JOC*Note*

Cycloadditions of 1,1-Disubstituted Benzocyclobutenes Obtained by C(sp^3)−H Activation

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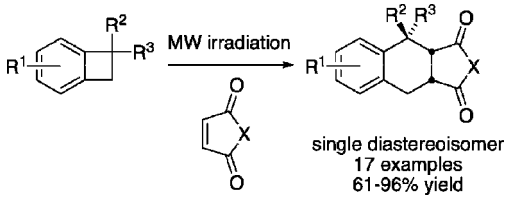
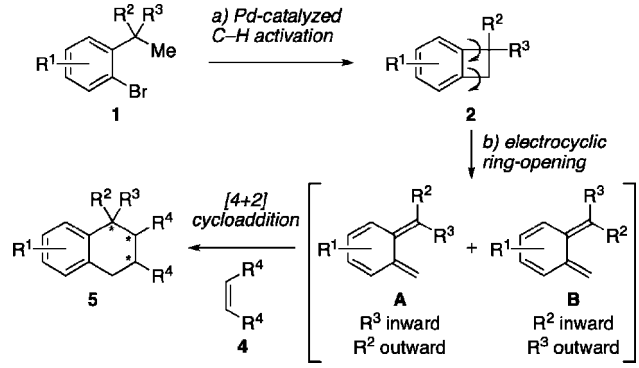


An efficient synthesis of polycyclic molecules has been performed by a sequence involving palladium-catalyzed C−H activation and [4 + 2] cycloaddition. The intermediate benzocyclobutenes underwent a microwave-enhanced electrocyclic ring-opening/cycloaddition process with complete torquoselectivity and diastereoselectivity.

Benzocyclobutenes (BCBs) are important intermediates in organic synthesis that have been widely used in [4 + 2] cycloadditions and other pericyclic reactions for the construction of polycyclic molecules.[1] Indeed, the thermolysis of a BCB generates a very reactive *o*-xylylene by electrocyclic ring-opening, and this intermediate can be trapped in situ by an internal or external dienophile to give the corresponding cycloadduct. This sequence has been widely applied in natural product synthesis in the past three decades.[2] In spite of their recognized synthetic interest, BCBs are only accessible by a few methods that show limited compatibility with substituents on the aromatic and cyclobutene rings. We recently described the synthesis of functionalized BCBs by the palladium-catalyzed C−H activation of benzylic methyl groups.[3] This method shows an unprecedented chemoselectivity and thus extends the array

SCHEME 1. Overall Synthetic Strategy



of available BCBs as substrates for pericyclic reactions.[4] In this paper, we report on [4 + 2] cycloadditions performed from such BCBs under microwave irradiation.

Our overall synthetic strategy is highlighted in Scheme 1. Substituted BCBs **2** obtained from aryl bromides **1** by C−H activation could generate *o*-xylylene isomers **A** and **B** upon thermolysis, the ratio of which defines the torquoselectivity of the cyclobutene ring-opening. Trapping of **A** and/or **B** with an appropriate dienophile (**4**) should lead to the formation of cycloadducts **5**. The torquoselectivity of the electrocyclic ring-opening of benzocyclobutenes has been studied computationally by Houk[5] and Santelli,[6] who showed that it is mainly governed by electronic effects. In the case of 1,1-disubstituted BCBs (R^2 and $R^3 \neq H$), synergistic or antagonist effects of these substituents can thus be anticipated. Since intermolecular cycloadditions of *o*-xylylenes under normal electronic demand are known to occur mainly with *endo* selectivity, the relative configuration of cycloadducts **5** is expected to reflect the torquoselectivity of the electrocyclic ring-opening of BCBs **2**. In contrast to 1-monosubstituted BCBs, very little work has been published on intermolecular cycloadditions from 1,1-disubstituted BCBs.[5,7] Since the latter are now easily accessible from aryl bromides **1** by our C−H activation method,[3b] we decided to study the outcome of their intermolecular cycloaddition with various dienophiles.

We first examined the reaction of BCB **2a** (Table 1, entry 1) with *N*-methylmaleimide (**4a**). After a short optimization, it was found that heating a mixture of **2a** and **4a** in *o*-dichlorobenzene under microwave irradiation at 180 °C for 10 min furnished cycloadduct **5aa** in high yield as a single diastereoisomer (Table 1, entry 1). Microwave heating proved superior to conventional heating in the same solvent and at the same temperature, since in the latter case **5aa** was obtained after 3 h in 79% yield, together with traces of the other diastereoisomer **5ab** and styrene

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(1) (a) Mehta, G.; Kotha, S. *Tetrahedron* **2001**, *57*, 625. (b) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, *103*, 1539.

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(4) For our work on electrocyclizations, see: Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179–182.

(5) Jefford, C. W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157.

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(7) (a) Arnold, B. J.; Sammes, P. G.; Wallace, T. W *J. Chem. Soc., Perkin Trans. 1* **1974**, 415. (b) Kametani, T.; Tsubuki, M.; Shiratori, Y.; Kato, Y.; Nemoto, H.; Ihara, M.; Fukumoto, K.; Satoh, F.; Inoue, H *J. Org. Chem.* **1977**, *42*, 2672. (c) Matsuya, Y.; Ohsawa, N.; Nemoto, H *J. Am. Chem. Soc.* **2006**, *128*, 412.

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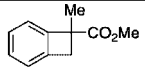
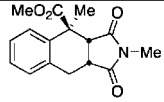
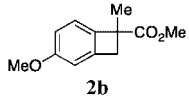
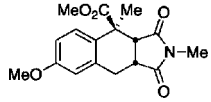
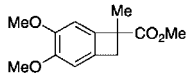
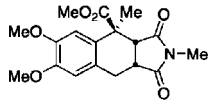
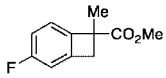
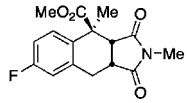
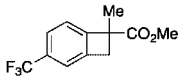
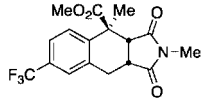
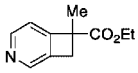
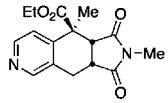
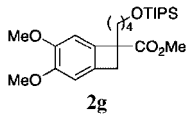
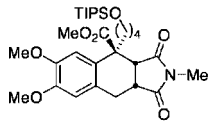
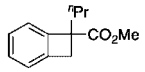
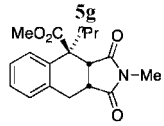
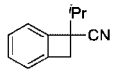
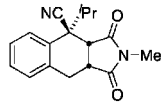
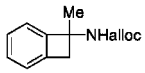
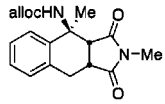
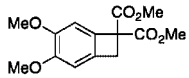
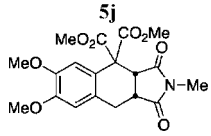
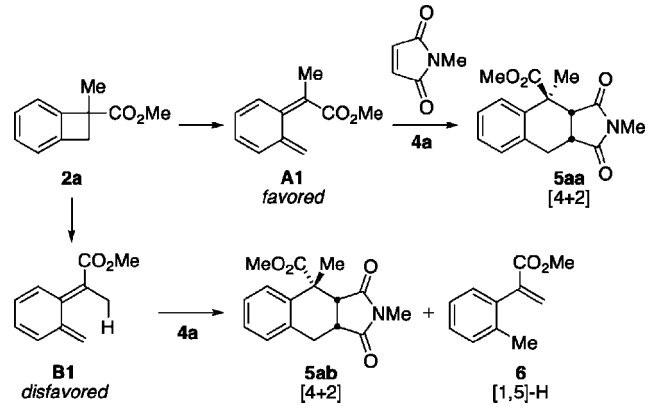
TABLE 1. Cycloaddition of 1,1-Disubstituted BCBs 2a−k and *N*-Methylmaleimide (4a)[a]

entry	BCB[b]	Product (±)	yield (%)
1	 **2a**	 **5aa**	93
2	 **2b**	 **5b**	79
3	 **2c**	 **5c**	96
4	 **2d**	 **5d**	87
5	 **2e**	 **5e**	81
6	 **2f**	 **5f**	63
7	 **2g**	 **5g**	81
8	 **2h**	 **5h**	70
9	 **2i**	 **5i**	72
10	 **2j**[c]	 **5j**	67
11	 **2k**	 **5k**	95

[a] Conditions: BCB (1 equiv), *N*-methylmaleimide (2 equiv), *o*-dichlorobenzene, microwave irradiation (P_{max} = 250 W), 180 °C, 10−20 min. [b] Synthesized as described in ref 3b. [c] Obtained in two steps from **2a** by hydrolysis and Curtius rearrangement; see the Supporting Information (alloc = allyloxycarbonyl).

6 (Scheme 2). It is known that high temperatures are required for the electrocyclic ring-opening of BCBs such as **2a**, that is 1,1-disubstituted and at the same time bears an electron-withdrawing group on the cyclobutene ring.[1,2] In accordance to previous work by Houk and co-workers,[5] the ring-opening

SCHEME 2. Torquoselectivity of the Electrocyclic Ring Opening of BCB 2a



of BCB **2a** is expected to occur in favor of *o*-xylylene **A1** due to the dominant outward rotation of the methyl group. Intermediate **A1** would then undergo an *endo*-selective cycloaddition with **4a** to give diastereoisomer **5aa**. In contrast, inward rotation of the methyl group would provide *o*-xylylene **B1**, that would furnish diastereoisomer **5ab** and olefin **6** by cycloaddition with **4a** and [1,5]-hydrogen shift, respectively.[7b,8]

The reactions of other 1,1-disubstituted BCBs **2b**−**k** with *N*-methylmaleimide **4a** were next examined under the same conditions (Table 1, entries 2−11). Cycloadducts **5b**−**k** were obtained in good to excellent yields as single diastereoisomers, the configuration of which was determined by NOESY experiments or X-ray diffraction analysis (see the Supporting Information for crystallographic data for compounds **5e** and **5h**). All cycloadducts **5aa** and **5b**−**j** have the same relative configuration, which reflects a complete outward torquoselectivity for the alkyl group. The reaction proved compatible with a variety of substituents on the benzene and cyclobutene rings, regardless of their electronic or steric properties. In particular, pyridocyclobutene **2f** gave rise to the original fused heterocycle **5f** in 63% yield (entry 6). In addition, diester **2k** furnished the corresponding cycloadduct **5k** in excellent yield despite the strong electron-withdrawing nature of the *o*-xylylene intermediate (entry 11).

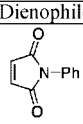
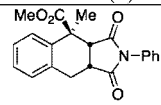
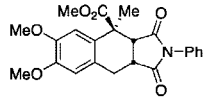
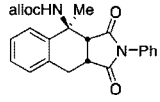
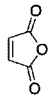
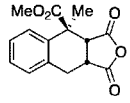
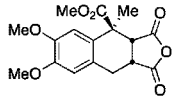
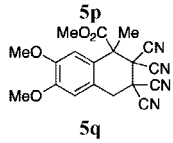
Next, we examined the cycloaddition of BCBs with other dienophiles. We found the reaction limited to activated dienophiles such as maleimides (**4a**,**b**), maleic anhydride (**4c**), and tetracyanoethylene (**4d**) (Table 2). With less activated dienophiles,[9] the formation of the [1,5]-hydrogen shift product (e.g., compound **6**, Scheme 2) became predominant. In spite of this limitation, good yields were achieved with dienophiles **4b**−**d** and the observed diastereoselectivity in favor of cycloadducts **5l**−**p** was again total and in the same sense.

The cycloaddition of 1-monosubstituted BCB **2l**, readily accessible by C−H activation,[3b] was also examined for the purpose of comparison with its 1,1-disubstituted counterparts (Scheme 3). Reaction with dienophile **4b** under the same conditions as above furnished an inseparable mixture of cycloadducts **5ra** and **5rb** in 1:8 ratio and 90% yield. This ratio reflects the major outward torquoselectivity of the ester group in accordance with previous work.[5] Compared to disubstituted analogue **2a** (Table 2, entry 1), the torquoselectivity of the

(8) Shishido, K.; Ito, M.; Shimada, S.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, *13*, 1943.

(9) For instance, benzoquinone, dimethyl acetylenedicarboxylate, phenyl vinyl sulfone, and 2-cyclohexen-1-one.

TABLE 2. Cycloaddition of Various 1,1-Disubstituted BCBs and Activated Dienophiles[a]

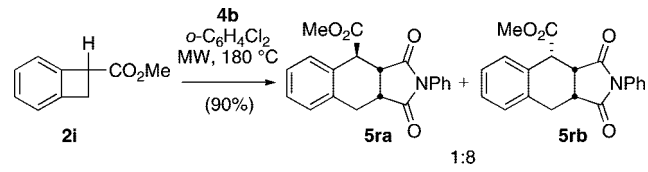
entry	BCB	Dienophile	Product (±)	yield (%)
1	**2a**	 **4b**	 **5l**	66
2	**2c**	**4b**	 **5m**	84
3	**2j**	**4b**	 **5n**	62
4	**2a**	 **4c**	 **5o**	61
5	**2c**	**4c**	 **5p**	68
6	**2c**	 **4d**	 **5q**	91

[a] Conditions: BCB (1 equiv), dienophile (2 equiv), *o*-dichlorobenzene, microwave irradiation (P_{max} = 250 W), 180 °C, 10−20 min.

electrocyclic ring-opening of **2l** is reversed, which further illustrates the strongly dominant outward rotation of alkyl groups observed for compounds **2a**−**j**.

In conclusion, tricyclic molecules were synthesized in good yields from 1,1-disubstituted benzocyclobutenes, that are now easily accessible by C(sp^3)−H activation, using a microwave-enhanced [4 + 2] cycloaddition. A high diastereoselectivity was observed in the cycloaddition step, which most probably reflects the dominant outward torquoselectivity of alkyl groups in the electrocyclic ring-opening step.

SCHEME 3. Cycloaddition of 1-Monosubstituted BCB 2l



Experimental Section

Representative Cycloaddition Procedure. Compound 5aa. A mixture of benzocyclobutene **2a** (40.5 mg, 0.23 mmol) and *N*-methylmaleimide **4a** (51 mg, 0.46 mmol) in *o*-dichlorobenzene (0.2 mL) was placed in a closed vessel and irradiated in a focused microwave reactor for 15−20 min at 180 °C (P_{max} = 250 W). The resulting mixture was directly purified by flash chromatography (heptanes, then heptanes/AcOEt 8:2) to give compound **5aa** as a colorless oil (61.4 mg, 93%): ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 7.33−7.26 (m, 2 H), 7.21 (ddd, J = 7.0, 7.0, 2.0 Hz, 1 H), 7.09 (d, J = 7.0 Hz, 1 H), 3.82 (d, J = 8.6 Hz, 1 H), 3.62 (s, 3 H), 3.43 (ddd, J = 8.6, 8.6, 1.8 Hz, 1 H), 3.15 (dd, J = 15.6, 1.8 Hz, 1 H), 2.72−2.64 (m, 4 H), 1.99 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 179.1, 176.9, 175.3, 137.0, 134.0, 128.4, 128.1, 127.8, 125.5, 53.2, 48.9, 47.0, 40.2, 29.7, 24.8, 20.8; IR (film) ν 2985, 2992, 1724, 1696, 1432, 1247, 1106, 984, 768, 628 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{17}NO_4Na$ $(M + Na)^+$ 310.1055, found 310.1046.

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Supporting Information Available: Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra for target compounds, and CIF files for **5e** and **5h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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