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An Efficient Synthesis of Arylcyclobutenes via Cross-Coupling of Aryl Halides with 1-(Tri-*n*-butylstannyl)cyclobutene

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Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

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Abstract—1-Tri-*n*-butylstannylcyclobutene, obtained from 1-bromocyclobutene by lithium/bromine exchange and transmetalation with chloro-tri-*n*-butylstannane, could be effectively converted with aryl halides into 1-arylcyclobutenes by the Stille cross-coupling procedure. Hetero-aryl halides like 2-bromopyridine and 2-iodothiophene were also successfully coupled, and in 1,3,5-tribromobenzene, 1,2,4,5-tetrabromobenzene and hexabromobenzene all bromine atoms could be exchanged.

Introduction

Although several strategies for the synthesis of cyclobutenes have been developed in the past,[1] this class of compounds is generally not easily accessible. In recent years, some routes to cyclobutenes via cycloalkylation have also been described.[2] However, the general applicability of these methods is limited. Herein we report on a convenient and general synthesis of arylcyclobutenes via the Stille reaction[3] of aryl halides with 1-tri-*n*-butylstannylcyclobutene (**3**). We have recently shown that 1-bromobicyclo[1.1.0]butane (**1**) is obtained from 1,1-dibromo-2-chlormethylcyclopropane and methyllithium.[4] The conversion of **1** into 1-bromocyclobutene (**2**) is achieved by acid-catalyzed rearrangement. Compound **2** has also been used as a precursor for an efficient synthesis of cyclobutanone.[5]

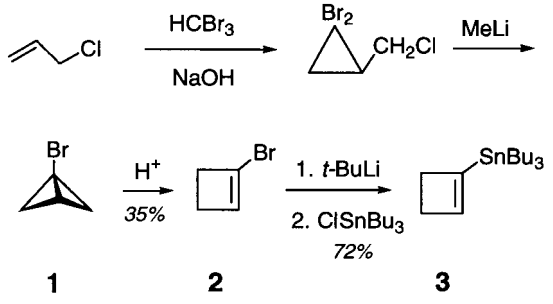
1-Tri-*n*-butylstannylcyclobutene (**3**) as cross-coupling partner was obtained from **2** with *tert*-butyllithium in ether followed by transmetalation with chlorotri-*n*-butylstannane. In Scheme 1 the synthesis of **3** is depicted.

Results

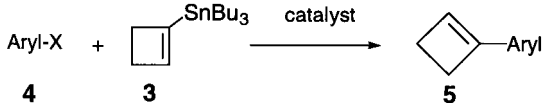
With the convenient route to **3**, effective cross-coupling reactions with a wide variety of aryl halides were possible. The reactions of **3** were carried out with iodides and bromides **4** in DMF at 65°C with $Pd(PPh_3)_4$ as a catalyst.[6] Approximately 5 mol percent of the catalyst were used (see Scheme 2). The corresponding 1-arylcyclobutenes **5** were isolated in good yields after reaction times of 18–48 h. Table 1 shows the results.

In addition to **4a**–**4m**, 4-iodoaniline and 4-iodo-(*N*,*N*)dimethylaniline were also treated with **3**, but the expected products were not formed. Obviously an amino group is not tolerated within the catalytic cycle of this reaction.[7] It is interesting to note that electron acceptor substituents (*p*-NO_2, *m*-CF_3, *p*-$COCH_3$) and electron donor substituents (*p*-OCH_3) give comparable results.

Having demonstrated that **3** reacts well with aryl monohalides, the dihalides **6a**–**d** were treated with two equivalents of **3** in the presence of 10 mol percent of $Pd(PPh_3)_4$, again in DMF at 65°C. Within 18–24 h, good



Scheme 1.



Scheme 2.

Keywords: Stille coupling; cyclobutenes; palladium catalysis.

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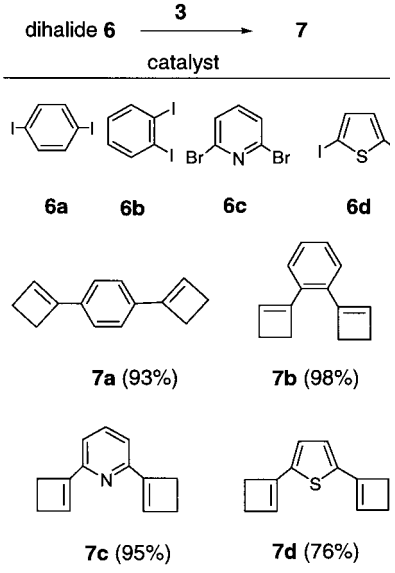
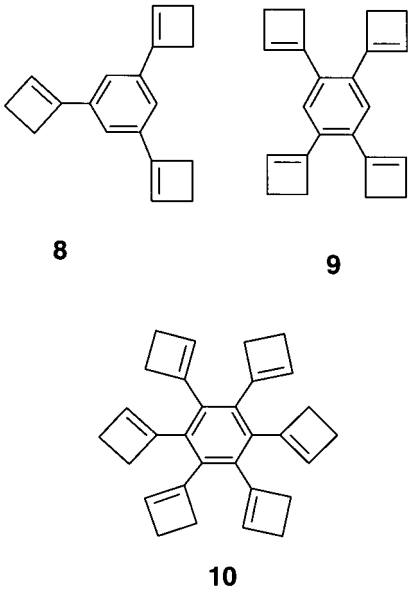
Table 1. Arylcyclobutenes **5** from **3** and arylhalides **4**

4, **5**	Aryl group of **4** and **5**	Halogen of **4**	Reaction time (h)	% Yield of **5**
a	4-tolyl	I	24	94
b	3-tolyl	I	24	85
c	2-tolyl	I	24	86
d	4-anisyl	I	24	87
e	3-anisyl	Br	48	98
f	2-thioanisyl	I	24	84
g	3-(trifluoro-methyl)phenyl	Br	18	96
h	4-nitrophenyl	I	24	98
i	4-(trimethyl-silyl)phenyl	Br	18	84
j	4-acetylphenyl	I	48	98
k	1-naphthyl	I	24	71
l	2-pyridyl	Br	24	97
m	2-thienyl	I	24	88



Scheme 3.



Scheme 4.

yields of **7a**–**d** could be isolated. The results are shown in Scheme 3.

The successful conversion of **6a**–**d** into the coupling products **7a**–**d** indicated that even higher halogenated benzenes could be used for the Stille coupling. Indeed, the efficiency of this cross-coupling reaction could be demonstrated using 1,3,5-tribromobenzene, 1,2,4,5-tetrabromobenzene and hexabromobenzene as starting materials. The reactions of **3** with these halides were carried out as described above, applying 6, 8, and, respectively 12 mol percent of $Pd(PPh_3)_4$ as a catalyst. The arylcyclobutenes **8**, **9** and **10** were isolated in 74, 54 and 52% yield (see Scheme 4).

Hexa(1-cyclobutenyl)benzene (**10**) is a waxy solid, which readily polymerized on contact with air. The ^{13}C NMR spectrum of **10** at room temperature showed 5 signals, indicating that the barrier of rotation around the bond connecting the benzene ring with the cyclobutene unit is easily surmounted at ambient temperature.

In conclusion, we have developed an efficient synthesis of arylcyclobutenes. Starting materials are readily available, the procedure is simple, the reaction conditions are mild and the yields are high.

Experimental

General

All reactions were carried out under nitrogen. Ether was freshly distilled from sodium, dimethylformamide (DMF) from calcium hydride. Flash chromatography was performed on silica gel 230–400 mesh. ^1H NMR spectra were recorded on a Bruker DPX 300 at 300 MHz, ^{13}C NMR on the same instrument at 75 MHz, using $CDCl_3$ as solvent. Mass spectra were obtained on a Finnigan MAT 95 SQ apparatus (70 eV).

1-Tri-*n*-butylstannylcyclobutene (3). *tert*-Butyllithium in hexane (11 ml, 1.7 M, 18.7 mmol) was added dropwise at −72°C to 1-bromocyclobutene (**1**) (1.33 g, 10.0 mmol) in ether (15 ml). After 2 h at 0°C, chlorotri-*n*-butyltin (3.25 g, 10.0 mmol) was added dropwise, the mixture was allowed to warm to room temperature and stirred for 2 h. The

mixture was quenched with saturated NH_4Cl solution, extracted with water and the ether layer dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo and purification by column chromatography (petroleum ether) afforded **3** (2.47 g, 72%) as a colorless liquid.

^{1}H NMR ($CDCl_3$): δ 0.86–0.91 (m, 15H), 1.28–1.32 (m, 6H), 1.45–1.51 (m, 6H), 2.62 (m, 2H), 2.86 (m, 2H), 6.44 (broad s, 1H). ^{13}C NMR ($CDCl_3$): δ 9.3 (CH_2), 13.7 (CH_3), 27.3 (CH_2), 29.2 (CH_2), 35.2 (CH_2), 37.3 (CH_2), 151.7 (CH), 155.0 (C_q). MS (EI): *m/z* (%) 343 (M^+-H, 4), 287 (100), 231 (56), 177 (60), 121 (28). HRMS ($C_{16}H_{32}Sn$) calcd: 343.1447, found: 343.1448.

General procedure for the cross-coupling reaction

Under nitrogen atmosphere, 0.50 mmol of **3** and 0.25 mmol of the aryl halide were dissolved in 3 ml of DMF followed by addition of 5.0 mol% of $Pd(PPh_3)_4$ (based on aryl halide). The resulting mixture was stirred at 65°C for 18–48 h. Ether (20 ml) was added, and the solution was washed with an aqueous KF solution and with brine. The organic layer was dried with anhydrous $MgSO_4$. After concentration of the organic solution, the oily residue was subjected to a silica gel chromatography using a mixture of petroleum ether and ethyl acetate as eluent. In all cases, the excess of **3** was found in the first fraction. All fractions containing the product were combined, the solvent removed in vacuo and the remaining oil was characterized by ^{1}H NMR, ^{13}C NMR, by MS and HRMS. The oils **5h**, **5j**, **7a**, **7c**, **8**, **9**, and **10** solidified slowly to a waxy mass.

^{1}H and ^{13}C NMR spectra of 4-(1-cyclobutenyl)toluene (**5a**), 4-(1-cyclobutenyl)anisole (**5d**) and 1-(1-cyclobutenyl)-3-(trifluoromethyl)benzene (**5g**) were identical to the reported literature values.[8,9]

3-(1-Cyclobutenyl)toluene (5b). Colorless oil, yield 85%. ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H), 2.52 (m, 2H), 2.79 (m, 2H), 6.27 (broad s, 1H), 7.16 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 21.3 (CH_3), 26.2 (CH_2), 28.7 (CH_2), 121.3, 124.8, 126.9, 128.3, 134.1(CH), 134.9 (C_q), 137.7 (C_q), 146.5 (C_q). MS (EI): *m/z* (%) 144 (M^+, 60), 129 (100), 115 (40), 91 (10). HRMS ($C_{11}H_{12}$) calcd: 144.0939, found: 144.0940.

2-(1-Cyclobutenyl)toluene (5c). Colorless oil, yield 86%. ^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H), 2.55 (m, 2H), 2.89 (m, 2H), 6.18 (broad s, 1H), 7.15–7.22 (m,4H). ^{13}C NMR ($CDCl_3$): δ 21.8 (CH_3), 26.8 (CH_2), 30.6 (CH_2), 125.7 (CH), 126.1, 127.4, 130.5, 131.2 (CH), 133.5 (C_q), 136.5 (C_q), 146.4 (C_q). MS (EI): *m/z* (%) 144 (M^+, 56), 129 (100), 115 (50), 91 (4). HRMS ($C_{11}H_{12}$) calcd: 144.0939, found: 144.0942.

3-(1-Cyclobutenyl)anisole (5e). Colorless oil, yield 98%. ^{1}H NMR ($CDCl_3$): δ 2.52 (m, 2H), 2.78 (m, 2H), 3.81 (s, 3H), 6.29 (broad s, 1H), 6.87–7.20 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 26.2 (CH_2), 28.7 (CH_2), 55.2 (CH_3), 109.5 (CH), 113.1, 116.8, 127.6, 129.3 (CH), 136.4 (C_q), 146.2 (C_q), 159.6 (C_q). MS (EI): *m/z* (%) 160 (M^+, 100), 145 (28), 129 (72), 115 (40), 102 (20), 91 (18). HRMS ($C_{11}H_{12}O$) calcd: 160.0888, found: 160.0888.

2-(1-Cyclobutenyl)thioanisole (5f). Colorless oil, yield 84%. ^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H), 2.58 (m, 2H), 2.92 (m, 2H), 6.51 (broad s, 1H), 7.14–7.22 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 15.2 (CH_3), 27.0 (CH_2), 30.7 (CH_2), 124.1, 124.2, 126.9, 127.5 (CH), 133.7 (CH), 137.7 (C_q), 144.5 (C_q). MS (EI): *m/z* (%) 176 (M^+, 40), 161 (100), 128 (50), 115 (15), 89 (8). HRMS ($C_{12}H_{11}S$) calcd:176.0651, found: 176.6450.

4-(1-Cyclobutenyl)nitrobenzene (5h). Yellow solid, yield 98%. ^{1}H NMR ($CDCl_3$): δ 2.52 (m, 2 H), 2.77 (m, 2 H), 6.47 (broad s, 1H), 7.35–8.11 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 26.8 (CH_2), 28.7 (CH_2), 123.8, 124.7 (CH), 133.2 (CH), 140.7 (C_q), 144.5 (C_q). MS (EI): *m/z* (%) 175 (M^+, 60), 158 (65), 128 (100), 101 (25), 51 (30). HRMS ($C_{10}H_9NO_2$) calc: 175.0632, found: 175.0632.

4-(1-Cyclobutenyl)trimethylsilylbenzene (5i). Colorless oil, yield 84%. ^{1}H NMR ($CDCl_3$): δ 0.26 (s, 9H), 2.52 (m, 2H), 2.84 (m, 2H), 6.30 (broad s, 1H), 7.38–7.50 (m, 4H). ^{13}C NMR ($CDCl_3$): δ −1.2 (CH_3), 26.3 (CH_2), 28.7 (CH_2), 123.4 (CH), 127.5, 133.3 (CH), 134.9 (C_q), 139.6 (C_q), 146.4 (C_q). MS (EI): *m/z* (%) 202 (M^+, 100), 159 (4), 128 (4), 73 (8). HRMS ($C_{13}H_{18}Si$): calcd: 202.1177, found: 202.1176.

4-(1-Cyclobutenyl)acetophenone (5j). Colorless waxy solid, yield 98%. ^{1}H NMR ($CDCl_3$): δ 2.56 (m, 2H), 2.58 (s, 3H), 2.82 (m, 2H), 6.45 (broad s, 1H), 7.38 (m, 2H), 7.92 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 26.5 (CH_2), 26.6 (CH_3), 28.7 (CH_2), 124.1, 128.5, 130.9 (CH), 135.7, 139.1, 145.4, 197.6 (C_q). MS (EI): *m/z* (%) 172 (M^+, 55), 147 (35), 129 (100), 115 (20), 77 (20), 51 (10). HRMS ($C_{12}H_{12}O$) calcd: 172.0883, found: 172.0882.

1-(1-Cyclobutenyl)naphthalene (5k). Colorless oil, yield 71%. ^{1}H NMR ($CDCl_3$): δ 2.66 (m, 2H), 3.04 (m, 2H), 6.54 (broad s, 1H), 7.41–8.46 (m, 7H). ^{13}C NMR ($CDCl_3$): δ 27.0 (CH_2), 31.3 (CH_2), 124.4 (CH), 125.2 (CH), 126.3 (CH), 128.0 (CH), 128.6 (CH), 134.1 (C_q), 137.4 (C_q), 145.6 (C_q). MS (EI): *m/z* (%) 180 (M^+, 95), 152 (100), 127 (70), 89 (35), 51 (15). HRMS ($C_{14}H_{12}$) calcd: 180.1017, found: 180.1023.

2-(1-Cyclobutenyl)pyridine (5l). Colorless oil, yield 97%. ^{1}H NMR ($CDCl_3$): δ 2.50 (m, 2H), 2.84 (m, 2H), 6.63 (broad s, 1H), 7.05–8.51 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 26.5 (CH_2), 28.6 (CH_2), 132.4 (CH), 119.1, 121.9, 136.1, 149.4 (CH), 146.4 (C_q), 152.8 (C_q). MS (EI): *m/z* (%) 130 (M^+-H, 100), 104 (6), 78 (4). HRMS (C_9H_9N) calcd: 130.0657 (M^+-H), found: 130.0661.

2-(1-Cyclobutenyl)thiophene (5m). Colorless oil, yield 88%. **5m** decomposed slowly during the recording of the NMR spectra. ^{1}H NMR ($CDCl_3$): δ 2.49 (m, 2H), 2.74 (m, 2H), 5.97 (broad s, 1H), 6.86–7.08 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 27.3 (CH_2), 30.2 (CH_2), 123.3 (CH), 124.4, 126.0, 127.2 (CH), 139.3 (C_q), 140.2 (C_q). MS (EI): *m/z* (%) 136 (M^+, 96), 108 (48), 97 (28), 69 (8). HRMS calcd: 136.0346, found: 136.0344.

1,4-Di(1-cyclobutenyl)benzene (7a). Waxy solid, yield 93%. ^{1}H NMR ($CDCl_3$): δ 2.53 (m, 4H), 2.79 (m, 4H),

6.27 (broad s, 2H), 7.29 (s, 4H). ^{13}C NMR ($CDCl_3$): δ 26.3 (CH_2), 28.7 (CH_2), 124.2 (CH), 127.1 (CH), 137.3 (C_q), 146.2 (C_q). MS (EI): *m/z* (%) 182 (M^+, 60), 153 (34), 129 (100), 115 (20), 105 (6). HRMS ($C_{14}H_{14}$) calcd: 182.1096, found: 182.1097.

1,2-Di(1-cyclobutenyl)benzene (7b). Colorless oil, yield 98%. ^{1}H NMR ($CDCl_3$): δ 2.50 (m, 4H), 2.86 (m, 4H), 6.20 (broad s, 2H), 7.20 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 26.7 (CH_2), 31.2 (CH_2), 127.1 (CH), 127.5 (CH), 131.4 (CH), 133.6 (C_q), 146.7 (C_q). MS (EI): *m/z* (%) 181 (M^+-H, 16), 167 (100), 153 (60), 128 (18), 115 (20). HRMS ($C_{14}H_{14}$) calcd: 181.1017 (M^+-H), found: 181.1010.

2,6-Di(1-cyclobutenyl)pyridine (7c). Yellow solid, yield 95%. ^{1}H NMR ($CDCl_3$): δ 2.48 (m, 4H), 2.81 (m, 4H), 6.53 (broad s, 2H), 7.04–7.50 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 26.5 (CH_2), 28.8 (CH_2), 117.5 (CH), 132.6 (CH), 136.3 (CH), 146.7 (C_q), 152.6 (C_q). MS (EI): *m/z* (%) 182 (M^+-H, 100), 154 (20), 129 (18), 102 (20), 77 (16). HRMS ($C_{13}H_{13}N$) calcd: 182.0969 (M^+-H), found: 182.0964.

2,5-Di(1-cyclobutenyl)thiophene (7d). Colorless oil, yield 95%. ^{1}H NMR ($CDCl_3$): δ 2.49 (m, 4H), 2.72 (m, 4H), 5.95 (broad s, 2H), 6.70 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 27.3 (CH_2), 30.1 (CH_2), 123.6 (CH), 126.3 (CH), 140.2 (C_q), 148.1 (C_q). MS (EI): *m/z* (%) 188 (M^+, 100), 160 (20), 148 (24), 135 (20), 115 (28), 91 (10). HRMS ($C_{12}H_{12}S$) calcd: 188.0659, found: 188.0654.

1,3,5-Tri(1-cyclobutenyl)benzene (8). Colorless solid, yield 74%. ^{1}H NMR ($CDCl_3$): δ 2.53 (m, 6H), 2.80 (m, 6H), 6.31 (broad s, 3H), 7.19 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 26.2 (CH_2), 28.8 (CH_2), 119.0 (CH), 127.6 (CH), 135.0 (C_q), 146.2 (C_q). MS (EI): *m/z* (%) 234 (M^+, 64), 205 (20), 183 (30), 165 (80), 132 (64), 105 (38), 84 (54). HRMS ($C_{18}H_{18}$) calcd: 234.1408, found: 234.1406.

1,2,4,5-Tetra(1-cyclobutenyl)benzene (9). Colorless solid, yield 54%. ^{1}H NMR ($CDCl_3$): δ 2.50 (m, 8H), 2.85 (m, 8H), 6.20 (broad s, 4H), 7.03 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 26.7 (CH_2), 31.2 (CH_2), 126.7 (CH), 131.6 (CH), 132.3 (C_q), 146.3 (C_q). MS (EI): *m/z* (%) 286 (M^+, 12), 257 (64), 229 (88), 202 (100), 189 (68), 165 (50), 152 (30), 115 (14). HRMS ($C_{22}H_{22}$) calcd: 286.1720, found: 286.1719.

1,2,3,4,5,6-Hexa(1-cyclobutenyl)benzene (10). Colorless solid, yield 52%. ^{1}H NMR ($CDCl_3$): δ 2.45 (m, 12H), 2.71 (m, 12H), 5.91 (broad s, 6H). ^{13}C NMR ($CDCl_3$): δ 27.4 (CH_2), 34.3 (CH_2), 133.0 (CH), 133.8 (C_q), 146.7 (C_q). MS (EI): *m/z* (%) 390 (M^+, 4), 333 (24), 306 (100), 263 (60), 226 (10), 138 (20). HRMS ($C_{30}H_{30}$) calcd 390.2348, found 390.2349.

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