (e) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (f) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (g) Sasaki, M.; Noguchi, T.; Tachibana, K. *J. Org. Chem*. **2002**, *67*, 3301.

(10) (a) Nozoe, T.; Mukai, T.; Tezuka, T. *Bull. Chem. Soc. Jpn*. **1961**, *34*, 619. (b) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840. (c) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc*. **1976**, *98*, 4887. (d) Trost, B. M. *Chem. Rev.* **1978**, *78*, 363. (e) Tamura, Y.; Maeda, H.; Choi, H. D.; Ishibashi, H. *Synthesis* **1982**, 56. (f) Katritzky, A. R.; Saczewski, F.; Marson, C. M. *J. Org. Chem.* **1985**, *50*, 1351. (g) Brown, R. F. C.; Coulston, K. J.; Eastwood, F. W.; Fallon, G. D. *Aust. J. Chem.* **1986**, *39*, 189. (h) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q.; Kim, S.; Kessabi, J. *Org. Lett.* **1999**, *1*, 807.

(11) Lew, C. S. Q.; Capon, B. *J. Org. Chem.* **1997**, *62*, 5344.

(12) (a) Farral, M. J.; Frechet, J. M. J. *J. Org. Chem.* **1976**, *41*, 3877. (b) De Smet, M. D.; Frechet, J. M. J.; Farral, M. J. *Polymer* **1979**, *20*, 675. (c) Frechet, J. M. J. *Tetrahedron* **1981**, *37*, 663. (d) Frechet, J. M. J.; Darling, G. D.; Itsuno, S.; Lu, P.-Z.; Vivas de Meftahi, M.; Rolls, W. A., Jr. *Pure. Appl. Chem.* **1988**, *60*, 353.

(13) Brown, H. C. *Organic Synthesis Via Boranes*; John Wiley and Sons: New York, 1975; p 258.

(14) De Smet, M. D.; Frechet, J. M. J.; Farral, M. J. *J. Org. Chem*. **1979**, *44*, 1774.

(15) Cheng, W.-C.; Lin, C.-C.; Kurth, M. J. *Tetrahedron Lett.* **2002**, *43*, 2967.

(16) (a) Marvell, E. N.; Li, T. H.-C. *J. Am. Chem. Soc.* **1978**, *100*, 883. (b) Kozikowski, A. P.; Ames, A. *Tetrahedron* **1985**, *41*, 4821.

10% aq HCl solution at −78 °C and was allowed to warm to rt. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried ($MgSO_4$), and concentrated. Trituration using 10% CH_2Cl_2 in hexane gave 14.5 g of **2e** as a white solid. The supernatant was concentrated and chromatographed using 20% EtOAc in hexane solution to afford another 2.5 g of **2e**, 2.5 g of recovered **1e**, and 3.47 g of [(phenylsulfanyl)methyl]phenyl sulfone. The total isolated yield of **2e** was 17.0 g (70%); the yield based on unrecovered starting material was 92%. For the major diastereomer: mp 163−165 °C; IR 3505, 3065, 2954, 2833, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67−6.58 (m, 14H), 5.80 (m, 1H), 5.00−4.86 (m, 2H), 4.53 (s, 1H), 4.47 (s, 1H), 3.81 (s, 3H), 2.50 (m, 2H), 2.10 (m, 1H), 1.65 (m, 1H); MS IonSpec HiResMALDI calcd *m*/*z* for $C_{24}H_{26}O_4S_2Na$ ($(M + Na)^+$) 477.1170, found 477.1524. Anal. Calcd for $C_{25}H_{26}O_4S_2$: C, 66.05; H, 5.76. Found: C, 66.31; H, 5.83.

Representative Procedure:[6] 1-(4-Methoxyphenyl)-1-(phenylsulfanyl)hex-5-en-2-one (3e). At −78 °C, 11.0 mL of a 1.0 M solution of diethylaluminum chloride in hexane (11.0 mmol) was added to a solution of 5.0 g of **2e** (11.0 mmol) in dichloromethane (100 mL). After 5 min, TLC showed complete consumption of starting material, and the reaction was quenched with 50 mL of aq satd $NaHCO_3$. The mixture was filtered through Celite, washed with brine, dried ($MgSO_4$) and concentrated. Chromatography (10% EtOAc in hexane) gave 2.81 g (81%) of **3e**: IR 3070, 2904, 2837, 1716, 1644 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.31−6.83 (m, 9H), 5.67 (m, 1H), 4.95 (s, 1H), 4.94−4.88 (m, 2H), 3.78 (s, 3H), 2.66 (m, 2H), 2.24 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 204.7, 159.7, 136.9, 134.1, 132.6, 130.0, 129.1, 127.9, 127.6, 115.5, 114.5, 63.4, 55.5, 39.4, 28.0. Anal. Calcd for $C_{19}H_{20}O_2S$: C, 73.04; H, 6.45. Found: C, 72.78; H, 6.37.

Representative Procedure:[8] 4-(4-Methoxyphenyl)-4-(phenylsulfanyl)nona-1,8-dien-5-one (4e). To a mixture of EtOH (6.0 mL) and THF (15.0 mL) cooled to 0 °C was added 4.8 mL of 2.5 M *n*-BuLi in hexane (12.0 mmol). The LiOEt solution was stirred at 0 °C for 20 min, whereupon a solution of 0.66 g (2.11 mmol) of **3e** in THF (30 mL) was added dropwise. After stirring and warming to rt over 10 min, 2.90 mL (34.3 mmol) of allyl bromide was added dropwise and the mixture heated at 75−80 °C for 3 h. The reaction was quenched with water and extracted with EtOAc. The extracts were washed with brine, dried ($MgSO_4$), and concentrated. Column chromatography (1% Et_2O in hexane) gave 0.653 g (88%) of 4-(4-methoxyphenyl)-4-(phenylsulfanyl)nona-1,8-dien-5-one (**4e**) as a colorless oil: IR 3075, 2974, 2906, 2837, 1669, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−6.84 (m, 9H), 5.84−5.65 (m, 2H), 5.04−4.88 (m, 4H), 3.80 (s, 3H), 2.74 (m, 1H), 2.68−2.66 (d, J = 6.4 Hz, 2H), 2.40 (m, 1H), 2.31−2.25 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 206.0, 159.2, 137.5, 136.7, 133.6, 130.7, 130.6, 129.4, 128.9, 128.9, 118.4, 115.4, 114.1, 68.8, 55.5, 38.8, 37.6, 29.1. Anal. Calcd for $C_{22}H_{24}O_2S$: C, 74.96; H, 6.86. Found: C, 75.13; H, 6.87.

Representative Procedure:[9] Synthesis of 2-(4-Methoxyphenyl)-2-(phenylsulfanyl)cyclohept-4-enone (5e). To a solution of Grubbs' catalyst (35 mg, 0.04 mmol) in CH_2Cl_2 (140.0 mL) was added a solution of 150 mg (0.42 mmol) of **4e** in of CH_2Cl_2 (10 mL). The resulting red solution was refluxed at 60−70 °C for 24 h. Another 0.1 equivt of Grubbs' catalyst (35 mg, 0.04 mmol) dissolved in CH_2Cl_2 (10 mL) was added and reflux continued for another 24 h. After concentration, the resulting brown oil was purified by column chromatography, eluting with 10% Et_2O in hexane to furnish 94 mg (69% isolated yield; 77% based on the recovery of 15 mg of **4e**) as a white solid: mp 127.1−129.0 °C; IR 2958, 2836, 1707, 1603 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−6.77 (m, 9H), 5.69 (m, 2H), 3.80 (s, 3H), 2.95 (m, 1H), 2.83−2.73 (m, 3H), 2.28 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 207.3, 159.0, 136.9, 131.8, 131.0, 130.8, 129.6, 129.1, 128.6, 126.3, 113.6, 71.6, 55.4, 38.5, 33.6, 26.9. Anal. Calcd for $C_{20}H_{20}O_2S$: C, 74.04; H, 6.21. Found: C, 74.29; H, 6.21.

Representative Procedure:[10] Synthesis of 2-(4-Methoxyphenyl)cyclohepta-2,4-dienone (6e). A solution of 130 mg (0.40 mmol) of **5e** in CH_2Cl_2 (80 mL) was cooled to −78 °C, and a solution of 0.96 g of 71% *m*-chloroperoxybenzoic acid (4.0 mmol) in CH_2Cl_2 (10 mL) was added. TLC analysis (70:30 Et_2O−hexane) showed complete loss of the starting material after 15 min. The cold reaction mixture was poured into a separatory funnel containing Et_2O (100 mL) and 100 mL of 10% aq Na_2SO_3 solution. The organic layer was separated, washed 2x with satd aq $NaHCO_3$, dried ($MgSO_4$), and concentrated. The residue was added to CCl_4 (20 mL) and refluxed at 50−60 °C overnight to give 57 mg of **6e** (67% isolated yield; 96% based on the recovery of 46 mg of oxidized **5e**) as a faintly light green oil: IR 3003, 2958, 2837, 1658, 1604 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.27−7.24 (m, 2H), 6.89−6.86 (m, 2H), 6.70−6.69 (d, J = 7.6, 1H), 6.42−6.36 (dt, 1H, J = 10.8 Hz, 5.6 Hz), 6.16−6.11 (ddt, 1H, J = 10.8 Hz, 7.6 Hz, 1.2 Hz), 3.81 (s, 3H), 2.87−2.84 (m, 2H), 2.50−2.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 201.5, 159.4, 142.1, 138.5, 134.7, 132.0, 130.1, 126.5, 113.7, 55.5, 42.5, 23.8; MS (ESI) *m*/*z* calcd for ($M + H^+$) 215.11, found 215.08.

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Supporting Information Available: Spectroscopic and analytical data for all compounds; experimental procedures for all compounds and for polymer-supported experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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