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Green synthesis of calixarenes derivatives: Mechanochemical-assisted key steps

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Abstract

Calixarenes are important scaffolds in the field of nanosciences, from sensing to therapeutics. Its synthesis and functionalization are still a challenging task, and new synthetic protocols are highly desirable. The selective functionalization of the lower rim of calix[4]arenes has been successfully achieved using a mechanochemical strategy, enabling a more sustainable and time-saving route, an easier synthesis and precluding the use of organic solvents. For comparison, the reactions were performed in a stainless-steel vibratory mill and in a planetary ball mill employing both stainless steel and zirconium oxide reactors. Using 25,26,27-tri-*O*-propyl-28-hydroxy-*p*-*tert*-butylcalix[4]arene **6** as the precursor, four advanced functional calixarenes were prepared, and the yields and experimental conditions compared with the conventional synthesis. For planetary-assisted grinding, the best results were obtained when the zirconium oxide reactor was used. In some cases, the vibratory-assisted grinding gave higher yields, thus showing the importance of the milling machine in the synthesis of this macromolecules. The effect of the balls number and size on the reactions yield was also explored.

Introduction

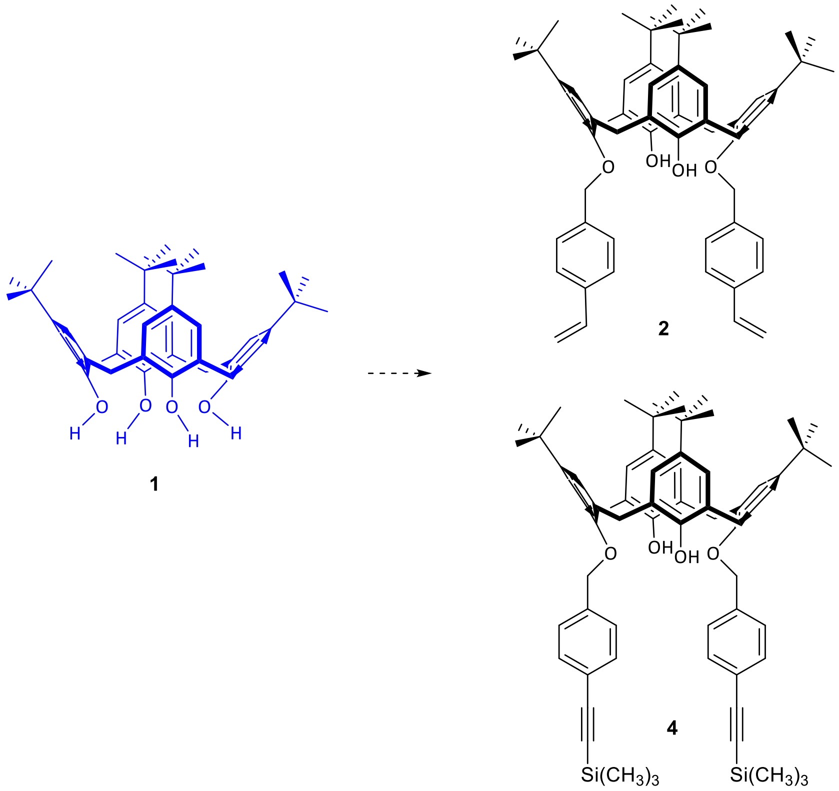
Synthetic macrocycles possess distinctive characteristics that make them appealing scaffolds. Over the past two decades, calixarenes have been extensively investigated as supramolecular systems due to their intra-molecular bow-shaped cavity, which has the ability to accommodate various types of molecular guests [1-3]. Besides the well-known sensing properties [4], interestingly, calixarenes are being captured to new fields, such as chemotherapeutics [5] and nanosciences [6,7].

Calixarene synthesis and functionalization are still challenging tasks, and the discovery of new, more efficient synthetic routes may lead to great advances in their study. Mechanosynthesis, being a simple, low-cost, and convenient solventless process offer great advantages over existing methodologies. Besides waste reduction and lower energy consumption, without compromising or even enhancing chemical transformations, the elimination of solubility issues due to the highly energetic elastic, plastic, and shear deformations, is an extraordinary feature. Therefore, mechanochemistry is a truly emergent green synthetic tool, and significative developments have been achieved al-ready in the last few years [8]. Although, the mechanosynthesis of calixarenes is rather unexplored [9-14]. One of the few examples is the preparation of several calix[4]resorcinarenes in high yield and purity at room temperature under solvent-free catalytic conditions by the direct reaction of an aldehyde and resorcinol, representing a feasible alternative to traditional solution chemistry [10]. Atwood *et al.* explored the single step direct synthesis of pyrogallol[4]arene in the cone conformation via a solvent free protocol, resulting in a pure self-assembled nano-capsule, comprising six macrocyclic building blocks [12]. More recently, a direct *O*-alkylation of *p*-*tert*-butyldihomooxacalix[4]arene with different *N*-(bromoalkyl)phthalimides and K_2CO_3 was attempted, revealing that mechanically-assisted synthesis is not a good method for these type of alkylations [13].

Herein, we present a new route for selected calixarene intermediates, privileging mechanochemistry as a greener choice.

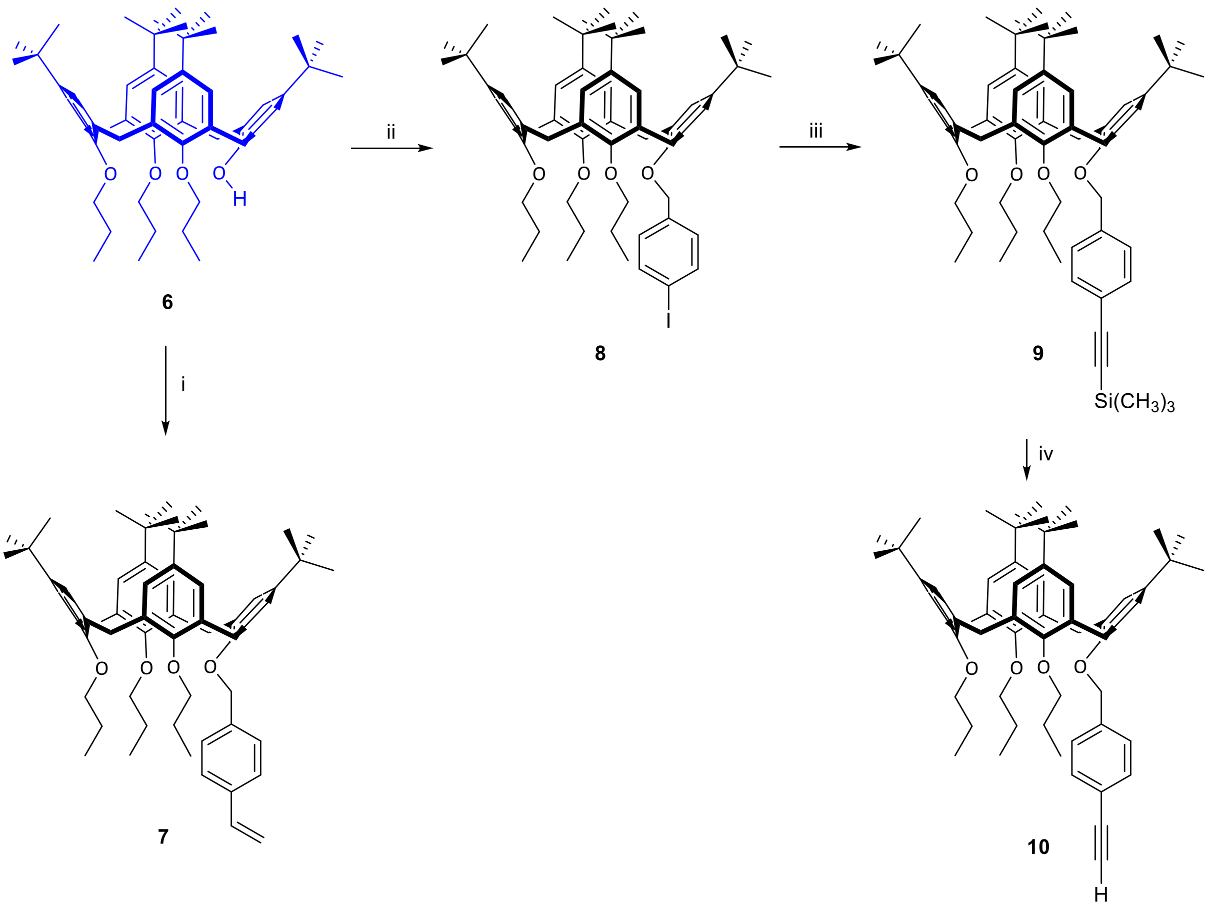
Results and Discussion

In previous work we studied the mechanosynthesis of advanced disubstituted calixarene intermediates starting from *p*-*tert*-butylcalix[4]arene 1 (Scheme 1) [14].



Scheme 1: Disubstituted functional calix[4]arenes (2-5) synthesised by mechanochemistry using a planetary ball mill.

The results obtained in this work were very promising and prompted us to further explore the mechanosynthesis of analogous calixarenes. Herein we present the full disclosure of new key steps for the mechanosynthesis of monosubstituted calixarene intermediates, also unveiling the influence of the reactor material (stainless steel *vs.* zirconium oxide) and the type of grinding machine. The functional calix[4]arenes were prepared starting from 25,26,27-tri-*O*-propyl-28-hydroxy-*p*-*tert*-butylcalix[4]arene **6** [15], and four functional calixarenes monomers, bearing monosubstituted aryl-vinyl or aryl-ethynyl pending units, were successfully prepared (Scheme 2).



Scheme 2: Mechanosynthesis of monosubstituted functional calix[4]arenes using vibratory and planetary ball milling: (i) calixarene **6**, NaH, 4-vinylbenzyl chloride, nitrobenzene, 500 rpm, 1 h; (ii) calixarene **6**, NaH, 4-iodobenzyl bromide, 500 rpm, 8 h; (iii) calixarene **8**, Et_3N, $Pd(OAc)_2$, CuI, PPh_3, ethynyltrimethylsilane, $MgSO_4$ anhydrous, cyclohexene, 500 rpm, 12 h; (iv) calixarene **9**, *n*-Bu_4NF, 500 rpm, 1 h.

Table 1: Comparison between conventional and mechanochemical-assisted synthesis of monosubstituted and disubstituted functional calix[4]arenes.

Calixarene	Conventional Synthesis			Mechanosynthesis			
				Vibratory mill[a]		Planetary mill[b]	
	Yield (%)	**Time (h)**	**Solvent**	**Yield (%)**	**Time (h)**	**Yield (%)**	**Time (h)**
2	48[16]	168	ACN[c]	-	-	10[14]	60
3	80[14], 81[17]	24	ACN[d]	-	-	27[14]	7
4	37[14], 82[17]	0.75	THF[d]	-	-	68[14]	8
5	46[17], 49[14]	0.5	THF[c]	70	1	58[14]	0.25
7	59	2	THF[d]	74	1	58	1
8	81	24	THF[d]	27 (48[e])	11	50	8
9	81	0.75	THF[d]	-	-	50[f]	12
10	77	0.5	THF[c]	50	1	16	1

[a]Frequency of 20 Hz using 2×10 mm stainless steel balls. [b]Rotation frequency of 500 rpm using 200 stainless steel balls. [c]Room temperature. [d]Refluxing conditions. [e]Frequency of 20 Hz using 3×5 mm stainless steel balls. [f]Calculated by ^{1}H NMR. ACN = acetonitrile, THF = tetrahydrofuran. Yields refer to isolated yields, except otherwise noticed.

All reactions were performed in a planetary ball mill using stainless steel or zirconium oxide reactors. In most cases, a lower yield or no reaction was observed when the stainless steel was used, thus showing the importance of reactor selection in this type of reactions. For comparison, calixarenes **7-10** were also synthesized by us using conventional conditions (Table 1).

Following our optimized mechanosynthesis protocol, monosubstituted functional calixarenes **7-10** were obtained, both using vibratory and planetary ball mills. As expected, some monosubstitution reactions occurred in higher yields and lower reaction times. For comparison, Table 1 summarizes yields and conditions for the mechanosynthesis of disubstituted (**2-5**) previously reported [14] and the monosubstituted calixarenes (**7-10**) prepared in this work.

In a previous work [14] we explored the synthesis of calixarenes **2-5** using only a planetary ball mill. Since in this work we studied the effect of the grinding machine (vibratory *vs.* planetary) and observed considerable differences in the yield (higher in some cases for a vibratory-assisted grinding) we also synthesised calixarene **5** using the vibratory mill. In fact, the yield of **5** increased from 58 to 70% just by changing the grinding machine. Therefore, this effect must be taken in account in future work, being expectable that the reported calixarenes **2-4** may be obtained in higher yields.

Comparing similar reactions (mono *vs.* disubstitution and conventional *vs.* mechanosynthesis), calixarene **7**, in contrast to **2**, was obtained in higher yield. The yield was also higher in this case when the vibratory mill was employed (74%, 58% using the planetary mill). Under conventional conditions the yield of **7** was lower (59%) than the reported (78% [18]). The reaction time was reduced to half, but a stronger base (NaH) was need (see the ^{1}HNMR spectrum of **7** in Figure S1, Supplementary Materials).

Calixarene **8** was also obtained in higher yield than **3**, but no significant differences were observed using the vibratory (48%) or the planetary ball mil (50%). The yield using conventional conditions (81%) was similar to the reported (80% [19]), which is higher, but the reaction time is three times more under these conditions.

In the case of calixarene **9**, using a Sonogashira–Hagihara cross-coupling, no reaction occurred using $Pd(Ph_3)_2Cl_2$ as catalyst, up to 17 h of reaction and increasing the rotation speed (650 rpm). Calixarene **9** was only obtained using $Pd(OAc)_2$, after 1 h and with a low yield (22%), which was increased to 50% after 12 h of reaction. The convention route led to the same yield (81%, reported 81% [19]).

Finally, calixarene **10** was obtained in moderate yield (50%) when the vibratory mill was used. In this case the yield of the conventional route was also higher (77%, reported 86% [19]) (see the ^{1}HNMR spectrum of **10** in Figure S2, Supplementary Materials).

To evaluate the influence of the balls number and size on the reaction yield, we performed a study using calixarene **8** synthesis in the vibratory mill (20 Hz) as a model reaction. Yields of 27, 41 and 48% were obtained using sets of 2×10 mm, 1×15 mm and 3×5 mm, respectively, which indicates that lower diameter balls in higher number lead to an increased yield (comparative to the same reaction performed in the planetary ball mill, 50%). The reactions carried out in the planetary ball mill always used 200 balls of 5 mm (50% of the reactor volume).

The influence of the rotation frequency in the planetary ball mill for this reaction was also evaluated. A yield of 22% was obtained after 1 h at 650 rpm (equipment maximum speed), in contrast with a yield of 50% at 500 rpm after 8 h. High speed ball milling could be a good option to increase the yield of this type of reactions, but since iron contamination also increases in this case, we believe that it will turn calixarenes purification very difficult due to the formation of iron inclusion complexes.

We also investigated the synthesis of calixarene **6** from *p*-*tert*-butylcalix[4]arene, envisaging a fully mechanosynthetic route on this type of calixarenes. However, using both vibratory and planetary ball mills, no conversion was observed.

Overall, the calixarenes mechanosynthesis, despite not always offering better yields if compared with the conventional route, leads to similar or slightly lower yields but with a great reduction of the reaction times, under greener conditions (solventless, lower energy).

Conclusion

In summary, we present the preparation of key calix[4]arenes monomers, precursors of important calixarene-based polymers, by mechanochemical-assisted protocols. Mechanosynthesis is shown as a sustainable and promising alternative for the synthesis of advanced calixarenes derivatives, by reducing reaction times and avoiding the use of organic solvents. Several calixarenes were synthesized in low to moderate yields in much faster reaction times under solventless conditions. The grinding machine (vibratory vs. planetary ball milling) as well as the reactor material (stainless steel vs. zirconium oxide) were found to have a key role in the reaction yield, with the vibratory mill and the zirconium oxide displaying positive effects. Despite the lower yields observed, in comparison to conventional protocols, we believe that there is still room for improvement by using different bases, grinding auxiliaries or catalytic systems. Importantly, the reported reactions may be also useful in other synthetic routes, thus contributing to a greener synthesis of small molecules or complex macromolecules like calixarenes.

Experimental

All the chemicals were purchased from Sigma-Aldrich and used without further purification unless specified. The melting points were measured in sealed capillaries on a Büchi 530 apparatus and are uncorrected. The obtained products were characterized by FT-IR and ^{1}H NMR. FT-IR spectra were acquired on a Perkin Elmer 1000 or on a Bruker Vertex 70 in transmission mode using KBr pellets. The NMR spectra were obtained in a Bruker-400 equipment (400 MHz) with $CDCl_3$ as the solvent and tetramethylsilane as the internal standard.

Calix[4]arene synthesis

The conventional synthesis of the calix[4]arene starting materials **6** [15], **7** [18], and **8-10** [19], followed the reported protocols. The mechanosynthesis were carried out both in a MM200 vibratory ball mill (Retsch) and in a PM100 planetary ball mill (Retsch). In the vibratory ball mill, we used a stainless-steel milling jar of 15 mL with balls of 5 or 10 mm in diameter. In the planetary ball mill, we used a stainless steel or a zirconium oxide milling jar of 50 mL, containing the corresponding 200 balls of 5 mm in diameter. The synthesis was optimized regarding the reaction time and the operating frequency of the equipment, according to the nature of the reactions.

Mechanosynthesis of ***7****. Vibratory ball mill:* To a stainless-steel reactor, containing two stainless steel balls of 10 mm in diameter, were added 20 mg (0.03 mmol) of **6**, 4.13 mg (4 equiv., 0.103 mmol) of sodium hydride (60% in mineral oil), 16.16 µL (4 equiv., 0.103 mmol) of 4-vinylbenzyl chloride and 0.4 µL of nitrobenzene. The mixture was grinded at a frequency of 20 Hz for 1 hour. The reaction was followed by TLC (dichloromethane:*n*-hexane 1:3). The oily yellow residue was recovered from the reactor using dichloromethane (15 mL) and the mixture next evaporated to dryness. The product was precipitated by the addition of cold methanol (3 mL). After acidification with a 2 M HCl solution, the mixture was extracted with dichloromethane (3x40 mL). The combined organic phases were washed with water, dried, and **7** obtained as a yellow resin (17 mg) in 74% yield.

Planetary ball mill: To a zirconium oxide reactor, containing 200 zirconium oxide 5 mm balls, were added 60 mg (0.08 mmol) of **6**, 12.39 mg (4 equiv., 0.31 mmol) of sodium hydride (60% in mineral oil), 48.5 µL (4 equiv., 0.31 mmol) of 4-vinylbenzyl chloride and 1.2 µL of nitrobenzene. The mixture was grinded at 500 rpm for 1 h, with rotation inversion cycles of 15 min (5 s pause between inversion cycles). The reaction was followed by TLC (dichloromethane:*n*-hexane 1:3). The yellow oily residue was recovered from the reactor using dichloromethane (50 mL) and then evaporated to dryness. The obtained dark yellow liquid was precipitated using cold methanol (10 mL). After acidification with a 2 M HCl solution, the mixture was extracted with dichloromethane (3x20 mL). The combined organic phases were washed with water, dried, and **7** obtained as a yellow resin (39.7 mg) in 58% yield. m.p. 126-129 °C (m.p. lit. [20] 127-130 °C). FT-IR (KBr) ν_{max} (cm^{-1}): 3086 (w, $=CH_2$), 1388, 1362 (m, $C(CH_3)_3$), 907 (m, $H_2C=CH$). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.46 and 7.42 (d, 4H, $H_2C=CH-Ar\underline{H}$, J = 8.3 Hz), 6.98-6.92 (m, 4H, $Ar\underline{H}$), 6.82-6.69 (m, 1H, $C\underline{H}=CH_2$), 6.63 (s, 2H, Ar$\underline{H}$), 6.58 (s, 2H, Ar$\underline{H}$), 5.78 (d, 1H, CH=C$\underline{H}_2$, J = 17.6 Hz), 5.26 (d, 1H, CH=C$\underline{H}_2$, J = 10.9 Hz), 4.79 (s, 2H, ArOC$\underline{H}_2$Ar), 4.41 (d, 4H, ArC$\underline{H}_2$Ar, J = 12.3 Hz), 4.38 (d, 4H, ArC$\underline{H}_2$Ar, J = 12.3 Hz), 3.81 (t, 4H, ArOC$\underline{H}_2$Ar, J = 7.4 Hz), 3.69 (t, 2H, ArOC$\underline{H}_2$Ar, J = 7.4 Hz), 3.13 (d, 4H, ArC$\underline{H}_2$Ar, J = 12.6 Hz), 2.10-1.77 (m, 6H, C$\underline{H}_2$-CH$_3$), 1.21 (s, 18H, C(C$\underline{H}_3$)$_3$), 1.02 (t, 6H, CH$_2$-C$\underline{H}_3$, J = 7.5 Hz), 0.99 (s, 9H, C(C$\underline{H}_3$)$_3$), 0.96 (s, 9H, C(C$\underline{H}_3$)$_3$), 0.80 (t, 6H, CH$_2$-C$\underline{H}_3$, J = 7.5 Hz).

Mechanosynthesis of **8**. *Vibratory ball mill*: To a stainless-steel reactor, containing two stainless steel balls of 10 mm in diameter, were added 20 mg (0.03 mmol) of **6**, 423 mg (4.1 equiv., 0.11 mmol) of sodium hydride (60% in mineral oil) and 18.79 mg (2.33 equiv., 0.06 mmol) of 4-iodobenzyl bromide. The mixture was grinded at a frequency of 20 Hz for 11 hours. The reaction was followed by TLC (dichloromethane:petroleum ether 1:1). The obtained white product was recovered from the reactor using dichloromethane (15 mL) and the mixture next evaporated to dryness. A 5% aqueous HCl solution (10 mL) was added to the residue, which was further extracted with chloroform (3x25 mL). The combined organic phases were dried, and the obtained product was macerated with methanol to give **8** as white crystalline solid (7 mg) in 27% yield.

Planetary ball mill: To a zirconium oxide reactor, containing 200 zirconium oxide 5 mm balls, were added 60 mg (0.08 mmol) of **6**, 12.69 mg (4.1 equiv., 0.32 mmol) of sodium hydride (60% in mineral oil) and 56.37 mg (2.33 equiv., 0.18 mmol) of 4-iodobenzyl bromide. The mixture was grinded at 500 rpm for 8 h, with rotation inversion cycles of 30 min (2.5 min pause between inversion cycles). The reaction was followed by TLC (dichloromethane:petroleum ether 1:1). The obtained white product was recovered from the reactor using dichloromethane (15 mL) and the mixture next evaporated to dryness. A 5% aqueous HCl solution (40 mL) was added to the residue, which was further extracted with chloroform (3x50 mL). The combined organic phases were dried, and the obtained product was macerated with methanol to give **8** as white crystalline solid (38.7 mg) in 50% yield. m.p. 148-150 °C (m.p. lit. [19] 149-151 °C). FT-IR (KBr) ν_{max} (cm^{-1}): 3040 (w, =C-H), 2961, 2872 (s, C-H), 1602, 1585 (m, C=C), 1482 (s, C-H), 1204, 1009, 869, 806 (s, =C-H). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (d, 2H, I-Ar$\underline{H}$, J = 8.0 Hz), 7.24 (d, 2H, I-Ar$\underline{H}$, J = 8.2 Hz), 6.90 (s, 4H, Ar$\underline{H}$), 6.66 (s, 2H, Ar$\underline{H}$), 6.62 (s, 2H, Ar$\underline{H}$), 4.77 (s, 2H, ArOC$\underline{H}_2$Ar), 4.38 (d, 2H, ArC$\underline{H}_2$Ar, J = 12.7 Hz), 4.34 (d, 2H, ArC$\underline{H}_2$Ar, J = 12.6 Hz), 3.81-3.68 (m, 6H, OC$\underline{H}_2CH_2CH_3$), 3.10 (d, 2H, ArC$\underline{H}_2$Ar, J = 12.5 Hz), 3.06 (d, 2H, ArC$\underline{H}_2$Ar, J = 12.5 Hz), 2.04-1.93 (m, 2H, C$\underline{H}_2CH_3$), 1.94-1.76 (m, 4H, C$\underline{H}_2CH_3$), 1.18 (s, 18H, C(C$\underline{H}_3)_3$), 1.05 (t, 3H, $CH_2C\underline{H}_3$, J = 7.4 Hz), 0.99 (s, 9H, C(C$\underline{H}_3)_3$), 0.95 (s, 9H, C(C$\underline{H}_3)_3$), 0.81 (t, 6H, $CH_2C\underline{H}_3$, J = 7.5 Hz).

Mechanosynthesis of ***9***. *Planetary ball mill*: To a zirconium oxide reactor, containing 200 zirconium oxide 5 mm balls, were added 200 mg (0.20 mmol) of **8**, 800 μL of Et_3N, 1.2 mg of $Pd(AcO)_2$ (2.5% molar, 5.1 μmol), 1.92 mg of CuI (5% molar, 10.1 μmol), 2.65 mg (5% molar, 10.1 μmol) of Ph_3P (recrystallized from *n*-hexane), 34.3 μL (1.2 equiv., 0.24 mmol) of ethynyltrimethylsilane, 1 g (5 equiv./mg) of anhydrous $MgSO_4$ and 40 μL (0.2 μL/mg) of cyclohexene. The mixture was grinded at 500 rpm for 12 h, with rotation inversion cycles of 30 min (2.5 min pause between inversion cycles). The reaction was followed by TLC (dichloromethane:*n*-hexane 1:4; 2 elutions). The obtained light brown residue was dissolved in dichloromethane (50 mL) and the mixture filtered to remove $MgSO_4$. The solution was evaporated to dryness and the residue was redissolved in dichloromethane (50 mL) and washed with a saturated NH_4Cl solution (2x50 mL) and water. The combined organic phases were dried, and the obtained solid recrystallized from dichloromethane/methanol to give **9** as light brown foam (41.8 mg) in 50% yield. ^1H NMR confirmed the presence of **9** and **8** in a 1:1 ratio.

Mechanosynthesis of **10**. *Vibratory ball mill*: To a stainless-steel reactor, containing two stainless steel balls of 10 mm in diameter, were added 20 mg (0.02 mmol) of **9** and 5.75 mg (1.1 equiv., 0.02 mmol) of TBAF. The mixture was grinded at a frequency of 20 Hz for 1 hour. The reaction was followed by TLC (dichloromethane:*n*-hexane 1:1). The residue was dissolved in dichloromethane (20 mL) and washed with a 10% aqueous HCl solution (20 mL) and water. The combined organic phases were dried and **10** was obtained as an off-white solid (8.7 mg) in 50% yield.

Planetary ball mill: To a zirconium oxide reactor, containing 200 zirconium oxide 5 mm balls, were added 50 mg (0.05 mmol) of **9** and 15.26 mg (1.1 eq., 0.06 mmol) of TBAF. The mixture was grinded at 500 rpm for 1 h, with rotation inversion cycles of 15 min (5 s pause between inversion cycles). The reaction was followed by TLC (dichloromethane:*n*-hexane 1:1). The residue was dissolved in dichloromethane (25 mL) and washed with a 10% HCl aqueous solution (25 mL) and water. The combined organic phases were dried and evaporated. The obtained residue was recrystallized from dichloromethane/methanol to give **10** as an off-white solid (7.6 mg) in 16% yield. m.p. 145-148 °C (m.p. lit. [19] 146-148 °C). FT-IR (KBr) ν_{max} (cm^{-1}): 3308, 3266 (s, C≡C-H), 3035 (w, =C-H), 2960, 2873 (s, C-H), 2113 (w, C≡C), 1604 (m, C=C), 1582, 1481 (s, C-H), 1204, 1123, 1009, 868, 820 (s, =C-H). ^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm): 7.51 (d, 2H, H-C≡C-Ar$\underline{H}$, J = 7.9 Hz), 7.45 (d, 2H, H-C≡C-Ar$\underline{H}$, J = 7.9 Hz), 6.91 (s, 4H, Ar$\underline{H}$), 6.65 (s, 2H, Ar$\underline{H}$), 6.61 (s, 2H, Ar$\underline{H}$), 4.82 (s, 2H, ArOC$\underline{H}_2$Ar), 4.38 (d, 2H, ArC$\underline{H}_2$Ar, J = 12.6 Hz), 4.36 (d, 2H, ArC$\underline{H}_2$Ar, J = 12.6 Hz), 3.85-3.64 (m, 6H, OC$\underline{H}_2$CH$_2$CH$_3$), 3.15-3.01 (m, 5H, ArC$\underline{H}_2$Ar (4H) and ≡C-$\underline{H}$ (1H)), 2.05-1.76 (m, 6H, C$\underline{H}_2$CH$_3$), 1.19 (s, 18H, C(C$\underline{H}_3$)$_3$), 1.05 (t, 3H, CH$_2$C$\underline{H}_3$, *overlapped*), 0.99 (s, 9H, C(C$\underline{H}_3$)$_3$), 0.96 (s, 9H, C(C$\underline{H}_3$)$_3$), 0.82 (t, 6H, CH$_2$C$\underline{H}_3$, J = 8.1 Hz).

Supporting Information

Supporting Information File 1

Copies of ^{1}HNMR spectra.

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