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Synthetic Methods

Apical Functionalization of Tribenzotriquinacenes

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Dedicated to Professor Gerhard Bringmann on the occasion of his 65th birthday

Abstract: The introduction of one alkyne moiety at the central carbon atom of the tripodal tribenzotriquinacene scaffold allows easy access to a great variety of apically functionalized derivatives. The spatially well-separated arrangement of different functional units on the convex face and outer rim was further proven by single-crystal X-ray studies. Subsequent modifications that feature a general protecting group-free strategy for the demethylation of protected catechols in the presence of a terminal alkyne group, an azide–alkyne Huisgen cycloaddition, and Sonogashira cross-coupling reactions showcase the high synthetic potential of this modular approach for tribenzotriquinacene derivatization.

Introduction

Bowl-shaped molecular entities[1] define a suitable rigid platform for either the spatially well-defined attachment of functional units,[2] convex/concave π interactions,[3] or the formation of cyclic[4] and cage-type[5] architectures. Prominent examples for such scaffolds include calixarenes,[6] cyclotriveratrylenes (CTVs),[7] cyclodextrins,[8] corannulenes,[9] or tribenzotriquinacenes (TBTQs)[10] that feature the orthogonal orientation of three annulated indane wings (Figure 1). Since the initial report on the 12d-methyl derivative of the parent TBTQ in 1984 by Kuck,[11] selective functionalization, especially at the outer rim,[12] has been intensively studied in recent years and suitable derivatives have been implemented in covalent organic cage compounds,[13] supramolecular aggregates,[14] metallosquares,[4] cryptophanes,[15] or fullerene receptors.[16] Less frequently, functionalization at the bridgehead[17] or *ortho*[18] positions has also been reported, thus showcasing the versatility of TBTQ as a curved aromatic building block. Regarding the apex, most of the known bowl-shaped molecules are either flat, for example, corannulenes, or possess narrow orifices, for example, calixarenes and CTVs. Instead, closed scaffolds such as TBTQs or subphthalocyanines[19] offer the additional benefit of an apical anchor group. In the case of subphthalocyanines, functionalization at the boron center has been reported with a variety of different functional groups.[19b] For TBTQs however, besides the parent hydrocarbon, only alkyl substituents, for example, methyl, ethyl, benzyl,[20] *n*-butyl,[13a] or *iso*-propyl,[21] have been implemented primarily to enhance solubility in organic solvents. To facilitate further functionalization on the convex exterior of the molecular bowl, it had been stated by Kuck a decade ago, that "…*in fact, introduction of a single functional group at the central carbon atom is a synthetically difficult task but an important challenge because this could offer a central point to connect larger building blocks.*"[10] However, the only example reported so far is the simultaneous introduction of amino or bromo groups at the apical and bridgehead positions.[22] Furthermore, unusual oxidation of an apical methyl group to a carboxyl group accompanied with oxyfunctionalization at all three bridgehead positions was observed under strongly oxidizing conditions.[23] However, the final product was not fully purified and characterized due to very poor solubility and volatility. Apart from that, to the best of our knowledge, no further examples of the apical functionalization of TBTQs have been presented, let alone the development of

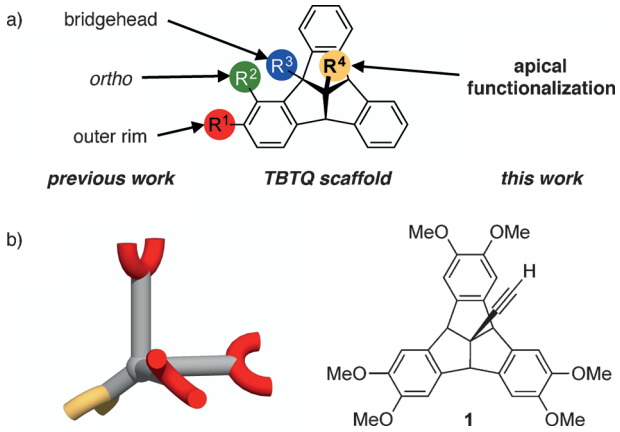

Figure 1. a) Different positions for functionalization on the TBTQ scaffold. b) Schematic representation of multifunctional TBTQ derivatives capable of both wing extension (red) and apical modification (yellow) with different functional groups and TBTQ **1** as a prototypical example for such rigid building blocks.

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a modular and widely applicable strategy to allow facile apical extension.

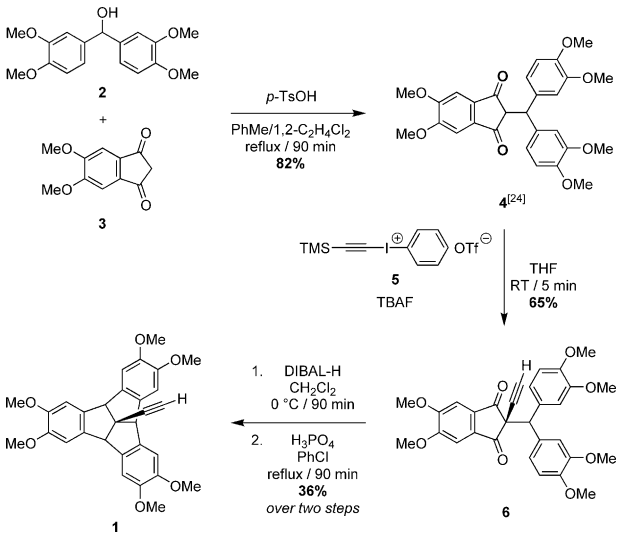
Results and Discussion

Herein, we report the easy and scalable synthesis of TBTQ **1**, which possesses an alkyne unit directly attached to the central carbon atom of the TBTQ core. Subsequent demethylation of the methoxy groups without intermediate protection of the terminal alkyne unit, postsynthetic modifications by utilizing the azide–alkyne click reaction and Sonogashira cross-coupling exemplarily showcase the tempting potential of apically attached acetylenes as privileged intermediates in TBTQ synthesis.

Recently, we implemented hexahydroxy TBTQs as tripodal vertices into dynamic covalent[5c,13] or supramolecular[14] cage compounds. The synthesis of these outer-rim functionalized building blocks was performed by following conventional synthetic protocols developed by other groups.[21,24] In a nutshell, an acid-catalyzed coupling of benzhydrol and indanedione derivatives leads to diketo compounds, which are ultimately transformed into TBTQs through reduction and subsequent cyclodehydration. To enhance the solubility of the final TBTQ-based assemblies, methyl or butyl substituents in the apical position were introduced at the indanedione stage.[13a,24] However, while trying to attach sterically more-demanding groups to provide higher solubility, for example, branched alkyl chains, we obtained significantly lower yields for the benzhydrol coupling and the final cyclization step with significant byproduct formation during cyclization due to undesired rearrangements.[18a] For a more suitable and modular approach, we therefore searched for alternative reaction pathways that fulfilled the following criteria: 1) reduced steric demand for higher yields in key steps, 2) introduction of the apical substituents in late steps along the synthetic route, 3) retention of the inherent threefold symmetry, which is actually not the case for elongated alkyl substituents due to the tetrahedral geometry of the sp^3-hybridized carbon atom, and 4) the potential for versatile postsynthetic modification.

Based on these considerations, we decided to aim for the implementation of a sterically less-demanding alkyne moiety at the 12d-position, thus featuring a linear extension off the convex face and the potential for several well-established reaction pathways for subsequent transformations. Based on earlier work regarding the direct C–H functionalization of the central carbon atom,[10] we worried about comparable reactivities for the C–H bonds at the bridgehead and apical positions. Therefore, we opted for the introduction of the alkyne unit prior to cyclodehydration, but after coupling between the benzhydrol and indanedione precursors, thus envisioning higher yields for both key steps along the synthetic route.

As a suitable substrate for those purposes, we synthesized the known diketone **4** from benzhydrol **2** and indanedione **3** in good yield (Scheme 1).[24] Because **4** still possesses one enolizable proton, we then searched for a mild method to couple **4** with an electrophilic alkyne synthon.[25] As a matter of fact, alkynyliodonium salt **5**[26] smoothly reacted with **4** in the presence of TBAF to give alkyne derivative **6**. After five minutes at room temperature followed by aqueous quenching, we could reproducibly isolate **6** in 65% yield; however, a longer reaction time resulted in the increased formation of unidentifiable decomposition products. The purification of **6** was achieved by means of simple column chromatography, and single crystals suitable for X-ray studies could be grown from hexane/Et_2O overnight. Indanedione **6** crystallized in the triclinic space group $P\bar{1}$[27] (Figure 2a), and the obtained molecular structure



Scheme 1. Synthesis of alkyne-functionalized TBTQ **1** (compound **4** was synthesized according to a reported procedure).[24] DIBAL-H = diisobutylaluminum hydride, OTf = trifluoromethanesulfonate, TBAF = tetrabutylammonium fluoride, TMS = trimethylsilyl, *p*-TsOH = *para*-toluenesulfonic acid.

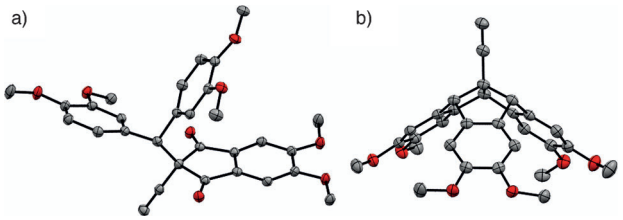


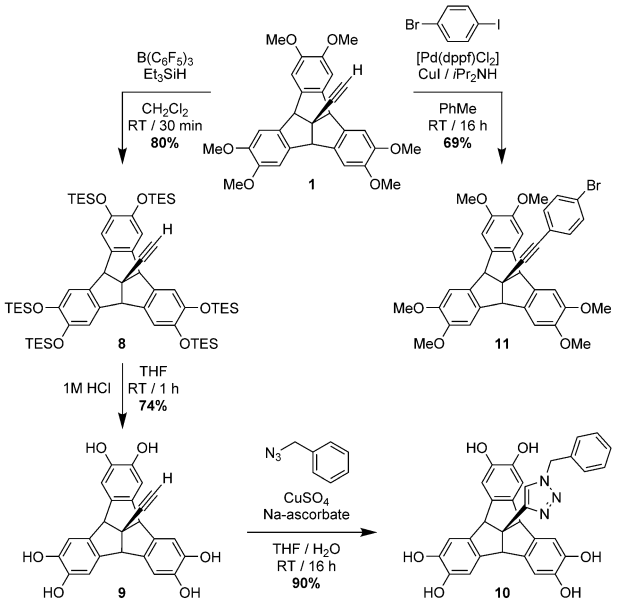
Figure 2. ORTEP representations of single-crystal X-ray structures of a) diketone **6** and b) TBTQ **1**. Thermal ellipsoids were set at 50% probability (C = gray, O = red; the H atoms were omitted for clarity).

provided additional evidence for the successful attachment of the alkyne moiety. Subsequent reduction of the carbonyl groups with DIBAL-H resulted in the quantitative formation of two diastereomeric indanediols **7** (obtained by the reduction of **6**; not shown in Scheme 1) in a 83:17 ratio. For apical alkyl substitutents of hexamethoxy derivatives, it has been revealed that only the *all-cis* isomer is formed.[24] For sterically less-demanding alkyne groups, however, the X-ray structure in Figure 2a might indicate that hydride attack from the opposite carbonyl face becomes more feasible, thus resulting in the formation of the observed isomeric mixture. Separation of the diastereomers is just about possible, but not necessary be-

cause exposure of the crude mixture **7** to a solution of orthophosphoric acid in chlorobenzene at reflux resulted in the efficient formation of the apically functionalized TBTQ **1** with a total yield of 36% for the reduction and cyclization steps. Again, single crystals suitable for X-ray studies could be obtained by recrystallization from EtOH. Hexamethoxy TBTQ **1** crystallized in the tetragonal space group $I4_1/a$,[28] and an ORTEP representation of the molecular structure is depicted in Figure 2b. It is clearly evident that the apical alkyne substituent is spatially well-separated at the convex face and points away from the bowl-shaped TBTQ scaffold, thus coinciding with the molecular axis. In total, **1** can be conveniently synthesized from readily available starting materials **2** and **3** in only four steps in 20% overall yield. Because none of the steps requires tedious chromatographic purification, gram quantities of **1** can be easily obtained within two weeks, thus making this apically functionalized TBTQ derivative a very versatile building block for further chemical transformations.

In this regard, both the deprotection of the methoxy groups for further functionalization at the outer rim and subsequent reactions at the apical alkyne moiety are worthwhile goals. For alkyl-functionalized TBTQs, methoxy groups can be conveniently deprotected with BBr_3.[13a,21] However, decomposition of the starting material and no product formation was observed in the case of **1**. In addition, the use of other Lewis acids, for example, BCl_3, $AlCl_3$[29] (also in presence of tetrabutylammonium iodide), or Me_3SiI,[30] did not result in efficient deprotection either. Similar obstacles during the attempted deprotection of methoxy groups in the presence of terminal alkyne groups have been reported by other groups. Therefore, silylation of the alkynes prior to methoxy deprotection followed by final removal of the silyl groups is usually applied.[31] As a more straightforward alternative, we herein report an elegant two-step process with initial exchange of the protective groups from methyl to triethylsilyl groups under reductive conditions followed by acidic cleavage of the silylated intermediate without the need for protection of the terminal alkyne.

Indeed, the reaction of **1** with triethylsilane in the presence of trispentafluorophenylborane as a Lewis acidic catalyst[32] smoothly exchanged protective groups, thus yielding silylated derivative **8** (Scheme 2), which possesses very good solubility in common organic solvents. Hence, this intermediate can be considered to be another versatile precursor for further transformations at the alkyne position. Acidic treatment in THF resulted in the smooth formation of triscatechol **9**, thus providing the possibility of orthogonal functionalization of the outer rim through the catechol units and the convex face through alkyne chemistry. To elaborate on the latter approach, we therefore performed two test reactions that utilized the azide–alkyne Huisgen cycloaddition and Sonogashira cross-coupling reaction for the straightforward apical attachment of readily available azides or aromatic halides. As an initial experiment, we used triscatechol **9** as the substrate for the click reaction with benzyl azide in the presence of catalytic amounts of $CuSO_4$ and sodium ascorbate in a THF/H_2O mixture to obtain triazole **10** in excellent yield. The fact that we could directly use unprotected **9** for this transformation highlights once again the advantages of our synthetic approach. Based on this modular strategy, fast and easy access to a great variety of substituted derivatives can be envisioned, while avoiding recurring optimization of catechol deprotection. In addition, such derivatives can serve as versatile building blocks by themselves for subsequent dynamic covalent reactions with boronate esters, supramolecular interactions involving hydrogen bonding, or other chemical transformations. The observation of supramolecular complexation between DCTB matrix molecules and free catechol **9** in MALDI-TOF measurements (see Figure S12 in the Supporting Information) might be a first indication in this direction.



Scheme 2. Modular deprotection and apical modification of TBTQ **1**. dppf = 1,1′-bis(diphenylphosphino)ferrocene, TES = triethylsilyl.

With the aim of retaining the inherent threefold symmetry of the TBTQ backbone after apical functionalization, we also performed a Sonogashira cross-coupling reaction of **1** with 1-bromo-4-iodobenzene. The reaction in toluene and in the presence of 4 mol% $[Pd(dppf)Cl_2]$ and CuI as a co-catalyst under basic conditions resulted in the clean formation of the alkynyl–phenyl derivative **11** in 69% yield. These two initial examples clearly show the broad synthetic applicability of **1**, **8**, and **9** as privileged intermediates in TBTQ chemistry.

Conclusion

We have presented a novel and versatile synthetic protocol for the introduction of one terminal alkyne unit at the apical position of the TBTQ scaffold. Key intermediate **1** could be synthesized in gram quantities by starting from readily available precursors. Furthermore, we have established a mild two-step deprotection sequence with either an exchange of the methoxy substitutents to more labile TES protecting groups or complete removal, thus leading to the unprotected triscatechol **9**. The fact that this transformation can be performed without inter-

mediate protection of the terminal alkyne unit renders this procedure a very useful protocol for methoxy deprotection in the presence of labile alkyne groups. Subsequent postsynthetic modification was exemplarily shown for the azide–alkyne Huisgen cycloaddition and Sonogashira cross-coupling reaction as two of the most versatile ways of attaching a great variety of readily available molecules at the apical alkyne moiety. Based on this modular approach, we strongly believe that most diverse tasks, such as better control of TBTQ solubility, immobilization on solid support, or exohedral functionalization of complex molecular architectures based on TBTQ building blocks, will be significantly simplified in future applications and we plan to report ongoing investigations in our laboratories along these lines in due course.

Experimental Section

General: All chemicals were purchased from the commercial suppliers Alfa Aesar, Merck, Acros, and Sigma Aldrich and were used without further purification. The solvents were distilled prior to use. CH_2Cl_2, toluene, and THF were dried by using the solvent purification system "PureSolv MD 5" from Innovative Technology. Column chromatography was carried out on glass columns individually packed with silica gel (grain size = 463 μm; Merck). TLC analysis was carried out on silica gel 60 F_{254} TLC aluminum foils (Merck). NMR spectroscopy was performed on Bruker avance 400 and Bruker avance dmx 600 spectrometers. Chemical shifts are indicated in ppm relative to an internal standard (^{1}H NMR: $\delta = 7.26$, 5.32, and 3.31 ppm for $CDCl_3$, CD_2Cl_2, and MeOD, respectively; ^{13}C NMR: $\delta = 77.16$, 53.84, and 49.00 ppm for $CDCl_3$, CD_2Cl_2, and MeOD, respectively). Signal multiplicities are denoted as s (singlet), d (doublet), t (triplet), and m (multiplet). Processing of the raw data was performed by using the program Topspin 3.0.[32] Mass-spectrometric analysis (MALDI) was carried out on an Autoflex II Bruker spectrometer with a *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB) matrix. Elemental analysis (%) was carried out on an Elementar CHNS 932 analyzer.

2-[Bis(3,4-dimethoxyphenyl)methyl]-5,6-dimethoxy-1*H*-indene-1,3(2*H*)-dione (**4**)[24] and phenyl[tri(methylsilylethynyl)]iodonium triflate (**5**)[26] were synthesized according to previously described procedures.

2-[Bis(3,4-dimethoxyphenyl)methyl]-2-ethynyl-5,6-dimethoxy-1*H*-indene-1,3(2*H*)-dione (6): A 250 mL round bottom Schlenk flask was charged with **4** (2.27 g, 4.61 mmol, 1 equiv) and put through three vacuum/N_2 flushing cycles. Dry THF (150 mL) was added to the reaction mixture, which turned yellow, followed by TBAF in THF (1 M, 6.91 mL, 6.91 mmol, 1.5 equiv). The obtained orange solution was stirred for 5 min, and then **5** (2.70 g, 5.99 mmol, 1.3 equiv) was added in one portion, thus resulting in an immediate color change to dark yellow. After stirring for 5 min under N_2, the solution was quenched by the addition of water (150 mL). The dark-yellow solution was extracted with CH_2Cl_2 (3× 200 mL). The organic phases were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the obtained crude oil was purified by column chromatography on silica gel with Et_2O/hexane (6:1, 8:1, and 10:1) as the eluents to give **6** as a yellowish solid (1.67 g, 65.4%). ^{1}H NMR (400 MHz, $CDCl_3$, RT): $\delta = 7.20$ (s, 2H; Ar-*H*), 7.14 (d, $J = 1.9$ Hz, 2H; Ar-*H*), 6.95 (dd, $J = 8.4$, 2.0 Hz, 2H; Ar-*H*), 6.67 (d, $J = 8.4$ Hz, 2H; Ar-*H*), 4.88 (s, 1H; C-*H*), 3.96 (s, 6H; O-CH_3), 3.83(s, 6H; O-CH_3), 3.78 (s, 6H; O-CH_3), 2.29 ppm (s, 1H; -C≡C-*H*); ^{13}C NMR (100 MHz, $CDCl_3$, RT): $\delta = 195.73$, 156.44, 148.31, 141.78, 136.56, 132.01, 122.06, 113.08, 110.71, 103.71, 79.17, 75.43, 57.58, 56.85, 56.42, 55.86, 55.78 ppm; MS (MALDI-TOF, DCTB): *m/z* 516.1 $[M]^+$; elemental analysis (%) calcd for $C_{30}H_{28}O_8 \cdot 0.5\,C_4H_{10}O$: C 69.43, H 6.01; found: C 69.52, H 6.02.

2-[Bis(3,4-dimethoxyphenyl)methyl]-2-ethynyl-5,6-dimethoxy-2,3-dihydro-1*H*-indene-1,3-diol 7: Compound **6** (3.00 g, 5.42 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (250 mL) in a 500 mL Schlenk flask and under N_2. The flask was subjected to cooling in an ice bath at 0 °C. Afterward, DIBAL-H in THF (1 M, 23.2 mL, 23.2 mmol, 4.3 equiv) was added dropwise over a period of 30 min. Subsequently, the solution was brought to room temperature and stirred under N_2 for 1 h. The reaction was quenched by the addition of water (100 mL) and the obtained suspension was stirred for 10 min. After the addition of 1.2 M aqueous HCl (100 mL), the intermediate colorless precipitate was dissolved again. The organic layer was separated and the water phase was extracted with CH_2Cl_2 (3×50 mL). The combined organic phases were washed with saturated aqueous solution (2×50 mL) of K_2CO_3 and brine (100 mL) and dried over Na_2SO_4. The crude product (3.10 g) was obtained as a colorless precipitate after solvent removal and directly used as a mixture of diastereomers without further purification (see Figure S4 in the Supporting Information for the ^{1}H NMR spectrum); MS (MALDI-TOF, DCTB): *m/z* 520.2 $[M]^+$.

TBTQ 1: Orthophosphoric acid (1.56 mL) was added to chlorobenzene (100 mL) in a 500 mL 3-necked round-bottom flask, and the mixture was heated to reflux at 140 °C for 30 min with vigorous stirring. A solution of crude **7** (3.10 g) in chlorobenzene (300 mL) was added dropwise to the solution at reflux through a dropping funnel. The solution was heated to reflux for another hour. A dark-violet precipitate appeared at the bottom of the flask and the color of the solution changed from dark yellow to dark red. Afterward, the solution was brought to room temperature and a saturated aqueous solution (200 mL) of K_2CO_3 was added. The mixture was extracted with $CHCl_3$ (3×100 mL). The combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4 followed by evaporation of the solvent to obtain the dark-brown crude product. The crude product was purified by column chromatography on silica gel with hexane/EtOAc (2:1, 1:1, and 1:2) as the eluent, and the yellowish product collected was recrystallized from EtOH to furnish **1** (1.03 g, 35.5% over two steps) as colorless single crystals. ^{1}H NMR (400 MHz, $CDCl_3$, RT): $\delta = 6.87$ (s, 6H; Ar-*H*), 4.90 (s, 3H; C-*H*), 3.87 (s, 18H; O-CH_3), 2.58 ppm (s, 1H; -C≡C-*H*); ^{13}C NMR (100 MHz, $CDCl_3$, RT): $\delta = 149.57$, 136.13, 107.07, 90.33, 72.69, 64.60, 58.93, 56.40 ppm; MS (MALDI-TOF, DCTB): *m/z* 484.2 $[M]^+$; elemental analysis (%) calcd for $C_{30}H_{28}O_6 \cdot 0.5\,C_2H_6O \cdot 1.5\,H_2O$: C 69.65, H 6.41; found: C 69.26, H 6.45.

TBTQ 8: A 100 mL round-bottom Schlenk flask was charged with **1** (400 mg, 0.748 mmol, 1.0 equiv) and put through three vacuum/N_2 flushing cycles. Dry CH_2Cl_2 (50 mL) and triethylsilane (1.35 g, 11.6 mmol, 15.5 equiv) were added to the reaction mixture. A solution of trispentafluorophenylborane (21.2 mg, 0.041 mmol, 0.05 equiv) in dry CH_2Cl_2 was added to the reaction mixture under N_2. Bubbles of methane evolved from the solution, which changed from colorless to yellow and finally to yellowish orange. After 30 min, trimethylamine (0.1 mL) was added and color changed to yellow. The solution was filtered through a celite pad and the filtrate was evaporated to dryness to obtain a crude colorless solid, which was then washed with distilled MeOH to obtain **8** as a pure colorless product (646 mg, 79.6%). ^{1}H NMR (400 MHz, $CDCl_3$, RT): $\delta = 6.71$ (d, $J = 0.5$ Hz, 6H; Ar-*H*), 4.72 (s, 3H; C-*H*), 2.55 (s, 1H; -C≡C-*H*), 0.97 (t, $J = 7.9$ Hz, 54H; SiCH$_2$CH_3), 0.73 ppm (q, $J = 7.9$ Hz, 36H; SiCH_2CH$_3$); ^{13}C NMR (100 MHz, $CDCl_3$, RT): $\delta = 146.70$, 137.17, 115.39, 91.37, 72.05, 64.03, 59.17, 6.83, 5.25 ppm; MS (MALDI-TOF,

DCTB): *m/z* 1084.6 $[M]^+$; elemental analysis (%) calcd for $C_{60}H_{100}O_6Si_6$: C 66.36, H 9.28; found: C 66.14, H 9.11.

TBTQ 9: Aqueous HCl solution (3.45 mL, 3.45 mmol, 15 equiv) was added to a 50 mL round-bottom flask charged with **8** (250 mg, 0.23 mmol, 1 equiv) and distilled THF (15 mL). The reaction mixture was stirred for 1 h at room temperature. Water (20 mL) was added to the mixture, which was extracted with EtOAc (3×50 mL). The combined organic phases were dried over Na_2SO_4, and the solvent was evaporated to obtain the crude product. MeOH (20 mL) was added to this crude product, and the solution was filtered. The filtrate was evaporated to obtain a colorless solid. The crude product was washed with CH_2Cl_2 (3×10 mL) to obtain **9** as a colorless powder (77.2 mg, 74%). ^{1}H NMR (400 MHz, MeOD, RT): $\delta = 6.77$ (d, $J = 0.4$ Hz, 6H; Ar-*H*), 4.59 (s, 3H; C-*H*), 2.84 ppm (s, 1H; -C≡C-*H*); ^{13}C NMR (100 MHz, MeOD, RT): $\delta = 146.21$, 136.97, 111.26, 92.15, 72.91, 65.45, 59.94 ppm; MS (MALDI-TOF, DCTB): *m/z* 400.1 $[M]^+$, 651.2 $[M + \text{DCTB} + \text{H}]^+$, 901.4 $[M + 2\,\text{DCTB} + \text{H}]^+$; elemental analysis (%) calcd for $C_{24}H_{16}O_6 \cdot 3\,H_2O$: C 63.43, H 4.88; found: C 63.34, H 4.89.

TBTQ 10: TBTQ **9** (20.0 mg, 0.04 mmol, 1.0 equiv) and benzyl azide (13.3 mg, 0.1 mmol, 2.5 equiv) were dissolved in THF (5 mL). Sodium ascorbate (0.5 mmol, 0.5 mL of a freshly prepared 1 M solution in water) was added, followed by copper(II) sulfate (1.6 mg, 0.01 mmol, in 1 mL of water). The solution was stirred overnight (18 h) at room temperature under N_2. Water (10 mL) was added to the mixture, which was extracted with EtOAc (3×10 mL), dried over Na_2SO_4, and evaporated to dryness. After washing the crude product with CH_2Cl_2 (3×5 mL), pure **10** was obtained as a colorless powder (23.2 mg, 89.6%). ^{1}H NMR (400 MHz, MeOD, RT): $\delta = 7.89$ (s, 1H; triazole *H*), 7.36–7.28 (m, 5H; CH_2-Ph-*H*), 6.81 (s, 6H; Ar-*H*), 5.53 (s, 2H; CH_2), 4.68 ppm (s, 3H; C*H*); ^{13}C NMR (100 MHz, MeOD, RT): $\delta = 158.00$, 146.18, 137.47, 136.87, 129.99, 129.48, 129.03, 121.61, 111.39, 66.17, 64.34, 54.92 ppm; MS (MALDI-TOF, DCTB): *m/z* 534.1 $[M + \text{H}]^+$; elemental analysis (%) calcd for $C_{31}H_{23}N_3O_6 \cdot 3\,H_2O$: C 63.37, H 4.97; N, 7.15; found: C 64.73, H 5.39; N, 6.28.

TBTQ 11: 1-Bromo-4-iodobenzene (43.8 mg, 0.103 mmol, 1.1 equiv), [Pd(dppf)Cl_2] (3.02 mg, 4.1 μmol, 0.04 equiv), CuI (0.786 mg, 4.1 μmol, 0.04 equiv), and diisopropylamine (2.5 mL) were dissolved in dry toluene (5 mL) in a Schlenk tube under N_2, and the mixture was degassed by three freeze-pump-thaw cycles. In another Schlenk tube, **1** (50.0 mg, 0.094 mmol, 1 equiv) was dissolved in dry toluene (5 mL) and also degassed by three freeze-pump-thaw cycles. The solution of **1** was slowly added dropwise to the other Schlenk tube. After the addition was complete, the reaction mixture was stirred overnight for 16 h under N_2. The solution was quenched by the addition of HCl solution (20 mL, 2 M) and extracted with distilled Et_2O (2×30 mL). A fluffy precipitate formed between the organic and water phases, and the aqueous phase was removed. The organic extract was washed with a saturated aqueous solution (30 mL) of K_2CO_3. EtOAc (20 mL) was added for a better separation of the organic and water layers. The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to dryness to obtain the crude product, to which Et_2O (50 mL) was added. After separation of a precipitate (Glaser product), the filtrate was evaporated to obtain a yellowish solid. This precipitate was purified by flash column chromatography on silica gel with hexane/EtOAc (1:1→0:1) as the eluent, and the yellowish product collected was dissolved in a minimum amount of Et_2O followed by the addition of hexane to furnish pure **11** as a colorless precipitate (41.2 mg, 68.9%). ^{1}H NMR (400 MHz, CD_2Cl_2, RT): $\delta = 7.43$ (d, $J = 8.7$ Hz, 2H; Br-Ar-*H*), 7.28 (d, $J = 8.7$ Hz, 2H; Br-Ar-*H*), 6.90 (s, 6H; Ar-*H*), 4.96 (s, 3H; C*H*), 3.83 ppm (s, 18H; O-CH_3); ^{13}C NMR (100 MHz, CD_2Cl_2, RT): $\delta = 150.04$, 136.28, 133.29, 131.86, 123.07, 122.22, 107.56, 97.12, 83.92, 64.84, 59.89, 56.54 ppm; MS (MALDI-TOF, DCTB): *m/z* 638.1, 640.1 $[M]^+$; elemental analysis (%) calcd for $C_{36}H_{31}BrO_6 \cdot 1.5\,C_4H_{10}O$: C 67.20, H 6.18; found: C 67.18, H 6.01.

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Keywords: alkynes · bowl-shaped molecules · click chemistry · Sonogashira cross-coupling · tribenzotriquinacenes

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[27] Supplementary crystallographic data for diketone **6** can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (CCDC 1477190); crystal data: $C_{30}H_{28}O_8 \cdot 0.5\,C_4H_{10}O$, $M = 553.58\ g\,mol^{-1}$, triclinic, $P\bar{1}$, $a = 10.6280(4)$, $b = 11.3725(4)$, $c = 13.4594(5)$ Å, $\alpha = 74.4890(10)$, $\beta = 88.2680(10)$, $\gamma = 65.9900(10)^\circ$; $V = 1426.20(9)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.289\ g\,cm^{-3}$, $\mu(Cu_{K\alpha}) = 0.769\ mm^{-1}$, $T = 100(2)$ K; 22240 independent measured reflections; F^2 refinement, $R1 = 0.0416$, $wR2 = 0.1023$ (observed), 5606 independent observed reflections ($R_{int} = 0.0240$) ($|F_0| > 4\sigma(|F_0|)$, $2\Theta \leq 144.39^\circ$), 371 parameters, no restraints.

[28] Supplementary crystallographic data for TBTQ **1** can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (CCDC 1477191); crystal data: $C_{30}H_{28}O_6$, $M = 484.52\ g\,mol^{-1}$, tetragonal, $I4_1/c$, $a = 31.7190(10)$, $b = 31.7190(10)$, $c = 10.8097(4)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90^\circ$, $V = 10875.6(8)$ Å^3, $Z = 16$, $\rho_{calcd} = 1.184\ g\,cm^{-1}$, $\mu(Cu_{K\alpha}) = 0.668\ mm^{-1}$, $T = 100(2)$ K; 77846 independent measured reflections; F^2 refinement, $R1 = 0.0409$, $wR2 = 0.0928$ (observed), 5576 independent observed reflections ($R_{int} = 0.0420$) ($|F_0| > 4\sigma(|F_0|)$, $2\Theta \leq 149.53^\circ$), 343 parameters, no restraints.

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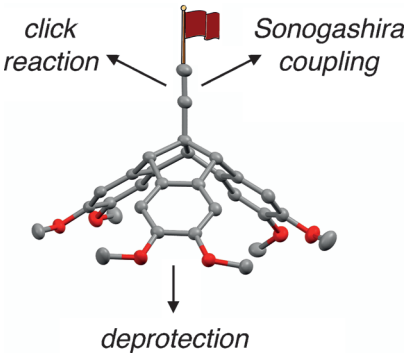
FULL PAPER

Reaching the top: The introduction of an alkyne moiety at the central carbon atom of the tribenzotriquinacene scaffold provides an anchor group for the facile apical functionalization of bowl-shaped molecules. Subsequent reactions, such as an azide–alkyne cycloaddition, Sonogashira cross-coupling reaction, or selective demethylation at the outer rim, were performed to highlight the synthetic potential of this approach (see picture).



Synthetic Methods

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Apical Functionalization of Tribenzotriquinacenes