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Phosphine-Catalyzed Cycloadditions of Allenic Ketones: New Substrates for Nucleophilic Catalysis

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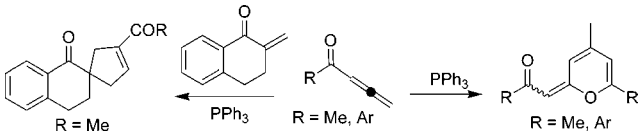
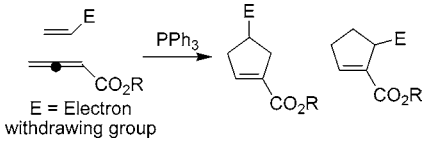


A range of phosphine-catalyzed cycloaddition reactions of allenic ketones have been studied, extending the scope of these processes from the more widely used 2,3-butadienoates to allow access to a number of synthetically useful products. Reaction of allenyl methyl ketone **4** with *exo*-enones afforded spirocyclic compounds in good regioselectivity and promising enantioselectivity via a [2 + 3] cycloaddtion. Aromatic allenyl ketones undergo a phosphine-promoted dimerization to afford functionalized pyrans, leading to a formal [2 + 4] Diels−Alder product, but did not react in the [2 + 3] cycloaddition. The results from other reactions that had found utility with 2,3-butadienoates are also reported.

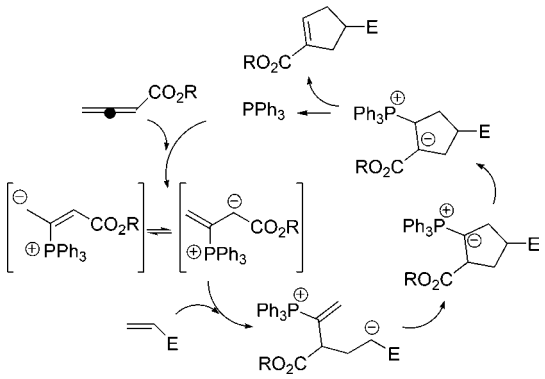
The phosphine-catalyzed [2 + 3] cycloaddition of electron deficient olefins with 2,3-butadienoate-derived 1,3-dipoles to give cyclopentenes was first reported by Lu in 1995 (Scheme 1).[1]

Since this disclosure, dipole additions to a range of electron-deficient double bonds have been realized,[2,3] and asymmetric versions employing chiral phosphines have also been successful.[4] The reaction is proposed to proceed via conjugate addition of the dipole resulting from reaction of the phosphine with the allene to the olefin, followed by ring closure, anion rearrangement, and elimination to regenerate the catalyst (Scheme 2). The major regioisomer can be rationalized as resulting from reaction at the more stable α-position of the initial dipole; however, steric constraints, for example, incorporation of a *β*-substituent on the enone,[4b] will favor *γ*-attack. For similar reasons, substitution at the α-position of the allene also led to preferential *γ*-attack during a [4 + 2] cyloaddition with tosylaldimines.[5] In a closely related reaction, exclusive *γ*-addition was seen on addition to an aldehyde, affording a [2 + 2 + 2] adduct.[6]

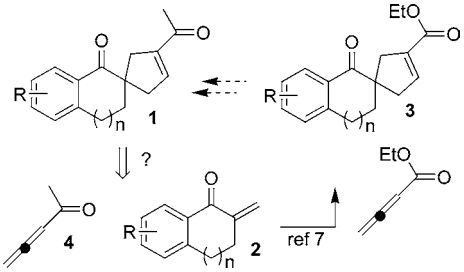
SCHEME 1. Phosphine-Promoted Cycloaddition



SCHEME 2. [2 + 3] Cycloaddition Mechanism



SCHEME 3. Proposed Cycloaddition



As part of an ongoing drug development program in our laboratories, a regio- and enantioselective synthesis of ketones with general structure **1** was required. We felt that these compounds could be accessed by the above-mentioned phosphine-catalyzed annulation strategy, as the use of exocyclic enones, such as **2**, to generate spirocyclic compounds **3** had also been reported by Lu.[7] To circumvent both the extra synthetic steps and the anticipated selectivity issues in converting the ester functionality in **3** to a ketone in **1**, the use of allenyl methyl ketone **4** as the dipole precursor in the cycloaddition was considered (Scheme 3). Surprisingly, there is no literature documentation of the use of allenic ketones in phosphine-catalyzed [2 + 3] cycloadditions, although the successful generation of the putative dipole has been demonstrated in one instance during a [8 + 2] cycloadditon with tropone.[8] In this paper we report the first successful use of allenyl methyl ketone in a range of phosphine-catalyzed [2 + 3] cycloaddition reactions and review the scope and limitations of these and other phosphine-promoted reactions compared to their allenoate equivalents.

(1) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906.

(2) For a review article see:- Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035.

(3) (a) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461.(b) Pham. T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369.(c) Lu, X.; Lu, Z.; Zhang. X. *Tetrahedron* **2006**, *61*, 457.

(4) (a) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (b) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (c) Jean. L.; Marinetti. A. *Tetrahedron Lett.* **2006**, *47*, 2141.(d) Scherer. A.; Gladysz, J. A. *Tetrahedron Lett.* **2006**, *47*, 6335.

(5) (a) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (b) Wurz. R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234.

(6) (a) Zhu, X. −F.; Henry, C. E.; Wang, J.; Dudding, T.; Kwon, O. Org. Lett. **2005**, *7*, 1387. (b) Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643.

(7) Du. Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901.

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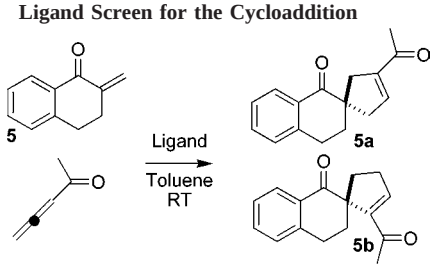
TABLE 1. Ligand Screen for the Cycloaddition



entry[a]	ligand	conversion[b]	**5a:5b**[b]	ee (**5a**)[b]
1	PPh_3	75	62:38	
2	Xantphos	31	82:18	
3	$P(o\text{-}Tol)_3$	0	-	
4	rac-BINAP	0	-	
5	PCy_3	18	95:5	
6	dppf	67	93:7	
7	PBu_3	81	97:3	
8	DIOP	90	90:10	61
9	DIOP[c]	90	97:3	62
10	Prophos	87	90:10	6
11	DIPAMP	85	87:13	34
12	Trost ligand	20	60:40	-
13	Pfaltz ligand	0	-	-
14	DIOP[d6]	100	97:3	68

[a] Reaction conditions: 0.5 M in toluene, 15 mol % ligand, 1.3 equiv of allene, room temperature, 12 h. [b] Based on HPLC. [c] At 0 °C. [d] Using 30 mol % phosphine, or slow addition of allene at 0 °C.

To assess the feasibility of this process, the reaction between the known enone, 2-methylene-3,4-dihydro-2*H*-naphthalen-1-one **5**[9] and allenyl methyl ketone **4**[10] was considered. On treatment of a toluene solution of **5** and the allene **4** (1.3 equiv) with 15 mol % triphenylphosphine, the reaction mixture turned yellow and continued to darken over a period of 12 h, after which time 75% conversion to a 62:38 ratio of two new compounds was observed. These were readily separable by chromatography and were confirmed to be the desired spirocycles **5a** and **5b** by simple NMR spectroscopy.[11] On the basis of this encouraging result, a number of readily available achiral and chiral phosphines were screened with a view to optimizing conversion and regioselectivity and to explore the possibility of obtaining asymmetric induction (Table 1).

As can be seen from Table 1, choice of phosphine catalyst had a significant effect on the reaction outcome. Notably, increasing steric hindrance at phosphorus led to reduced conversion compared to electronically related but less hindered phosphines (entries 3 vs 1 and 5 vs 7). Tributylphosphine provided the best conversion and selectivity of the achiral phsophines examined. In view of the high catalyst loadings typically required for these processes, the screen for chiral ligands to promote the cycloaddition was limited to commercially available and moderately priced phosphines.[12] The readily available DIOP gave both good regioselectivity and moderate enantioselectivity when used in catalytic amounts. A lower temperature (entry 9) increased the regioselectivity to 97%, while higher catalyst loading, or slow addition of the allene (entry 14), allowed for **5a** to be isolated in 68% ee.[13]

With optimum conditions defined, the generality of the spirocycle formation was explored using a range of exocyclic enones (Table 2).[14] On preparative scale, 20 mol % phosphine and 1.5 equiv of allene were used to ensure complete consumption of starting enone. Reactions promoted by triphenylphosphine generated genuine samples of the minor regioisomer and racemic material, and DIOP was used as the optimal chiral promoter.[15]

The cycloaddition was found to be a general process; enones derived from indanones, tetralones, and benzosuberone as well as from a chromanone (entry 5) all afforded the expected products. For DIOP-mediated reactions, good diastereoselectivites and modest enantioselectivites were also obtained. In general, yields were lower than in related reactions with allenoates, and a number of minor products were observed. The instability of the starting enones and their tendency to dimerize was also detrimental to reaction yields; however, the product spirocyclic enones were found to be stable for a number of months when stored at room temperature. Moreover, resubjection of these products to the reaction conditions did not afford any further cycloaddition products nor was any equilibration of isomers observed.

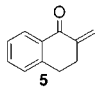
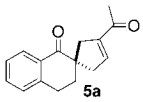
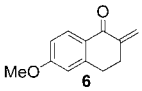
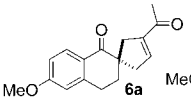
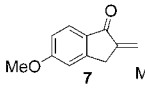
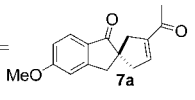
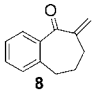
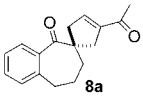
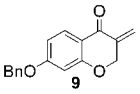
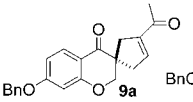
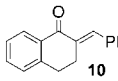
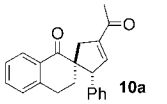
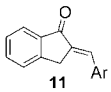
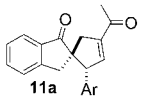
In line with expectation from Fu's work,[4b] use of substituted enones (entries 6 and 7) led to preferential attack of the dipole at the γ-position to give preferentially **10b** and **11b**.[16] Near complete selectivity was obtained when using PPh_3, while catalysts previously chosen to optimize α-attack (DIOP, PBu_3) afforded mixtures.

A number of other phosphine-catalyzed cycloaddition processes which had found utility using allenoates were also investigated (Scheme 4). In contrast to the ester equivalent, allenyl methyl ketone did not undergo phosphine-promoted cyclization with nonconjugated enones or enoates. Modest success was achieved on reaction with *N*-benzenesulfonylbenzaldimine to give a single isomer of the dihydropyrrole **12**. Reaction with 4-nitrobenzaldehyde was expected to afford a *E*/*Z* mixture of the [2 + 2 + 2] product **13**;[6] however, only a trace amount of this compound was seen. Instead, the isomeric **14** was obtained as a mixture of two diastereoisomers in 31% yield. It is thought that this reaction initially proceeds as proposed by Kwon but diverges from the proposed mechanism when the double bond isomerizes during the course of the reaction. The major isomer was confirmed to be the cis-isomer **14a** by NOE analysis.

To extend the scope of the annulation process, the [2 + 3] cycloaddition with an aromatic allenyl ketone was then considered. However, on attempted reaction of enone **5** with ketone **15**, the enone was recovered unchanged and two new products, both with masses corresponding to twice that of the allene, were formed (Scheme 5). After isolation and NMR analysis, these compounds were identified as the two double bond isomers of α-alkylidene pyran **16**.

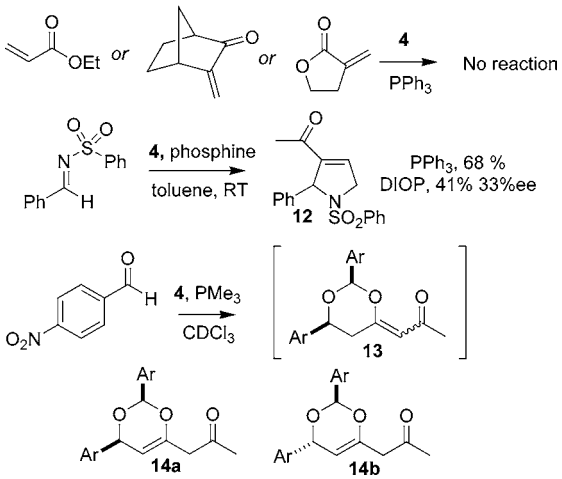
(8) Kumar, K.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 787.
(9) Gras, J.-L. *Tetrahedron Lett.* **1978**, *24*, 2111.
(10) Allenyl methyl ketone was prepared according to Constantieux, T.; Buono, G. *Organic Synthesis*; Wiley: New York, Coll. Vol. 10, p 595; Vol. 78, p 135.
(11) New compounds were characterised by ^1H and ^{13}C NMR and high resolution mass spectroscopy.
(12) The structure of the phosphine catalysts is given in the Supporting Information.
(13) The absolute stereochemistry of the cycloadducts was not determined.
(14) Enones were prepared according to Gras, J.-L. *Organic Synthesis*; Coll. Vol. 7, p 332, Vol. 60, p 88.
(15) No attempt was made to individually optimize the chiral phosphine for other substrates.
(16) The relative stereochemistry of the spirocycles **10b** and **11b** was not determined, but in line with Fu's work we assume the stereochemistry of the starting enone is preserved.

TABLE 2. Spirocyclizations of Exocyclic Enones

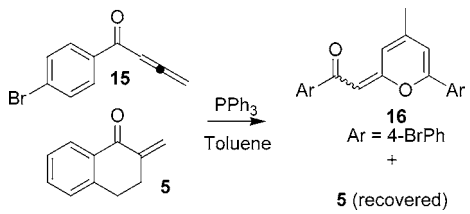
Entry[a]	Starting Enone	Products	Yield[b]	**a** : **b**[b]	Yield[c]	**a** : **b**[c]	ee (**a**)
1	 **5**	 **5a** **5b**	58	70 : 30	73	95 : 5	61
2	 **6**	 **6a** **6b**	64	62 : 38	75	91 : 9	77
3	 **7**	 **7a** **7b**	73	56 : 44	63	80 : 20	53
4	 **8**	 **8a** **8b**	82	54 : 46	80	90 : 10	46
5	 **9**	 **9a** **9b**	84	55 : 45	71	95 : 5	71
6	 **10**	 **10a** **10b**	72[d]	2 : 98	-	-	-
7	 **11**	 **11a** **11b**	61[d]	2 : 98	46[d]	85 : 15	30[e]

[a] Reaction conditions: 0.5 M in toluene, 20 mol % PPh_3 or DIOP, 1.5 equiv of allene, room temperature, 12 h. [b] Using PPh_3. [c] Using DIOP. [d] Yield based on recovered starting material. [e] ee for **11b**.

SCHEME 4. Other Phosphine-Promoted Cycloaddition Reactions

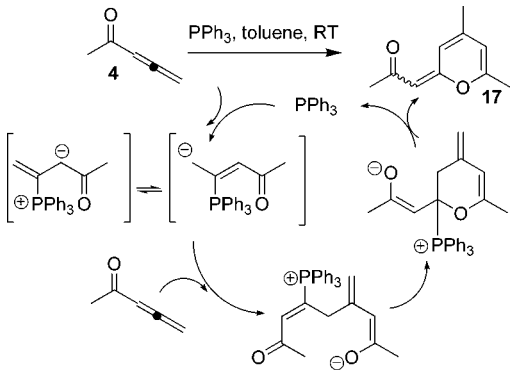


SCHEME 5. Formation of α-Alkylidene Pyran 16



Careful reexamination of the reaction mixtures from the previously studied cycloadditions of allenyl methyl ketone **4** (Table 2 and Scheme 4) indicated the presence of a common

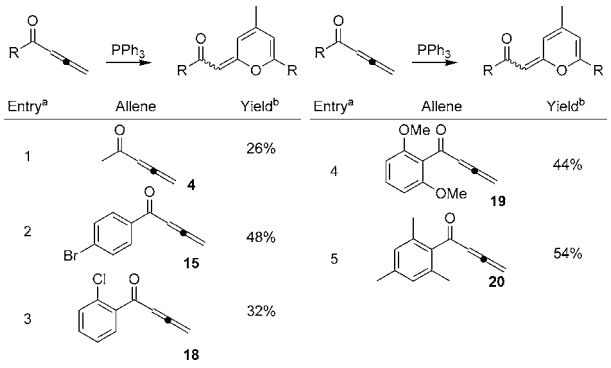
SCHEME 6. Mechanism for Formation of Pyran 17



byproduct (ca. 10%) which was found to be the related α-alkylidene pyran **17** (Scheme 6). In the absence of other substrates, treatment of allenyl methyl ketone with catalytic amounts of triphenylphosphine in toluene at room temperature afforded **17** in 26% isolated yield. This product is believed to result from conjugate addition at the γ-position of the dipole to the allene itself, followed by cyclization, anion rearrangement, and aromatization leading to a formal [4 + 2] Diels−Alder product. A palladium-catalyzed dimerization of allenyl ketones to afforded furans has been reported by Hashmi,[17] and cycloisomerizations using thermal[18] or catalytic[19] conditions have also afforded furans; however, we believe this is the first time a pyran

(17) (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1581. (b) Hashmi, A. S. K.; Ruppert, T. L; Knofel, T.; Bats, J. W. *J. Org. Chem.* **1997**, *62*, 7295.

TABLE 3. Dimerization of Allenyl Ketones



[a] Reaction conditions: 20 mol % PPh_3, 0.5 M in toluene, RT, 20 h. [b] Isolated yield of both isomers.

has been recovered as a dimerization product from an allenyl ketone.[20,18,19] Notably, the allene was stable in toluene at room temperature, consistent with the role of the phosphine in promoting this reaction.

The dimerization was found to be general reaction for a range of aromatic allenyl ketones. Treatment of the readily prepared ketones[21] with catalytic amounts of triphenylphosphine afforded the dimeric pyrans in moderate yields, typically with *E*/*Z* ratios of around 85/15 (Table 3).[22] The greater propensity of aryl allenyl ketones to undergo dimerization, in preference to addition to enones, can be rationalized based on the increased Michael acceptor properties of the aryl allenes when compared to their aliphatic equivalents.

Conclusions

In summary, we have demonstrated the use of allenyl ketones in a range of phosphine-catalyzed cycloaddition processes and outlined key differences between these reactions and previously published procedures using allenoates. Spirocyclic compounds can be prepared in good yield and diastereoselectivity via reaction with exocyclic enones, and modest enantioselectivity was obtained using a readily available commercial ligand. Reactions with imines and aldehydes have also been demonstrated, albeit in modest yields; however, nonconjugated enones and esters were not viable substrates for the allenyl ketone derived dipoles. The greater Michael acceptor properties of the ketones in this study as compared to allenonates has led to formation of an α-alkylidene pyran dimerization byproduct, and in the case of aromatic allenyl ketones this constitutes a synthetically useful method for the preparation of such compounds.

Experimental Section

General Procedure for [2 + 3] Cycloaddition of Exocyclic Enones and Allenyl Methyl Ketone 4. 3-Acetyl-3′,4′-dihydro-1′*H*-spiro[cyclopent-3-ene-1,2′-naphthalen]-1′-one (5a) and 2-Acetyl-3′,4′-dihydro-1′*H*-spiro[cyclopent-2-ene-1,2′-naphthalen]-1′-one (5b). To a stirred solution of enone **5** (283 mg, 1.79 mmol) and allenyl methyl ketone (220 mg, 2.69 mmol) in toluene (5.0 mL) under a nitrogen atmosphere at room temperature was added triphenylphosphine (94.0 mg, 0.358 mmol), and stirring was continued at the same temperature for 16 h after which time HPLC analysis indicated complete consumption of starting material to give a 62:38 mixture of **5a** and **5b**. The toluene was removed under vacuum, and the crude mixture purified by flash column chromatography (50:50 EtOAc:hexanes) gave 179 mg of **5a** and 77 mg of **5b** in 58% combined yield. Use of 186 mg of enone **5** with DIOP under the same conditions afforded a 95:5 mixture of **5a**:**5b** 190 mg of **5a** (60%ee) and 14 mg of **5b** in 72% combined yield.

5a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.6, 0.8 Hz, 1H), 7.47 (td, J = 7.6, 1.2 Hz, 1H), 7.30 (br t, J = 7.6 Hz, 1H), 7.22 (br d, J = 7.6 Hz, 1H), 6.88 (m, 1H), 3.31 (dq, J = 19.0, 2.0 Hz, 1H), 3.11 (dt, J = 17.6, 7.2 Hz, 1H), 3.02−2.96 (m, 1H), 2.95−2.91 (m, 1H), 2.71 (dq, J = 16.8, 2.0 Hz, 1H), 2.51 (dq, J = 19.0, 2.0 Hz, 1H), 2.34 (s, 3H), 2.17−2.12 (m, 2H): ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.1, 196.2, 143.3, 142.3, 141.8, 133.4, 131.1, 128.7, 128.2, 126.8, 51.7, 42.7, 39.3, 34.7, 26.5, 25.9: LCMS 263 (70, M + Na), 241 (100, M + H): HRMS Calcd for $C_{16}H_{17}O_2$, 241.1229, found 241.1225.

5b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (dd, J = 8.0, 1.2 Hz, 1H), 7.47 (td, J = 7.2, 1.2 Hz, 1H), 7.30 (br t, J = 7.6 Hz, 1H), 7.22 (br d, J = 7.6 Hz, 1H), 6.94 (t, J = 2.8 Hz, 1H), 3.10 (m, 1H), 2.90 (ddd, J = 16.8, 4.4, 2.8 Hz, 1H), 2.77 (td, J = 13.2, 4.4 Hz, 1H), 2.69−2.66 (m, 2H), 2.34 (s, 3H), 2.28−2.22 (m, 2H), 2.11−2.05 (m, 2H), 1.85 (ddd, J = 13.2, 4.4, 2.4 Hz, 1H): ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 199.8, 195.0, 149.5, 146.4, 143.4, 133.2, 131.9, 128.5, 128.1, 126.7, 59.5, 33.1, 31.5, 31.4, 27.0, 26.4: LCMS 263 (30, M + Na), 241 (100, M + H): HRMS Calcd for $C_{16}H_{17}O_2$, 241.1229, found 241.1232.

General Procedure for Dimerization of Aromatic Allenyl Ketones. (2*E*)-1-(4-Bromophenyl)-2-[6-(4-bromophenyl)-4-methyl-2*H*-pyran-2-ylidene]ethanone (16). To a stirred solution of ketone **15** (92.0 mg, 0.412 mmol) in toluene (3.0 mL) under a nitrogen atmosphere at room temperature was added triphenylphosphine (11.0 mg, 0.042 mmol), and stirring was continued for 2 h. The toluene was removed under vacuum and the crude mixture purified by flash column chromatography (EtOAc:hexanes 1:1) to afford 44.0 mg of **16** (85:15 *E:Z*) as a bright orange oil in 48% yield.

^{1}H NMR *E*-isomer (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.82 (d, J = 6.8 Hz, 2H), 7.65−7.59 (m, 6H), 6.41 (s, 1H), 6.36 (s, 1H), 2.22 (s, 3H): ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 186.2, 167.1, 155.5, 147.9, 139.8, 132.2, 131.4, 130.3, 129.0, 126.8, 125.9, 125.1, 116.9, 106.5, 93.1, 21.9: LCMS 445, 447, 449 (100, M + H): HRMS Calcd for $C_{20}H_{15}O_2Br(79)_2$, 444.9439, found 444.9458.

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Supporting Information Available: Experimental procedures and spectroscopic data for spirocycles **5a**,**b**−**11b**, pyrans in Table 3, and for compounds **12**, **14a**, and **14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) ^{1}H and ^{13}C spectroscopic data of **17** differs significantly to that reported for the furan dimer in reference 17.

(21) Aromatic allenyl ketones were prepared by Dess−Martin oxidation and isomerization of homopropargylic alcohols as described in reference 17a. The alcohols were prepared by zinc-mediated propargylation of the corresponding benzaldehyde: Wu, W.-L.; Yao. Z.-J.; Li, Y.-L.; Li, J.-C.; Xia, Y.; Wu, Y.-L. *J. Org. Chem.* **1995**, *60*, 3257.

(22) The *E*/*Z* double bond isomers were not separable by chromatography.