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Synthesis of functionalized biaryl compounds via ring expansion of alkenylcyclobutenones

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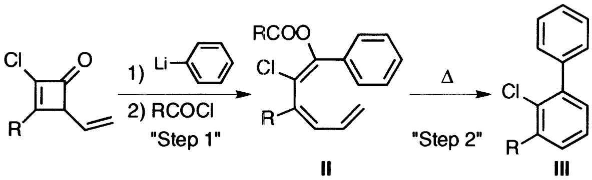
Abstract—Various functionalized biaryls are accessible via a simple two-step process. Treatment of alkenylcyclobutenones with aryllithium provides ring-opened trienes, which are smoothly cycloaromatized under thermal conditions. © 2002 Elsevier Science Ltd. All rights reserved.

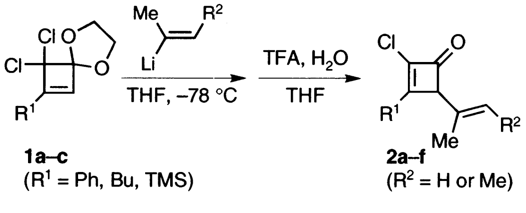
Biaryl structures are found in various significant compounds, ranging from biologically active natural products such as vancomycin to chiral ligands for asymmetric catalysis such as BINAP.[1] Herein, we report a new synthetic method of highly substituted biaryls starting from alkenylcyclobutenone derivatives as summarized in Eq. (1): the reaction of alkenylcyclobutenone **I** with an aryllithium followed by an acid chloride produces a ring-opened triene **II** (step 1), which undergoes a thermal ring closure via 6π-electrocyclization and elimination of a carboxylic acid (step 2) to give biaryl **III**.[2,3]



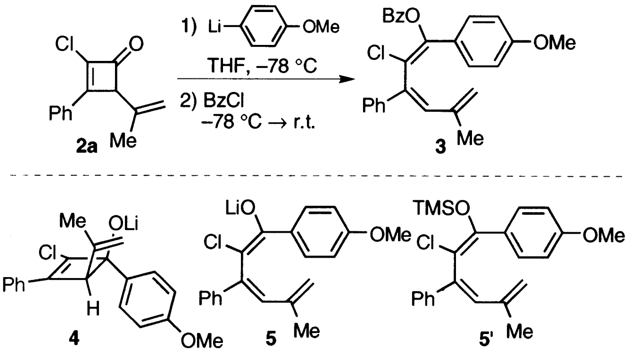
(1)

Eq. (2) shows the ready availability of starting materials, cyclobutenones **2a**–**f**, by the SN2′ reaction of dichlorocyclobutenone acetals **1a**–**c**[4] with 2-propenyl- or 2-butenyllithium, and subsequent acid hydrolysis as reported previously.[5]

(2)



Aryllithium addition and ring opening (step 1): Upon treatment of **2a** with 4-methoxyphenyllithium (1.3 equiv.) in THF at −78°C followed by the addition of benzoyl chloride (−78°C→room temperature), triene **3** was obtained as a single isomer in 99% yield (Eq. (3)).[6] The geometry of **3** was tentatively assigned as shown below, assuming that the addition of aryllithium to **2a** occurs selectively from the opposite side to the isopropenyl group to give adduct **4**, which, in turn, undergoes conrotatory ring opening with a torquoselectivity[7] that the oxido group rotates outward to deliver the lithium enolate **5**, which is eventually benzoylated. This assignment was supported by an X-ray analysis of a congener **7d**.[9]



(3)

When the above reaction was immediately quenched with TMSCl instead of benzoyl chloride at −78°C, obtained was enol silyl ether **5′** (92% yield), suggesting that the ring-opening occurs quickly at low temperature.

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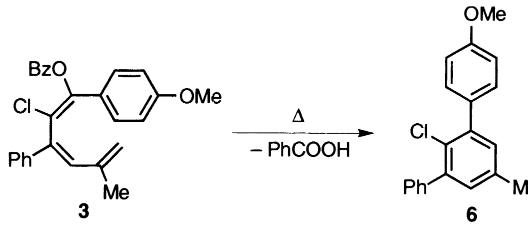
6π-Cyclization and elimination (step 2): As the initial attempt for the formation of biaryl compounds, triene **3** was heated in refluxing toluene, where triene **3** was slowly consumed, giving the desired biaryl **6** in 37% yield (entry 1). Ascribing the lower yield to polymerization of the triene caused by the benzoic acid formed in situ, we employed pyridine as an acid scavenger with a boiling point similar to that of toluene. The yield was slightly improved, albeit still unsatisfactory. After a series of optimization experiments, we were pleased to find suitable conditions to obtain the cyclized product **6** in high yield. When triene **5** was heated at 140°C in pyridine–xylene mixture (1:4), the yield of **6** was improved to 81% yield (entry 3) (Scheme 1).[8]



3 **6**

Entry	Conditions	Yield/%
1	toluene reflux, 36 h	37
2	pyridine reflux, 30 h	47
3	pyridine, xylene (1 : 4), 140 °C, 26 h	81

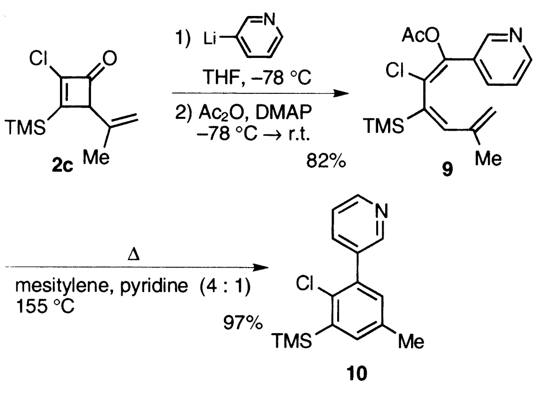
Scheme 1.

Representative experimental procedures are as follows. *Synthesis of triene 3*: To a solution of 4-bromoanisole (68.7 mg, 0.367 mmol) in THF (2.0 mL) was slowly added *t*-BuLi (1.49 M in pentane, 0.49 mL, 0.73 mmol) at −78°C. After stirring for 45 min, alkenylcyclobutenone **2a** (57.8 mg, 0.278 mmol) in THF (2.0 mL) was added to the mixture, which was followed by addition of benzoyl chloride (69.8 mg, 0.496 mmol) in THF (1.0 mL). After warming to room temperature in 1 h, the reaction was quenched with sat. aq. $NaHCO_3$. The products were extracted with EtOAc (×3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified with PTLC (hexane/EtOAc = 8/2) to give triene **3** (119 mg, 99%) as a colorless oil.

Synthesis of biaryl ***6***: A solution of triene **3** (39.6 mg, 0.108 mmol) in pyridine (0.5 mL) and xylene (2.0 mL) was heated at 140°C for 26 h. After cooling to room temperature, the solution was acidified with 1 M HCl. The products were extracted with EtOAc (×3), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by PTLC (hexane/EtOAC = 9/1) to give **6** (23.0 mg, 81%) as a colorless oil.

The protocol was applied to other substrate combinations as summarized in Table 1. As entry 1 shows, reaction of alkenylcyclobutenone **2a** with 2,4-xylyllithium followed by the addition of benzoyl chloride gave triene **7a** in 90% yield. Although higher reaction temperature was required (pyridine–mesitylene, 165°C), **7a** was smoothly converted to the corresponding biaryl **8a** in 89% yield. Similarly, cyclobutenones **2b** and **2c**, having a butyl or a trimethylsilyl group on the four membered ring, were good substrates for the reaction (entries 2 and 3). Furthermore, as entry 4 shows, 2,6-xylyllithium could also be incorporated into the reaction scheme, and the reaction with **2c** afforded triene **7d**[9] in 97% yield. As for the subsequent cyclization of **7d**, a fairly long time was necessary for the complete cyclization, and we obtained a sterically congested compound **8d** in 67% yield (entry 4). Likewise, the reactions of alkenylcyclobutenone **2d** and **2e**, having an additional β-substituent on the olefin, with 2,4-xylyllithium or 1-naphthyllithium gave trienes **7e** and **7f**, which were converted to the corresponding biaryls **8e** and **8f** in high yields, respectively (entries 5 and 6). Similar thermal reaction of triene **7g**, prepared from **2f** with 2,6-xylyllithium, proceeded slowly, even though refluxed at *o*-dichlorobenzene in the presence of 2,6-lutidine, giving lower yield of product **8g** (entry 7). All attempts, by changing solvents or protecting group, failed to give satisfactory results.[10]

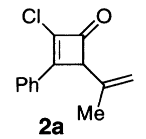
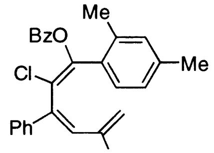
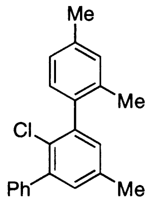
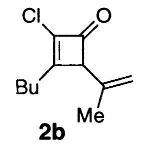
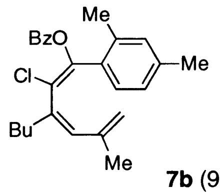
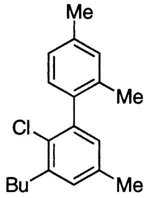
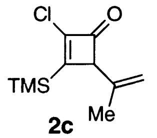
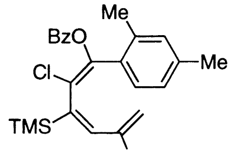
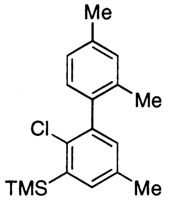
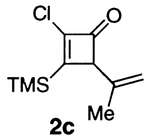
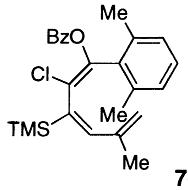
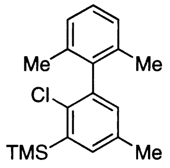
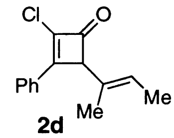
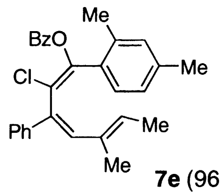
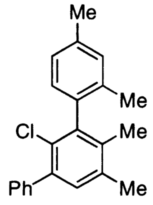
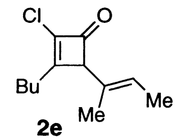
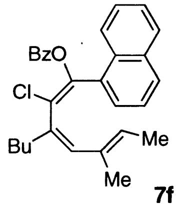
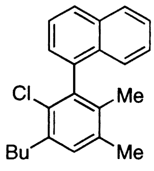
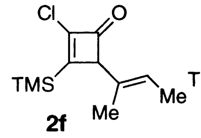
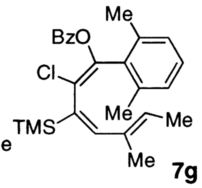
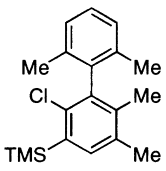
The protocol was also applicable for the synthesis of hetero-biaryl compounds as shown in Eq. (4). Upon treatment of **2c** with 3-pyridyllithium[11] in THF at −78°C followed by the addition of Ac_2O in the presence of a catalytic amount of DMAP (−78°C→room temperature), triene **9** was obtained in 82% yield. Thermolysis of **9** (pyridine–mesitylene, 155°C) proceeded smoothly to give biaryl **10** in 97% yield (Eq. (4)).



(4)

In summary, the present two-step approach to the functionalized biaryls reacting by alkenylcyclobutenones and aryllithium should find utility in natural product synthesis, and further studies are currently underway in our laboratories.

Table 1.

Entry	Cyclobutenone	Triene (Yield)	Conditions,[b] Time	Biaryl (Yield)
1	 **2a**	 **7a** (90%)	A, 11 h	 **8a** (89%)
2	 **2b**	 **7b** (94%)	A, 18 h	 **8b** (81%)
3	 **2c**	 **7c** (91%)	A, 16 h	 **8c** (90%)
4	 **2c**	 **7d** (97%)	A, 100 h	 **8d** (67%)
5	 **2d**	 **7e** (96%)	A, 31 h	 **8e** (79%)
6	 **2e**	 **7f** (88%)	A, 13 h	 **8f** (80%)
7	 **2f**	 **7g** (90%)	B, 55 h	 **8g** (22%)

[a] All new compounds were fully characterized by spectroscopic means and combustion analysis.

[b] Conditions A: pyridine, mesitylene, (1 : 4), 165 °C; Conditions B: 2,6-lutidine, *o*-dichlorobenzene (1 : 4), 185 °C.

References

1. For recent reviews, see: (a) Bringmann, G.; Breuning, M.; Tasler, S. *Synthesis* **1999**, 525–558; (b) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 977–991; (c) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263–303; (d) Anctil, E. J.-G.; Snieckus, V. *J. Organomet. Chem.* **2002**, *653*, 150–160.
2. Recently, we developed a new synthetic method of hindered 1-arylnaphthalene derivatives via ring expansion of benzocyclobutenones, see: Hamura, T.; Miyamoto, M.; Matsumoto, T.; Suzuki, K. *Org. Lett.* **2002**, *4*, 229–232.
3. Formation of six-membered ring carbocycles in this type of reactions: (a) Liu, F.; Liebeskind, L. S. *J. Org. Chem.* **1998**, *63*, 2835–2844; (b) Morwick, T. M.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 627–635; (d) Taing, M.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 329–340; (d) Perri, S. T.; Moore, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 1897–1905; (e) Danheiser, R. L.; Gee, S. K.; Perez, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 806–810.
4. (a) Danheiser, R. L.; Sard, H. *Tetrahedron Lett.* **1983**, *24*, 23–26; (b) Danheiser, R. L.; Savariar, S. *Tetrahedron Lett.* **1987**, *28*, 3299–3302; (c) Danheiser, R. L.; Savariar, S.; Cha, D. D. *Organic Synthesis*, Wiley, New York, 1993, Collect. Vol. VIII, pp. 82–86; (d) Hassner, A.; Dillon, J. L., Jr. *J. Org. Chem.* **1983**, *48*, 3382–3386.
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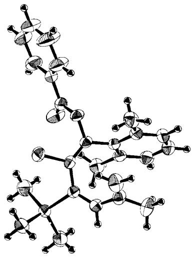
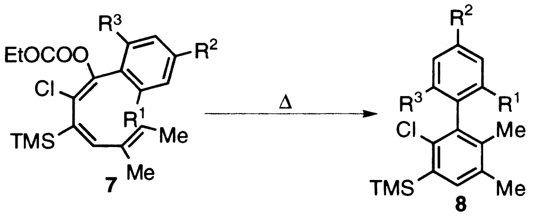
8. The attempts at an anion-accelerated cyclization of lithium enolate **5** were unfruitful. Heating of the silyl ether **5′** also gave no cyclized product.
9. We thank Dr. Akiko Sekine, Tokyo Institute of Technology, for X-ray analysis. The ORTEP drawing of **7d** is shown below. Crystallographic data reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-193917. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).



7d

10. In most cases, thermal reactions of the corresponding ethyl carbonate **7**, prepared by the reaction of the lithium trienolate with ethyl chloroformate, proceeded smoothly to give the corresponding biaryls in high yields. For example, heating of **7h** in DMSO at 155°C gave **8h** in 91% yield. This protocol was attractive in that the reaction can be performed under neutral conditions. However, the reaction of sterically congested substrate **7i**, again, gave the lower yield of product (see below).



Entry	Triene				conditions	Yield/%	
	R^1	R^2	R^3	**7**		**8**	
1	H	OMe	H	**7h**	DMSO, 155 °C 2 h	**8h**	91
2	Me	H	Me	**7i**	*o*-dichlorobenzene reflux, 72 h	**8i**	26

11. 3-Pyridyllithium was generated by halogen–lithium exchange of the corresponding bromopyridine and *n*-BuLi (THF, –78°C).