Synthesis of Symmetrical and Nonsymmetrical Bisthienylcyclopentenes

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Abstract: Diarylethenes possess unique structural properties, which enabled them to find widespread applications in the field of photochromism. Nowadays, bisthienylcyclopentenes (BTCs) present the most popular subfamily of these compounds, which are widely used as Ptype chromophores. This minireview summarises the main strategies for the synthesis of symmetrical and nonsymmetrical BTCs. In addition, attention is drawn to desymmetrisations achieved by monosubstitutions, which is not frequently utilised, although it can be highly advantageous. This is supported with some of the authors' latest results.

Keywords: bisthienylcyclopentenes • diarylethenes • dithienylcyclopentenes • dithienylperfluorocyclopentenes • nonsymmetrical diarylethenes • photochromism

Introduction

Bisthienylcyclopentenes (BTCs) are a subtype of diarylethenes, one of the most popular P-type photochromes. Their success lies not only in their thermal irreversibility, but also in their high fatigue resistance and fast response times.^[1] Although these compounds most often called diarylethenes, dithienylethenes, bisthienylethenes or dithienylperfluorocyclopentenes, we use the name bisthienylcyclopentenes, which in our opinion offers the most precise structural description of these molecules. The number of reports in the field have shown growing tendency (Figure 1); 2257 publications have been published up to date, of which 191 are patents and 143 are general reviews.

A leading review, focusing mainly on the fundamental properties and applications of diarylethenes was published by Irie in 2000.^[2] During our work with nonsymmetrical BTCs we observed the lack of publications dealing with the synthesis of this successful family of compounds. This work summarises the available synthetic approaches towards symmetrical and nonsymmetrical BTCs. It is not the aim of this minireview to give an exhaustive overview of the published literature, but rather to highlight the recent developments in the field of BTC synthesis. In the second half of this work we concentrate particularly on the synthesis of nonsymmetrical analogues and report our recent findings as well. Finally, we would like to highlight monosubstitution of BTCs

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Figure 1. Distribution of the number of publications in the field.

(based on selective monolithium-halogen exchange) as a viable desymmetrisation method.

Synthesis of Bisthienylcyclopentenyl Core

For the synthesis of these compounds two conceptually different methods exist. The majority of these syntheses are based on the substitution of octafluorocyclopentene with substituted thiophene derivatives (Scheme 1). In this formal



R² = H, halogen, alkyl, O-alkyl R³ = halogen usually Br

R⁴ = H, halogen, alkyl, aryl, O-alkyl, S-alkyl, heteroaryl

Scheme 1. General conditions of the formal substitution reaction of octafluorocyclopentene.

substitution reaction the preformed lithiated thiophene reacts with octafluorocyclopentene to give F-BTCs according to an addition–elimination mechanism.^[3] The high volatility (b.p.: 26–28 °C) of octafluorocyclopentene can account for lower yields; however, the conditions of lithium–halogen exchange probably play a major role in this reaction.^[4] The reaction is usually conducted in etheral solvents such as THF or Et₂O, using half equivalent of octafluorocyclopentene at low temperatures (–80 to –60 °C). At these temperatures, side reactions such as heteroatom-directed metalations or unwanted lithium–halogen exchange are minimised, which otherwise might strongly deteriorate yields.

Yields are highly dependent on the substitution pattern of the thiophenyl unit (Table 1). Reaction conditions may vary

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Table 1. Substituent effect in the formal substitution reaction of octa-fluorocyclopentene.



slightly; however, some general considerations might be drawn from analogues synthesised under identical conditions. Thiophenyl units bearing an electron-withdrawing group tend to give lower yields, while the presence of an electron-donating or a conjugative group increases yields (entries 1-5, Table 1).^[3,5] Electronic effects transferred through aromatic substituents are much less apparent.^[6] Thiophene units bearing a heteroalkyl or heteroaromatic groups tend to give low yields (entry 6, 23%), which might be attributed to the cumulated effect of the coordinating groups obstructing the desired lithium-halogen exchange.^[7] It is worth noting that 4,4'-substituted analogues, such as benzothiophenes (entry 1) or dimethylthiophenes (entry 2), can also be obtained by this method. These compounds have improved fatigue resistance compared to the analogous thiophene derivatives. The substituents at the 4,4'-positions are believed to obstruct an irreversible rearrangement, which is the main fatigue process upon irradiation of these compounds.^[2]

Symmetrical dihalo-BTCs, such as chloride **1**, are versatile intermediates as the halogen can be converted to a great variety of other moieties (vide supra). When using substituted dihalothiophenes for preparing F-BTCs, the 4-position always has to be accommodated with the more reactive halogen, or otherwise the sulfur atom would govern selectivity to give preferentially the 2-substituted product, by stabilising the negative charge more efficiently at the 2-position.^[8] In terms of accessibility, stability, and selectivity chlorobromomethylthiophene is a useful intermediate when following this route. It is commercially available or can be synthesised in two steps from 2-methylthiophene (Scheme 2).^[9]



Scheme 2. Synthesis of dichloro F-BTC 1.

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Recently, Shinokubo et al. reported a novel method to synthesise F-BTCs using Suzuki–Miyaura coupling.^[10] The method utilises 1,2-dichlorohexafluorocyclopentene which is much less volatile (b.p.: 90 °C) than octafluorocyclopentene and therefore easier to work with. Furthermore, this way organolithium species are also avoided and carbonyl or cyano derivatives can be obtained in one step in low to moderate yields (entries 2–6, Table 2). In the course of C–H functionalisation studies (vide supra) the same group published the synthesis of an H-BTC analogue by the same method (entry 1).^[11]

Another widespread method creates the cyclopentenyl motif in an intramolecular McMurry reaction rather than starting from a halogenated cyclopentene. In 1997, Fan published the synthesis of a dihydrothiophene-bridged bisthienyl analogue using the McMurry reaction.^[12] The same method was later adapted by Feringa et al. to the synthesis of BTCs, which were achieved in three or four steps from readily available 2-methylthiophene (Scheme 3).^[13] Many perhydro BTC (H-BTC) analogues have since been synthesised by this method. Migulin's review nicely describes the utility of McMurry reaction in the synthesis of BTCs and other dihetarylethenes.^[14]

György Szalóki obtained his M.Sc. degree in Chemical Engineering from the Budapest University of Technology and Economics in 2005. After working at AMRI Hungary for a year as a research chemist he accepted a Marie Curie Fellowship at the National Hellenic Research Foundation in Athens. He received his Ph.D. from University College London in 2012, where he worked on the synthesis of novel ferrocenyl ligands and their applications in asymmetric catalysis. Since then, he has been working with Jean-Luc in the field of photochemistry at the University of Bor-



deaux. In the course of this work they design and synthesise multiaddressable photochromic switches mainly based on bisthienylcyclopentenes (BTCs).

Jean-Luc Pozzo was awarded diplomas from Paris VI University (1987) and the National School of Chemistry of Paris (ENSCP, 1989) followed by an M.Sc. degree from Aix-Marseille II University (1990). His Ph.D. (1993) from Université de la Méditerranée (Marseilles, France) focussed on T-type photochromes, such as chromenes and naphthooxazines. Essilor International—PPG Industries offered him a grant for an industrial post-doctoral stay on tunable ophthalmic lenses. Since 2002, he has been full Professor at the University of Bordeaux developing photoswitchable



NLOphores and gelators, as well as multiaddressable self-assemblies and bi- and triphotochromics. He was appointed Dean of the Chemistry Department in 2011. Table 2. Suzuki–Miyaura coupling of 1,2-dichloro-hexafluorocyclopentene with thiophenyl boronic acids/esters.

	ArB(OR) ₂ + (3 equiv) + $X X$	Pd ₂ (dba ₃)]·CHCl ₃ , PCy ₃ ,CsF, toluene/H ₂ O, reflux, 16h		R = F or H, X = Cl or Br	
Entry	$ArB(OR)_2$	R	Х	Pd [mol%]	Yield [%]
1	B(OH) ₂	Н	Br	2.5	89 ^[a]
2	B(OH) ₂	F	Cl	1	88
3	B(OH) ₂	F	Cl	1	82
4	MeO ₂ C	F	Cl	10	63
5	ОНС	F	Cl	10	45
6		F	Cl	10	29

[a] Conditions: [Pd(PPh_3)_4], Na_2CO_3, toluene/EtOH (1:1); pin=pinacol ester.



Scheme 3. Synthesis of symmetrical chlorides 1 and 2 using the McMurry reaction.

Derivatisation of the Bisthienylcyclopentenyl Core

The 2,2'-dichloro BTCs can be further derivatised by electrophilic substitution giving access to a wide range of compounds in moderate to excellent yields (Table 3).^[15] The aldehyde moiety proved to be particularly useful as it can be functionalised in many different ways to extend the π conjugation of the BTC system. To achieve this, Wittig^[16] and Knoevenagel^[17] reactions have been most frequently applied. Other interesting structures, containing imidazole,^[18] triazole,^[19] rhodanine,^[20] indolinooxazolidine^[21] or phenanthroline^[22] groups have also been reported.

When using borates as electrophiles, diboronic acid and ester derivatives can be isolated; however, they undergo rapid deboronation.^[23] Borononic esters can be reacted in situ with aryl bromides in a Suzuki reaction to give diarylated products (Table 4).^[24] This one-pot procedure is the most common way of arylating H- and F-BTC analogues.^[24b,25] Al-



though yields might be low in certain cases (entries 3, 4 and 7), symmetrical analogues with valuable functional groups (halogen, aldehyde, hydroxyl, nitrile) can be accessed this way. In these reactions consistently higher yields were achieved when H-BTCs were used. During our work with sym-

metrical diarylated BTCs, we found that *n*BuLi was not reactive enough to affect complete dilithium-halogen exchange of dichloride 2 and a mixture of the mono- and disubstituted products was isolated. Switching to *t*BuLi greatly improved the yield (from 50 to 81 %, entry 8).

Transition-metal couplings were also tested by Feringa et al. in order to obtain diarylated analogues.^[13a] Kumada coupling gave the monosubsti-

tuted product in low yield (40%). The double Kumada coupling was achieved later by Branda in moderate to good yields.^[26] On the other hand, diarylation by Suzuki coupling was not successful. Since then, there have been a few independent reports on successful Suzuki–Miyaura coupling of H- and F-BTC dihalogenides in low to good yields (38– 81%).^[27] In 2009 Hermes et al. reported the Suzuki– Miyaura coupling reaction of dichloride **1** and aromatic boronic acids/esters with high yields (Table 5).^[9a]

During our work we were unable to reproduce the same yields starting from dichloride **1**. Under identical conditions the yields were lower for phenyl (entry 1, Table 6) and moderate for the other functionalised analogues. Therefore, the more reactive dibromide **3** and diiodide **4** were synthesised in good yields (76 and 87%, respectively) according to literature precedents.^[15a,26] These analogues showed highly improved reactivity, which resulted in shorter reaction times (entries 2 and 3 Table 6). It is worth noting that bromide **3**

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dichlorides 1 and 2.

 $(R)_{6}$ 1) nBuLi (2-2.5 mol%), THF 2) B(OnBu)₃, 3) ArBr, [Pd(PPh₃)₄] (2-10 mol%), R 1: R = F 2: R = H Na₂CO₃, THF Entry R Yield [%] Ar F 1 55 СНС F 2 52 F 3 23 F 4 42 OMe 5 Н 83 Η 6 76 7 Η 35 8 Н 81^[a] OMe

[a] tBuLi was used in first step.

Table 5. Double Suzuki-Miyaura coupling of dichloride 1 with different aryl boronic acids/esters.



was reactive enough in Suzuki-Miyaura couplings to make this approach feasible towards aryl-substituted BTCs. This was later exploited in our desymmetrisation studies (vide supra).

Palladium-catalysed direct arylation of simple bisthienylcyclopentene has also been reported by Shinokubo et al.^[11] The method was tested on a wide range of analogues, which gave good yields (63-78%) under optimised conditions

Table 4. One-pot electrophilic substitution/Suzuki-Miyaura coupling of Table 6. Comparison of the reactivity of dihalogenides 1, 3 and 4 in Suzuki-Miyaura coupling.[a]



Entry	SM ^[b]	Х	<i>t</i> [h]	Yield [%]	
1	1	Cl	18	mono, 0	di, 72
2	3	Br	3	mono, 0	di, 75
3	4	Ι	2	mono, 0	di, 95

[a] General conditions: ArB(OH)₂ (2.2 equiv), [Pd(PPh₃)₄], (10 mol%), Na₂CO₃, DME/H₂O (4:1), reflux. [b] SM = starting material.

(Scheme 4). The only example of H-BTC gave a lower yield than the corresponding F-BTC analogue.

Diiodide-substituted H-BTC analogues can also be derivatised using Sonogashira coupling (Table 7).[15c,28]



Scheme 4. Diarylation of simple bisthienylcyclopentene using C-H functionalisation.

Table 7. Sonogashira coupling of diiodide.



Synthesis of Nonsymmetrical BTCs

Several groups have made attempts to tune the photochromic properties of these compounds; therefore, the number of synthesised nonsymmetrical BTCs has increased over the last decade. To form nonsymmetrical BTCs, a highly selective reaction is needed to allow desymmetrisation to occur at some point during the synthesis. In 1995 Irie published a protocol to synthesise a monosubstituted F-BTC analogue, using only an equimolar amount of thiophene derivative and octafluorocyclopentene.^[29] Since then, this approach has been applied to the synthesis of many nonsymmetrical F- BTC derivatives (Table 8).^[15a,30] The analogues are synthesised in a stepwise manner, using previously synthesised thiophene units (**A** and **B**). As in the first step, monosubstitution is the aim and excess of the octafluorocyclopenetene

Table 8. Synthesis of nonsymmetrical F-BTCs ${\bf 6}$ using stepwise substitution.



can be used. Unfortunately, the utilisation of organolithium reagents limits this method to protected carbonyls/hydroxyls

and nonhalogenated aromatics. In addition, only F-BTCs can be synthesised by this method. The yields of the second substitutions are generally lower than the first ones. Yoshida et al. sucessfully adapted integrated flow microreactor systems to this approach.^[31] These systems have proven efficient in controlling selectivity in reactions of highly reactive intermediates, such as lithiated species.

This stepwise method is widely used; however, a few other isolated reports have also been published that follow a different approach. Wuest reported the synthesis of a nonsymmetrical cyclopentene analogue by two consecutive Suzuki–Miyaura couplings using 1,2-dibromocyclopentene (Scheme 5).^[32] Although, this analogue is not a BTC derivative, Wuest's protocol was later adapted by Shinokubo to the synthesis of symmetrical BTCs (see Table 2). This example also implies that stepwise Suzuki coupling is feasible towards the synthesis of nonsymmetrical BTCs as well.

Shinokubo et al. tested their C–H functionalisation protocol (vide infra) on simple bisthienylcyclopentenes.^[11] The first monosubstitution gave monofunctionalised F-BTCs in low yields (32–36%, Scheme 6). In this case they planned to achieve monosubstitution by using one equivalent of the aryliodide coupling partner, which might had been responsible for the low yields. In the second arylation an excess (3.9 equiv) of aryliodides were used; however, possibly due to increased steric hinderance, the yields were only slightly higher (37–40%) then in the first steps. Doucet and Guerchais independently reported a protocol using the same strategy under modified conditions.^[33] In the course of their work they synthesised 13 nonsymmetrical analogues from low to excellent yields (21–94%).

The McMurry reaction has also been applied to the synthesis of a nonsymmetrical H-BTC, by Migulin et al. (Scheme 7).^[34] This way, a versatile intermediate was obtained, which was selectively derivatised in the following step.

Unsymmetrically functionalised F-BTCs can be obtained from dihalogenides as well, such as **1**, **3** or **4**, by using Suzuki–Miyaura coupling. We were interested to see wheth-



Scheme 5. Synthesis of a nonsymmetrical H-BTC using Suzuki-Miyaura coupling.



Scheme 6. Stepwise arylation of simple bisthienylcyclopentene using C-H functionalisation.



Scheme 7. Synthesis of a nonsymmetrical H-BTC using the McMurry reaction.

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er monosubstitution can be achieved by using only a small excess (1.2 equiv) of the boronic acid. The results of mono Suzuki coupling of dihalogenides **1**, **3**, and **4** with phenylboronic acid are depicted in Table 9. The yields are unoptimised

Table 9. Monoarylation of dihalogenides 1, 3 and 4.



[a] SM=starting material. [b] Isolated yields of SM/monoproduct/diproduct, respectively.

and only serve as a comparison of the reactivity of the different dihalogenides 1, 3, and 4. Dichloride 1 gave the best selectivity, where the product was isolated in moderate yield (44%, entry 1). The results also showed that by using the more reactive dibromide 3 or diiodide 4 the major product became the disubstituted analogue (entries 2 and 3).

Following this, we focused on other desymmetrisation methods, such as electrophilic substitution using mono lithium-halogen exchange. We conducted a series of experiments where dichlorides **1** and **2** were treated with with a slight excess (1.05 equiv) of *n*BuLi and quenched with different electrophiles (Table 10).^[37] The corresponding monolithiated species were formed in good yield in each case, which was confirmed by TLC. In addition, the NMR analysis of the crude reaction mixtures showed the presence of only the starting material, mono- and disubstituted products. When using different electrophiles such as water or TMSCI similar

Table 10. Substitution study of dichlorides **1** and **2**.



Entry	Product	SM ^[a]	R	E+	Е	Ratio	Yield [%]
1	7	1	F	DMF	CHO	12/74/14 ^[b]	7/65/7 ^[c]
2	8	1	F	H_2O	Н	11/74/15 ^[b]	N.A. ^[e]
3	9	1	F	TMSCl	TMS	14/73/13 ^[b]	N.A.
4	10	2	Η	DMF	CHO	6/78/16 ^[d]	1/73/15 ^[f]

[a] SM=starting material. [b] Ratio of SM/monoproduct/diproduct respectively (based on crude NMR spectroscopic data). [c] Isolated yields of SM/monoproduct/diproduct respectively. [d] Ratio of byproduct/monoproduct/diproduct, respectively (based on crude NMR spectroscopic data). [e] N.A. = not available (separation was not possible). [f] Isolated yields of byproduct/monoproduct/diproduct respectively.

results were obtained (Table 10, entries 1–3), which led us to believe that this ratio (selectivity) does not depend on the nature of the electrophile but only on the stability of the lithiated species. Perhydro analogue 2 was more reactive compared to perfluoro analogue 1 (entries 1 and 4). Not only the monoaldehyde 10 was isolated in higher yield (73%), but the starting material 2 was completely consumed. A doubly substituted by-product 11 was also isolated upon purification.

Our results are in accordance with a previous report on monoformylation of H-BTC and monoarylations of F-BTC analogues.^[13a,35] The latter gives access to monoarylated products in good yields (Table 11). Although monoarylation





yields may vary but some high yielding cases (entries 1 and 2) imply that in situ formation of borate ester is complete. Lower yields (entries 3–5) are probably the result of a less efficient Suzuki reaction between the borate ester and the aryl bromide. The yields of the second arylations are usually somewhat lower than those of the first ones (entries 1–3). The H-BTC analogues tend to give slightly higher yields than the corresponding F-BTCs. In the second step usually *t*BuLi is used to promote lithiation as in some cases *n*BuLi or *s*BuLi proved to be ineffective.^[13a] This one-pot method (substitution followed by Suzuki coupling) can be successfully applied to the synthesis of nonsymmetrical aryl-substituted BTCs.

Functionalisation, using organolithium reagents, offers a good starting point for desymmetrisation, due to its high selectivity (see Tables 10 and 11). On the other hand, for the functionalisation of the second thiophene unit, milder transition-metal coupling reactions are advised. This would extend the scope of this approach to functionalised derivatives, such as aldehydes, ketones, nitriles, esters, halogenides,

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amides, which might be sensitive to organolithiums otherwise. As monochloride **7** was not sufficiently reactive in Suzuki coupling, halogen derivatives **14** and **15** were synthesised (Table 12).^[37] Selectivity of the lithium-halogen ex-

Table 12. Monoformylation study of dibromide 3 and diiodide 4.

x-4	S S S	1) <i>n</i> BuLi Et ₂ O, χ 2) DMF –78 °C	i or <i>t</i> BuLi (1.02 equ _78 °C, 10 min (2 equiv), C, 3 h			
	3: X = Br 4: X = I			14: X 15: X	= Br = I	
Entry	SM ^[a]	Х	Product	RLi	Yield [%]	
1	3	Br	14	<i>n</i> BuLi	64	
2	3	Br	14	tBuLi	59	
3	4	Ι	15	nBuLi	49	
4	4	Ι	15	tBuLi	20	

[a] SM = starting material.

change was somewhat lower. To improve selectivity, the lithium-halogen exchange was conducted at low temperatures $(-78 \,^{\circ}C)$, while the reaction was monitored by TLC. Under these conditions, bromoaldehyde **14** was isolated in good (Table 12, entry 1, 64%) while the iodoaldehyde **15** in a moderate yield (entry 3, 49%). Using the more reactive *t*BuLi led to lower yields in both cases (entries 2 and 4).^[36]

As it was expected, bromoaldehyde 14 showed highly im-

proved reactivity compared to chloroaldehyde **7** (entries 1–8, Table 13).^[37] A range of novel functionalised derivatives **16– 23** were synthesised in good to excellent yields (entries 9–16). In general, the enhanced reactivity of bromide **14** enabled us to conduct the reactions under milder conditions. The temperatures could be decreased to

50 or 70 °C instead of the usual reflux temperature (105 °C) and the amount of boronic acid could be reduced from 2.2 to 1.5 equivalents. Under these conditions the increased reactivity of bromide **14** resulted in shorter reaction times, yet higher yields compared to those reactions starting from chloride **7**. An additional result also nicely supports this vast difference in reactivity. In the reactions of chloride decomposition took place due to increased reaction times, while a great part of the starting material stayed unreacted (entries 1–8). On the other hand, in reactions using bromide **14** the usual byproduct was the protonated aldehyde **24**, which implies that oxidative addition occurred and the palladium species was formed to a greater extent that can be assumed purely from the yields.

At the same time with our desymmetrisation studies, Branda et al. reported the synthesis of H-BTC derivative **25**, according to the same strategy. The title compound **25** was synthesised in two steps via the corresponding monobro-

онс~	F_{6} F_{6} $F_{7} = CI$ $F_{7} = CI$ $F_{7} = CI$	ArB(OR) ₂ (1.5 [Pd(PPh ₃) ₄] (10 Na ₂ CO ₃ , DME/H ₂ O (4:1)	equiv),) mol%), ▶	онс Ls	F6 S 16-23 + F6 S	24
Entry	Product	R	Х	Т	t	Yield
				[°C]	[h]	[%]
1	16	NMe ₂	Cl	70	20	12(61) ^[a]
2	17	Cl	Cl	50	20	5(37) ^[a]
3	18	OMe	Cl	70	20	31(31) ^[a]
4	19	CHO ^[b]	Cl	70	20	17(43) ^[a]
5	20	CN	Cl	70	20	18(54) ^[a]
6	21	CO_2Me	Cl	70	20	15(47) ^[a]
7	22	COMe	Cl	70	20	10(47) ^[a]
8	23	Н	Cl	50	2	99/1 ^[c]
9	16	NMe ₂	Br	70	2	97
10	17	Cl	Br	50	2	96
11	18	OMe	Br	50	2	94
12	19	CHO ^[b]	Br	70	2	88
13	20	CN	Br	70	2	76
14	21	CO ₂ Me	Br	70	2	72
15	22	COMe	Br	70	2	63
16	23	Н	Br	50	2	13/87 ^[c]

Table 13. Suzuki-Miyaura coupling of monoaldehydes 7 and 14.

[a] Yields in parentheses refer to the recovered starting material. [b] In the case of aldehyde analogue 2.2 equivalents of boronic acid was used. [c] Ratio of starting material/product (based on crude NMR spectroscopic data).

Scheme 8. Synthesis of nonsymmetrical aldehyde 25.

mide, which had good reactivity in the following Suzuki coupling (Scheme 8).^[36]

Summary

This review examined the syntheses of symmetrical BTCs, a group of compounds with promising photochromic properties. In addition, key synthetic approaches towards nonsymmetrical analogues were also discussed. We also reported our recent findings concerning the desymmetrisation strategies of symmetrical BTCs. It highlights the great selectivity, which can be achieved by monosubstitutions of dichloride 1. In order to further improve this approach bromoaldehyde 14 was synthesised, which showed a significantly improved reactivity in consecutive Suzuki–Miyaura couplings. It is our belief that this approach is generally superior to other desymmetrisation methods in terms of versatility and overall

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yield. In addition, the method can be applied to both F- and H-BTCs. Further developments of monolithium–halogen exchange is currently underway in our laboratory. Overall, this work is aimed to serve as a useful collection for synthetic organic/photochemists aiming to design and synthesise novel BTC derivatives.

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- [37] Experimental and characterisation data of compounds 7, 10 and 14– 22 can be found in the Supporting Information.

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