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Stereoselective Formation of Triphenylene Ketals

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Dedicated to Professor Julius Rebek, Jr. on the occasion of his 65th birthday

Abstract: The oxidative trimerization of catechol ketals by $MoCl_5$ or $MoCl_5$/$TiCl_4$ mixtures leads preferentially to the *all-syn* stereoisomer of the corresponding triphenylene ketal. The concomitant metal salts of the oxidative coupling most probably form a multinuclear template that directs the diastereoselectivity in a subsequent isomerization step under electrophilic conditions. Several functionalities can serve as coordination sites for the multinuclear metal chloro clusters. Suitable functional groups have to be stable towards the strong electrophilic and oxidizing conditions. Therefore, esters, nitriles, nitro derivatives, triazoles, and pyridines are successfully employed. Based on the flexibility and size of the substrate, different reagent mixtures lead to the stereoselective formation of the *all-syn* derivatives.

Keywords: C–C coupling · diastereoselectivity · molybdenum · oxidation · triphenylene ketal

Introduction

C_3 symmetric scaffolds play an important role in nature and supramolecular chemistry.[1] To achieve functional concave structures, it is necessary to place all binding sites on one side of the scaffold with a convergent orientation.[2] The *all-syn* stereoisomer can be generated by two different convergent synthetic strategies. First, optically pure starting materials are used and by specific fusion the desired *all-syn* derivative is formed. This strategy was realized, for example, in the synthesis of cyclic hexapeptides.[3] The major drawback of this approach is the required enantiopure starting materials or intermediates, which afford a multistep synthesis.[4] This leads to an intrinsically chiral C_3-symmetric platform in which the efficient induction of stereoinformation is only realized in a few examples.[5] As a second strategy, the *all-syn* stereoisomer (**A**) can be obtained in a statistical mixture with the less symmetric *anti*,*anti*,*syn* derivative (**B**) (Figure 1). The statistical formation strongly favors the generation of **B**, the less symmetric product, leading to a ratio of 3:1 for **B**/**A**. This challenge was solved in an elegant manner for the hexasubstituted benzenes; conformational control is achieved with an alternating orientation of the substituents.[6] This concept can be exploited for truxenes after statistical formation of an **A**/**B** mixture, which is then deprotonated and subsequently alkylated.[7] Extending the methodology to more expanded central moieties than benzene failed, therefore, separation of the statistical **A**/**B** mixture has to be performed and is eventually followed up by a recycling or an isomerization step of the cleft with nanoscale dimension.

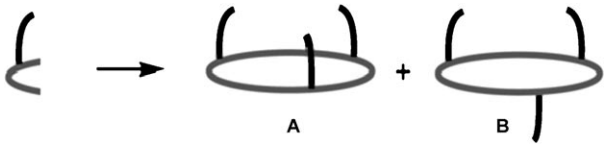

Figure 1. Stereochemistry of concave and C_3 symmetric scaffold formation.

Triphenylene ketals are unique concave clefts that exhibit an electron-rich central core. This platform led to the first artificial caffeine receptor[8] and supramolecular systems for the enantiofacial differentiation of heterocyclic substrates,[9] and it also exhibits a strong affinity towards oxopurines in

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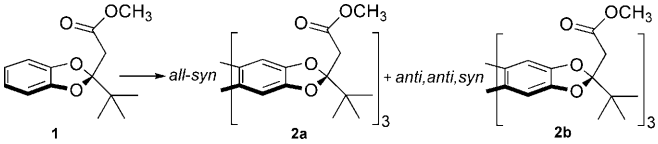
the presence of aqueous media.[10] Triphenylene ketals represent triketals of 2,3,6,7,10,11-hexahydroxytriphenylene and can be synthesized by oxidative trimerization of the corresponding catechol ketals, employing $MoCl_5$[11] or anodic protocols.[12,13] If functionalized benzo[1,3]dioxols are subjected to these methods, the statistical mixture is produced, yielding more than 75% of the undesired stereoisomer. A repetitive sequence of isomer separation and isomerization under strong acidic conditions allows the formation of larger quantities of the *all-syn* functionalized triphenylene ketal.[13] A more efficient approach to these compounds would facilitate access to these platforms and promote their application. Herein, we report a stereoselective formation of triphenylene ketals by the action of $MoCl_5$ or $MoCl_5/TiCl_4$ mixtures.

Results and Discussion

$MoCl_5$ is a very powerful reagent for the oxidative coupling of arenes.[14] In contrast with other metal salts in higher oxidation states, the molybdenum reagent prefers oxidative coupling versus ketal cleavage. The use of additional Lewis acids binds concomitant hydrogen chloride and keeps the reaction mixture electrophilic, which is often accompanied by higher reaction rates and improved yields.[15] Application of this reagent mixture was tested to enhance the yield of oxidative trimerization reactions (Scheme 1).



Scheme 1. Oxidative trimerization of catechol ketal **1**.

2-Substituted-2-*tert*-butylbenzo[1,3]dioxoles[16] were used as substrates because the isomeric triphenylene ketals are easily separated. We used the methoxycarbonylmethyl derivative **1** because the *all-syn* product, **2a**, is a key intermediate of previous receptor studies.[8,10] If $MoCl_5$ is used as the sole reagent, products **2a** and **2b** are formed according to statistics in 12 and 37% yield, respectively (Table 1, entry 1).

Table 1. Stereoselective oxidative trimerization of **1** by addition of Lewis acids.

Entry	Conditions[a]	Yield of **2a** [%]	Yield of **2b** [%]
1	$MoCl_5$ (2 equiv), 2 h	12	37
2	$MoCl_5$ (2 equiv), $SiCl_4$ (2 equiv), 2 h	11	38
3	$MoCl_5$ (2 equiv), $SnCl_4$ (2 equiv), 2 h	14	48
4	$MoCl_5$ (2 equiv), $TiCl_4$ (2 equiv), 2 h	50	22
5	$MoCl_5$ (2 equiv), $TiCl_4$ (1 equiv), 2 h	15	42
6	$MoCl_5$ (2 equiv), $TiCl_4$ (4 equiv), 2 h	48	23
7	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 2 h	52	25
8	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 8 h	68	4

[a] Equivalents are in relation to **1** and reactions were carried out at 0°C in CH_2Cl_2.

When using silicon tetrachloride as an additive no improvement was observed, whereas addition of tin(IV) chloride increased the total yield of **2** to 62%, but still as a statistical mixture of stereoisomers (Table 1, entries 2 and 3). Switching to $TiCl_4$ as scavenger for HCl leads to a significant amelioration; the triphenylene ketals are isolated in a total yield of 72%. Most surprisingly, a reversal of the isomeric distribution in contrast with the statistical expectation was found (Table 1, entry 4). Variation of the $MoCl_5/TiCl_4$ ratio revealed that an equimolar mixture of these metal chlorides is beneficial for the formation of **2a** (Table 1, entries 5–7). Optimal results are obtained when 3 equivalents of both components are applied for a longer time, providing 68% yield of **2a** and only 4% of the less symmetric isomer **2b** (Table 1, entry 8). The conversion of **1** with three equivalents of $MoCl_5$ and $TiCl_4$ was carried out with a systematic variation of reaction time (Figure 2). The total yield of **2** for each run is relatively constant (in the range of 72–79%), although a tremendous reversal of the isomeric ratio is observed. After a reaction time of 15 min, the ratio **2a**/**2b** is 0.26 (as expected by the statistics). With time, a stereoselective isomerization is observed, resulting in a ratio **2a**/**2b** of about 17 after 480 min. Most likely, the metal salts—reagent and reagent waste—form a template that promotes the stereoselective isomerization. A multinuclear chlorocluster has to be anticipated because the ester groups of the triphenylene ketal **2a** are more than 11 Å apart. During the course of the reaction $MoCl_4$ is formed. A hexameric cyclic species of $MoCl_4$ is known and would be large enough for a template.[17]

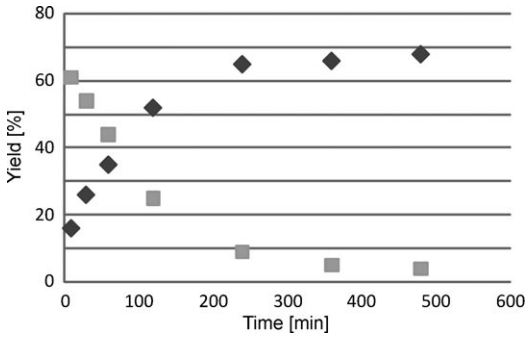


Figure 2. Change in isomeric ratio of triphenylene ketals **2a** (◆) and **2b** (■) during the course of reaction.

To gain insight into the isomerization of **2a** and the required metal species, we subjected **2a** to various Lewis acids in dichloromethane at room temperature (Table 2). Addition of tin tetrachloride or titanium tetrachloride rendered isomerization, but did not favor the *all-syn* derivative, **2a** (Table 2, entries 1 and 2). Applying mixtures of $MoCl_5$ and $TiCl_4$ changed the scene dramatically and **2a** was formed by isomerization in up to 96% yield (Table 2, entries 3 and 4).

Variation of the amount of Lewis acidic components clearly reveals that three equivalents of $TiCl_4$ and at least one equivalent of $MoCl_5$ are essential for the triphenylene

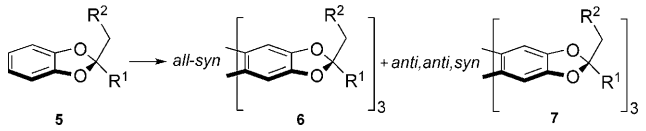
Table 2. Isomerization reactions of *anti*,*anti*,*syn*-isomer **2b**.

Entry	Conditions[a]	Yield of **2a** [%]	Yield of **2b** [%]
1	$TiCl_4$ (9 equiv), 2 h	19	58
2	$SnCl_4$ (9 equiv), 8 h	16	78
3	$MoCl_5$ (6 equiv), $TiCl_4$ (9 equiv), 2 h	95	trace
4	$MoCl_5$ (3 equiv), $TiCl_4$ (9 equiv), 2 h	96	trace
5	$MoCl_5$ (1 equiv), $TiCl_4$ (9 equiv), 2 h	92	trace
6	$MoCl_5$ (1 equiv), $TiCl_4$ (3 equiv), 2 h	92	trace
7	$MoCl_5$ (1 equiv), $TiCl_4$ (2 equiv), 4 h	58	26

[a] All reactions were carried out in CH_2Cl_2 at room temperature.

ketal formation (Table 2, entries 6 and 7). Isolation and characterization of **2a** with bound molybdenum and/or titanium fragments proved to be difficult.[18] $MoCl_5$ might act as an oxidant, generating a radical cation of **2**, which allows ring opening of the dioxole and subsequent isomerization of ketal moieties.

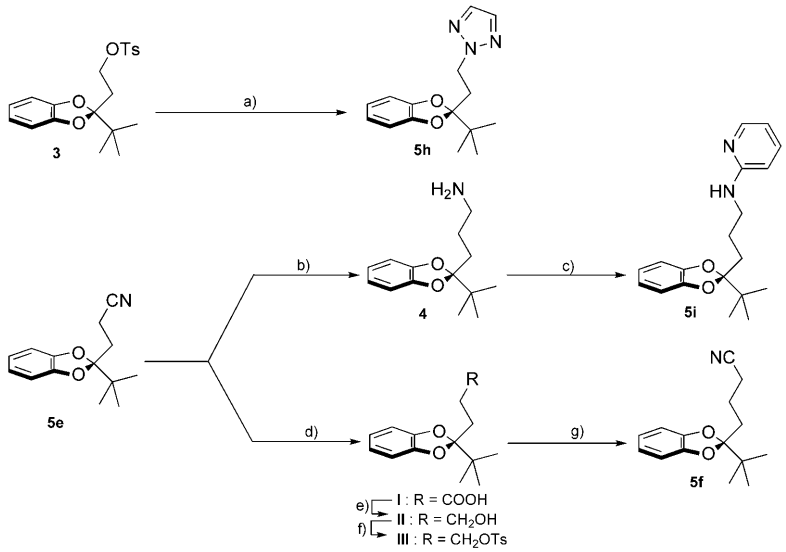
To elucidate the scope of the *syn*-selective oxidative trimerization (Scheme 2), a variety of functionalized 2-*tert*-butylbenzo[1,3]dioxoles (**5a**–**5i**) were synthesized (Scheme 3). Recently, the preparation of most substrates was reported.[16] The heterocyclic derivatives, **5h** and **5i**, are prepared from tosylate **3** and nitrile **5e**, respectively. The 1,2,3-triazole was installed by nucleophilic substitution on **3**, and was concomitant with triazole substitution at nitrogen N1 to afford the regioisomer of **5h**. Reduction of nitrile **5e** provides the amine **4**, which was thermally arylated with 2-bromopyridine to give **5i**.[19] The homologue **5f** was synthesized from **5e** by standard transformations.



Scheme 2. *Syn*-selective oxidative trimerization.

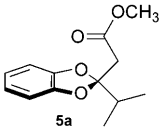
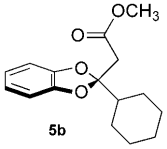
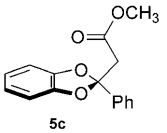
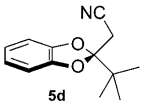
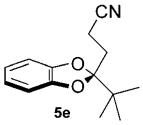
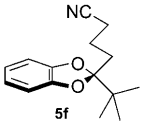
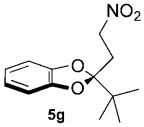
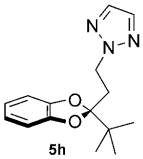
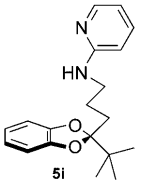
First, variation on the unfunctionalized side of the triphenylene was studied (Table 3). A high degree of steric demand is beneficial for the stability of benzo[1,3]dioxoles under electrophilic conditions,[11a] therefore, we used substrates with a *tert*-butyl group (Table 3, entries 4–9). Isopropyl and cyclohexyl substituents can be employed as well, leading to the *syn*-selective oxidative coupling reaction (Table 3, entries 1 and 2). In the latter example, only the desired stereoisomer of the triphenylene ketal was observed (Table 3, entry 2a). The use of $MoCl_5$ as the sole reagent leads to a complete reversal of selectivity with moderate yields for **6b** and **7b** (Table 3, entry 2b). Substrates with aryl substituents in position 2 are not applicable to this transformation because the ketal center is also benzylic and, therefore, prone to electrophilic cleavage. During the course of the reaction, compound **5c** is consumed without detection of **6c** or **7c** as products (Table 3, entry 3).

Second, different coordinating groups for a multinuclear metal cluster were envisioned for the reaction. The cyano group was used instead of the ester moiety. With this substrate, a slow, *syn*-selective oxidative trimerization is observed when using the $MoCl_5/TiCl_4$ mixture. Faster and better results were obtained by the application of $MoCl_5$ as the sole reagent (Table 3, entry 4). Subjecting the homologue substrate **5e** to the various conditions indicated that the metal template might be similar to substrate **1** because the $MoCl_5/TiCl_4$ mixture provided the best results (Table 3, entry 5). A propylene spacer between benzo[1,3]dioxole and the coordinating moiety of the template seems to allow interaction between different types of clusters and the triphenylene architecture. Therefore, both reaction conditions ($MoCl_5$ and the $MoCl_5/TiCl_4$ mixture) give better results than statistics, but are not truly selective (Table 3, entry 6). Nitro substituents are also suitable for this stereoselective trimerization reaction because their oxygen atoms can interact with an electrophilic chlorocluster (Table 3, entry 7). Reduced flexibility in the spacer renders higher yields and better stereoselectivity. If the Lewis basic center for coordination to the template is the fourth atom away from position 2 of the benzo[1,3]dioxole moiety, the $MoCl_5/TiCl_4$ combi-



Scheme 3. Synthesis of functionalized catechol ketals: a) 1,2,3-triazole, K_2CO_3, DMF, RT, 2 d, 36%; b) $LiAlH_4$, diethyl ether, 0°C, 30 min, 91%; c) 2-bromopyridine, 2,2,6,6-tetramethylpiperidine, 221°C, 16 h, 53%; d) NaOH, EtOH, H_2O, 100°C, 17 h, 80%; e) $LiAlH_4$, diethyl ether, 0°C, 15 min, 93%; f) TsCl, pyridine, overnight, RT, 87%; g) NaCN, DMSO, 80°C, 3 h, 88%.

Table 3. Scope of the stereoselective oxidative trimerization of **5**.

Entry	Starting material	Conditions[a]	Yield of **6** [%]	Yield of **7** [%]
1	 **5a**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 8 h	41 (**6a**)	6 (**7a**)
2a	 **5b**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 10 h	48 (**6b**)	–
b		$MoCl_5$ (3 equiv), 2 h	7	24 (**7b**)
3	 **5c**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), up to 10 h	–	–
4a	 **5d**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 15 min	19 (**6d**)	54 (**7d**)
b		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 3 h	36	33
c		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 5 h	48	20
d		$MoCl_5$ (3 equiv), CH_2Cl_2, 0 °C, 15 min	52	22
5a	 **5e**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 15 min	21 (**6e**)	58 (**7e**)
b		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 3 h	33	36
c		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 5 h	41	21
d		$MoCl_5$ (3 equiv), 15 min	18	51
e		$MoCl_5$ (3 equiv), 3 h	25	47
6a	 **5f**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 15 min	27 (**6f**)	63 (**7f**)
b		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 3 h	33	50
c		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 4 h	38	42
d		$MoCl_5$ (3 equiv), 15 min	20	55
7a	 **5g**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 15 min	23 (**6g**)	58 (**7g**)
b		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 3 h	35	40
c		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 5 h	47	28
d		$MoCl_5$ (3 equiv), 15 min	23	21
8a	 **5h**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 1 h	25 (**6h**)	44 (**7h**)
b		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 2 h	31	33
c		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 4 h	41	22
d		$MoCl_5$ (3 equiv), 1 h	45	35
e		$MoCl_5$ (3 equiv), 2 h	41	32
9a	 **5i**	$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 1 h	13 (**6i**)	28 (**7i**)
b		$MoCl_5$ (3 equiv), $TiCl_4$ (3 equiv), 1 h	14	18
c		$MoCl_5$ (3 equiv), 1 h	31	23

[a] All reactions were carried out in CH_2Cl_2 at 0 °C.

nation of reagents gives better results in terms of *syn* selectivity and yield. This is the case for substrates **5e** and **5g** (Table 3, entries 5 and 7). For smaller or larger spacings, $MoCl_5$ as the sole reagent is recommended. Five- and six-membered heterocycles can also serve as ligands for the multinuclear template in the oxidative trimerization process. Substrate **5h**, with a 1,2,3-triazole-2-yl substituent, can be stereoselectively trimerized by using the $MoCl_5/TiCl_4$ mixture (Table 3, entry 8). If the same protocol is applied to the pyridine derivative, **5i**, the best stereoselectivity can be obtained by using $MoCl_5$ as the oxidant and templating precursor (Table 3, entry 9). Assignment of the *all-syn* or *anti*,*anti*,*syn* configuration can be done in most cases by ^{1}H NMR spectroscopy. The signals for the triphenylene unit are uniform, whereas the resonances for the side arms of the *anti*,*anti*,*syn* isomer are distinct, despite of their distance of more than 11 Å (see the Supporting Information). Furthermore, the molecular structures and stereochemistries of **7d** and **6h** were unequivocally proven by the X-ray analysis of suitable single crystals. In the solid state, the tricyano derivative, **7d**, exhibits centered polar groups on different sides of the triphenylene plane, which reveals the *anti*,*anti*,*syn* nature of the isomer (Figure 3). The *all-syn* compound **6h** exposes the triazolo moieties on the same side of the molecule (Figure 4). Due to the packing of the individual triphenylene ketals, the arms with the heterocycles are partially tilted. However, the concave arrangement gives space for the binding of a template or other molecules in nanoscale dimensions; the average distance of Lewis basic nitrogen atoms is in the range of 12 Å.[20] In both structures the central triphenylene ketal architecture is bent. The distances between the centroids of the outer six-membered rings of the triphenylene unit and the least-squares plane defined by the atoms of the inner ring are 8.0(2), 11.2(2), and −23.5(2) pm for **7d**[21] and 0.9(1), 15.5(1), and 2.4(1) pm for **6h**.

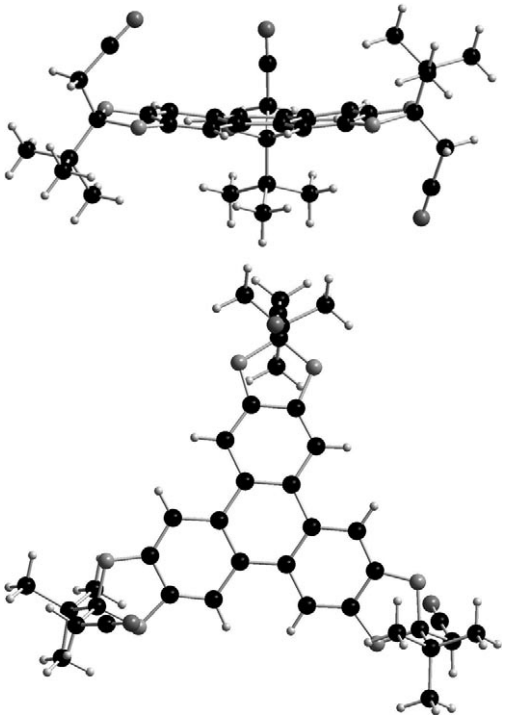


Figure 3. Molecular structure of **7d** by X-ray analysis; top: side view, bottom: top view.

Conclusion

The first *syn*-selective oxidative trimerization of catechol ketals was found, paving the way to an attractive synthetic access to these nanoscale-dimension clefts. The transformation consists of a nonselective oxidative coupling process, which yields a statistical mixture in which the *anti*,*anti*,*syn* isomer dominates. A subsequent in situ isomerization can occur with partially reduced molybdenum chlorides, or with $TiCl_4$ as an additive, to form a multinuclear chlorocluster that allows templating of polar groups that are more than 11 Å apart. Esters, cyano, nitro, triazolo, and pyridine moieties can serve as polar groups for binding to the template. Selectivity for the *syn* versus *anti*,*anti*,*syn* isomer in the conversion of catechol ketals can be up to a ratio of 17:1, respectively. Furthermore, isomerization of the less symmetric isomer to the *all-syn* derivative can be achieved in up to 96% yield. Although the nature of the multinuclear chlorocluster is not known, protocols using either the $MoCl_5$/$TiCl_4$ mixture or $MoCl_5$ as the sole reagent will affect the stereoselective triphenylene ketal formation. These findings clearly demonstrate that $MoCl_5$, and reagent mixtures thereof, are more than simple oxidants and might find application in other stereoselective coupling reactions.

Experimental Section

General: For details of all instumentation used, please see the Supporting Information.

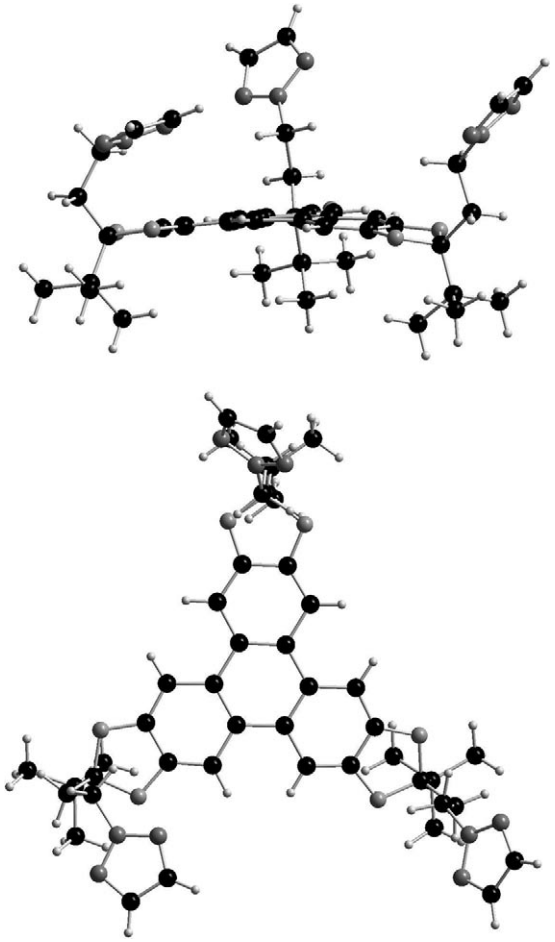


Figure 4. Molecular structure of **6h** by X-ray analysis; top: side view, bottom: top view.

Compound 5h: A mixture of 1,2,3-triazole (0.42 g, 6.0 mmol) and K_2CO_3 (3.00 g, 22 mmol) in DMF (30 mL) was stirred at RT for approximately 30 min before tosylate **3**[16] (1.54 g, 4.00 mmol) was added. The reaction mixture was stirred at RT for 2 d, poured onto ice water, and extracted with ethyl acetate (100 mL). The organic portion was washed with H_2O (3×100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, and filtered. Evaporation of the solvent afforded a residue that was purified by column chromatograpy (cyclohexane/ethyl acetate, 9.5:0.5) to give **5h** (0.4 g, 36%) and **5h′** (0.6 g, 54%), both as colorless powders. **5h**: $R_f=$ 0.55 (70% cyclohexane/ethyl acetate); m.p. 68–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.06$ (s, 9H), 2.65–2.69 (m, 2H), 4.52–4.56 (m, 2H), 6.71–6.78 (m, 4H), 7.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 24.2, 34.2, 40.4, 49.4, 107.5, 121.1, 122.1, 134.0, 148.4; MS (ESI+): *m*/*z*: 296.1 $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{15}H_{19}N_3NaO_2$: 296.1375 $[M+Na^+]$; found: 296.1369. **5h′**: $R_f=0.21$ (70% cyclohexane/ethylacetate); m.p. 95–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.04$ (s, 9H), 2.65 (t, $J=7.1$ Hz, 2H), 4.46 (t, $J=7.1$ Hz, 2H), 6.72–6.81 (m, 4H), 7.44 (s, 1H), 7.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=24.3$, 34.9, 40.5, 44.9, 107.6, 121.4, 122.1, 123.9, 133.4, 148.4; MS (ESI+): *m*/*z*: 296.1 $[M+Na]^+$; HRMS: *m*/*z* calcd for $C_{15}H_{19}N_3NaO_2$: 296.1375 $[M+Na^+]$; found: 296.1369.

Compound 4: $LiAlH_4$ (0.05 g, 1.3 mmol) was added to an ice-cold solution of nitrile **5e**[16] (0.1 g, 0.43 mmol) in diethyl ether (10 mL), The reaction mixture was stirred for 30 min at 0 °C and then carefully poured onto ice water. *t*BuOMe (30 mL) was added and this mixture was filtered through a pad of Celite. The organic phase was separated and washed several times with H_2O (5×30 mL) and brine (30 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to give **4** (0.091 g, 91%) as a col-

orless oil. R_f=0.12 (70% cyclohexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.02 (s, 9H), 1.45–1.53 (m, 4H), 1.92–1.98 (m, 2H), 2.64 (t, J=7.1 Hz, 2H), 6.64–6.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.4, 25.9, 31.1, 40.3, 42.1, 106.8, 120.5, 123.6, 149.0; MS (ESI+): m/z: 236.1 $[M+H]^+$; HRMS: m/z calcd for $C_{14}H_{22}NO_2$: 236.1651 $[M+H^+]$; found: 236.1645.

Compound 5i: A sealed tube was charged with amine **4** (0.1 g, 0.425 mmol), 2-bromopyridine (0.67 g, 4.25 mmol), and 2,2,6,6-tetramethylpiperidine (0.08 mL, 0.425 mmol). The mixture was kept at 221 °C (oil bath temperature) for 16 h. The mixture was cooled to RT, dissolved in CH_2Cl_2 (20 mL), and transferred into a 50 mL flask. After evaporation of the solvent, the crude product was purified by column chromatography (cyclohexane/ethyl acetate, 8:2) to give **5i** (0.069 g, 53%) as a colorless powder. R_f=0.13 (80% cyclohexane/ethyl acetate); m.p. 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.03 (s, 9H), 1.65–1.72 (m, 2H), 2.04–2.07 (m, 2H), 3.23–3.27 (m, 2H), 4.55 (br s, 1H), 6.28–6.30 (m, 1H), 6.51–6.54 (m, 1H), 6.67–6.74 (m, 4H), 7.33–7.40 (m, 1H), 8.00–8.04 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.2, 24.5, 31.3, 40.4, 42.2, 106.5, 107.0, 112.6, 120.7, 123.6, 137.5, 147.8, 149.1, 158.6; MS (EI, 70 eV): m/z (%): 312.2 (24) $[M]^+$; HRMS: m/z calcd for $C_{19}H_{24}N_2O_2$: 312.1838 $[M]^+$; found: 312.1834.

Compound I: A solution of nitrile **5e** (0.5 g, 2.2 mmol) in ethanol (10 mL) was treated with a 10% aqueous solution of NaOH (5 mL). The reaction mixture was heated at reflux for 17 h before the mixture was diluted with H_2O (50 mL). The solution was cooled to RT and acidified with 1 M hydrochloric acid (10 mL). The formed solid was filtered off, rinsed with pure water (3×50 mL), and subsequently dried under high vacuum (1×10^{-1} mbar) to give acid **I** (0.43 g, 80%) as a colorless powder. R_f=0.11 (80% cyclohexane/ethyl acetate); m.p. 155–156 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.05 (s, 9H), 2.30–2.35 (m, 2H), 2.41–2.46 (m, 2H), 6.66–6.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.4, 27.3, 29.2, 40.3, 107.2, 121.0, 122.8, 148.8, 179.4; MS (EI, 70 eV): m/z (%): 250.1 (16) $[M]^+$; HRMS: m/z calcd for $C_{14}H_{18}O_4$: 250.1205 $[M]^+$; found: 250.1211.

Compound II: $LiAlH_4$ (0.15 g, 3.6 mmol) was added to an ice-cooled solution of acid **I** (0.3 g, 1.2 mmol) in diethyl ether (10 mL). The reaction mixture was stirred for 15 min at 0 °C and then carefully poured onto ice water. *t*BuOMe (30 mL) was added and the mixture was filtered through a Celite pad. The organic phase was separated and washed several times with H_2O (5×50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and evaporated to give **II** (0.26 g, 93%) as a colorless oil. R_f= 0.21 (80% cyclohexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 1.05 (s, 9H), 1.58–1.67 (m, 2H), 2.02–2.07 (m, 2H), 3.21 (s, 1H), 3.62 (t, J=6.4 Hz, 2H), 6.64–6.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 24.5, 25.5, 30.1, 40.4, 26.8, 107.0, 120.6, 123.7, 149.1; MS (EI, 70 eV): m/z (%): 236.1 (14) $[M]^{+\cdot}$; HRMS: m/z calcd for $C_{14}H_{20}O_3$: 236.1412 $[M]^{+\cdot}$; found 236.1415.

Compound III: A solution of **II** (0.236 g, 1.0 mmol) in pyridine (10 mL) was treated with 4-toluenesulfonyl chloride (0.3 g, 1.5 mmol). The reaction mixture was stirred for 8 h at RT, then poured onto ice water. The formed solid was filtered off, washed with pure water (3×50 mL), and desiccated under high vacuum (1×10^{-1} mbar) to give tosylate **III** (0.34 g, 87%) as a colorless powder. R_f=0.54 (80% cyclohexane/ethyl acetate); m.p. 118–119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.99 (s, 9H), 1.67–1.73 (m, 2H), 1.92–1.96 (m, 2H), 2.44 (s, 3H), 4.01 (t, J=6.2 Hz, 2H), 6.62–6.74 (m, 4H), 7.32–7.34 (m, 2H), 7.75–7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=21.6, 21.9, 24.4, 30.0, 40.3, 70.6, 107.0, 120.8, 123.1, 127.9, 129.8, 133.1, 144.7, 148.8; MS (EI, 70 eV): m/z (%): 390.1 (8) $[M]^+$; HRMS: m/z calcd for $C_{21}H_{26}O_5S$: 390.1501 $[M]^+$; found: 390.1502.

Compound 5f: A mixture of tosylate **III** (0.2 g, 0.51 mmol) and sodium cyanide (0.04 g, 0.77 mmol) in dimethylsulfoxide (10 mL) was stirred at 80 °C for 2 h, then poured onto ice water. The formed solid was filtered off, rinsed with pure water (3×50 mL), and subsequently desiccated under high vacuum (1×10^{-1} mbar) to give **5f** (0.11 g, 88%) as a colorless powder. ***Attention!*** The filtrate has to be treated with $[FeSO_4{\cdot}7H_2O]$ in acidic media to bind the highly toxic cyanide. R_f=0.37 (85% cyclohexane/ethyl acetate); m.p. 63–64 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.05 (s, 9H), 1.72–1.79 (m, 2H), 2.09–2.13 (m, 2H), 2.34 (t, J=7.1 Hz, 2H), 6.70–6.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.2, 18.4, 24.4, 32.7, 40.4, 107.2, 119.3, 120.9, 123.0, 148.7; IR $\tilde{\nu}$=2247 cm^{-1} (CN); MS (EI, 70 eV): m/z (%): 245.1 (12) $[M]^+$; HRMS: m/z calcd for $C_{15}H_{19}NO_2$: 245.1416 $[M]^+$; found: 245.1415.

General procedure for the oxidative trimerization with $MoCl_5$: Under an inert atmosphere $MoCl_5$ (1.64 g, 6.0 mmol) was dissolved in CH_2Cl_2 (50 mL). The mixture was cooled to 0 °C and a solution of ketal (2.0 mmol) in CH_2Cl_2 (5 mL) was added rapidly. The mixture was stirred at 0 °C for the given time (see Table 3). After the conversion the mixture was partitioned between ethyl acetate (100 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (2×50 mL) and the combined organic fractions were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica by using mixtures of cyclohexane and ethyl acetate. The corresponding yields with respect to reaction time are given in Table 3.

General procedure for the oxidative trimerization with $MoCl_5$/$TiCl_4$ mixtures: Under an inert atmosphere $MoCl_5$ (1.64 g, 6.0 mmol) was dissolved in CH_2Cl_2 (50 mL), then $TiCl_4$ (0.65 mL, 6.0 mmol) was added. The mixture was cooled to 0 °C and a solution of ketal (2.0 mmol) in CH_2Cl_2 (5 mL) was added rapidly. The mixture was stirred at 0 °C for the given time (see Table 3). After the conversion the mixture was partitioned between ethyl acetate (100 mL) and a saturated aqueous solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with ethyl acetate (2×50 mL) and the combined organic fractions were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous $MgSO_4$, and subsequently concentrated under reduced pressure. The crude product was purified by column chromatography on silica by using mixtures of cyclohexane and ethyl acetate. The corresponding yields with respect to time and reagent mixture are given in Table 3.

Compound 2a (*all-syn*): R_f=0.10 (80% cyclohexane/ethyl acetate); m.p. 226–227 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 27H), 3.09 (s, 6H), 3.44 (s, 9H), 7.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.1, 39.0, 41.0, 51.9, 100.0, 121.4, 124.5, 148.7, 168.9; MS (ESI+): m/z: 767.3 $[M+Na]^+$; elemental analysis calcd (%) for $C_{42}H_{48}O_{12}$ (744.8233): C 67.74, H 6.50; found: C 67.73, H 6.47.

Compound 2b (*anti,anti,syn*): R_f=0.24 (80% cyclohexane/ethyl acetate); m.p. 263–264 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.12 (s, 27H), 3.09 (s, 6H), 3.39–3.42 (m, 9H), 7.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 24.0, 38.9, 40.9, 51.8, 99.9, 121.4, 124.6, 148.7, 168.9; MS (ESI+): m/z: 767.3 $[M+Na]^+$; HRMS: m/z calcd for $C_{42}H_{48}NaO_{12}$: 767.3038 $[M+Na^+]$; found: 767.3033.

Compound 6a (*all-syn*): R_f=0.11 (80% cyclohexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (d, J=6.8 Hz, 18H), 2.49 (sept, J= 6.8 Hz, 3H), 3.06 (s, 6H), 3.60 (s, 9H), 7.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.2, 36.0, 40.6, 52.0, 100.8, 119.9, 124.6, 147.9, 168.8; MS (ESI+): m/z: 725.3 $[M+Na]^+$; HRMS: m/z calcd for $C_{39}H_{42}NaO_{12}$: 725.2568 $[M+Na^+]$; found: 725.2564.

Compound 7a (*anti,anti,syn*): R_f=0.18 (80% cyclohexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.05–1.13 (m, 18H), 2.46–2.54 (m, 3H), 3.01–3.07 (m, 6H), 3.59–3.62 (m, 9H), 7.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=16.2, 36.0, 40.6, 51.9, 100.7, 119.9, 124.6, 148.0, 168.7; MS (ESI+): m/z: 725.3 $[M+Na]^+$; HRMS: m/z calcd for $C_{39}H_{42}NaO_{12}$: 725.2568 $[M+Na^+]$; found: 725.2564.

Compound 6b (*all-syn*): R_f=0.20 (80% cyclohexane/ethyl acetate); m.p. 120–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24–1.29 (m, 6H), 1.59–1.70 (m, 12H), 1.79–1.94 (m, 12H), 2.08–2.15 (m, 3H), 3.05 (s, 6H), 3.60 (s, 9H), 7.69 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.8, 26.0, 26.9, 40.5, 45.6, 52.0, 100.7, 119.5, 124.6, 147.9, 168.8; MS (ESI+): m/z: 823.4 $[M+H]^+$; HRMS: m/z calcd for $C_{48}H_{55}O_{12}$: 823.3688 $[M+H^+]$; found: 823.3664.

Compound 7b (*anti,anti,syn*): R_f=0.32 (80% cyclohexane/ethyl acetate); m.p. 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24–1.29 (m, 6H), 1.63–1.70 (m, 12H), 1.80–1.95 (m, 12H), 2.08–2.16 (m, 3H), 3.05 (s, 6H), 3.58–3.59 (m, 9H), 7.69 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=25.8, 25.9, 26.0, 40.5, 45.6, 52.0, 100.7, 119.5, 124.5, 147.9, 168.8; MS (ESI+):

m/z: 823.4 [*M*+H]$^+$; HRMS: *m/z* calcd for $C_{48}H_{54}NaO_{12}$: [*M*+Na$^+$] 845.3507; found: 845.3505.

Compound 6d (*all-syn*): R_f=0.20 (80% cyclohexane/ethyl acetate); m.p. 209–210°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.17 (s, 27H), 3.10 (s, 6H), 7.80 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.4, 29.1, 40.4, 101.2, 115.0, 119.6, 125.0, 147.8; MS (ESI+): *m/z*: 668.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{39}H_{39}N_3NaO_6$: [*M*+Na$^+$] 668.2737; found: 668.2731.

Compound 7d (*anti,anti,syn*): R_f=0.26 (80% cyclohexane/ethyl acetate); m.p. 288–289°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.15 (s, 27H), 3.10 (s, 6H), 7.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.3, 26.9, 40.4, 101.1, 115.1, 119.6, 125.0, 147.8; MS (ESI+): *m/z*: 668.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{39}H_{39}N_3NaO_6$: 668.2737 [*M*+Na$^+$]; found: 668.2731. X-ray crystal structure analysis for **7d**: plate-like, colorless crystals were obtained by evaporation of a solution of **7d** in CH_2Cl_2 at ambient conditions; formula: $C_{39}H_{39}N_3O_6$; M_r=645.73; crystal size: 0.32×0.24×0.04 mm; a=30.9263(9), b=14.2342(4), c=37.3935(14) Å; $\alpha=\gamma$=90°, β=101.030(3)°; V=16156.9(9) Å^3; ρ_{calcd}=1.062 g cm^{-3}; μ=0.072 mm^{-1}, no absorption correction was applied; Z=16; monoclinic; space group *C*2/*c*, λ=0.71073 Å; T=123(2) K, ω, and ϕ scans, 88731 reflections collected; 19508 independent (R_{int}=0.1283); completeness to θ=28.00°: 99.9%; 872 refined parameters, R^1=0.0879, wR^2=0.2716; largest difference peak and hole: 0.528 and −0.418 e Å^{-3}.

Compound 6e (*all-syn*): R_f=0.13 (87% cyclohexane/ethyl acetate); m.p. 220–221°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.10 (s, 27H), 2.47 (s, 12H), 7.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.9, 24.3, 30.3, 40.6, 100.3, 119.2, 122.8, 124.6, 148.7; MS (ESI+): *m/z*:710.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{42}H_{45}N_3NaO_6$: 710.3206 [*M*+Na$^+$]; found: 710.3201.

Compound 7e (*anti,anti,syn*): R_f=0.21 (87% cyclohexane/ethyl acetate); m.p. >300°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 27H), 2.43–2.49 (m, 12H), 7.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=10.9, 24.3, 30.3, 40.6, 100.3, 119.2, 122.8, 124.6, 148.7; MS (ESI+): *m/z*: 710.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{42}H_{45}N_3NaO_6$: 710.3206 [*M*+Na$^+$]; found: 710.3201.

Compound 6f (*all-syn*): R_f=0.27 (83% cyclohexane/ethyl acetate); m.p. 272–273°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.10 (s, 27H), 1.78–1.85 (m, 6H), 2.19–2.25 (m, 6H), 2.36 (t, J=7.0 Hz, 6H), 7.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.2, 18.4, 24.4, 32.7, 40.5, 99.9, 119.2, 124.0, 124.3, 149.0; MS (ESI+): *m/z*: 752.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{45}H_{51}N_3NaO_6$: 752.3676 [*M*+Na$^+$]; found: 752.3699.

Compound 7f (*anti,anti,syn*): R_f=0.36 (83% cyclohexane/ethyl acetate); m.p. 274–275°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.11 (s, 27H), 1.76–1.81 (m, 6H), 2.20–2.24 (m, 6H), 2.36 (t, J=7.0 Hz, 6H), 7.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=17.2, 18.4, 24.4, 32.7, 40.5, 99.9, 119.2, 124.1, 124.3, 149.0; MS (ESI+): *m/z*: 752.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{45}H_{51}N_3NaO_6$: 752.3676 [*M*+Na$^+$]; found: 752.3629.

Compound 6g (*all-syn*): R_f=0.18 (92% cyclohexane/ethyl acetate); m.p. >300°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.12 (s, 27H), 2.87 (t, J=7.2 Hz, 6H), 4.49 (t, J=7.1 Hz, 6H), 7.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.2, 31.9, 40.7, 70.0 100.5, 122.6, 124.7, 148.4; MS (ESI+): *m/z*: 770.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{39}H_{45}N_3NaO_{12}$: 770.2901 [*M*+Na$^+$]; found: 770.2895.

Compound 7g (*anti,anti,syn*): R_f=0.31 (92% cyclohexane/ethyl acetate); m.p. 252–253°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.13 (s, 27H), 2.87 (t, J=7.1 Hz, 6H), 4.47 (t, J=7.1 Hz, 6H), 7.69 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.2, 31.9, 40.7, 69.9, 100.5, 122.6, 124.7, 148.4; MS (ESI+): *m/z*: 770.3 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{39}H_{45}N_3NaO_{12}$: 770.2901 [*M*+Na$^+$]; found: 770.2895.

Compound 6h (*all-syn*): R_f=0.15 (85% cyclohexane/ethyl acetate); m.p. 206–207°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.12 (s, 27H), 2.76–2.79 (m, 6H), 4.60–4.65 (m, 6H), 7.55 (s, 6H), 7.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.3, 34.2, 40.7, 49.3, 100.2, 123.0, 124.5, 134.1, 148.8; MS (ESI+): *m/z*: 836.4 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{45}H_{51}N_9NaO_6$: 836.3860 [*M*+Na$^+$]; found: 836.3855. X-ray crystal structure analysis for **6h**: plate-like, colorless crystals were obtained by evaporation of a solution of **6h** in CH_2Cl_2 at ambient conditions; formula $C_{45}H_{51}N_9O_6$; M_r=813.95; crystal size: 0.60×0.60×0.02 mm; $a=b$=17.5402(6), c=67.560(3) Å; $\alpha=\beta=\gamma$=90°; V=20785.5(14) Å^3; ρ_{calcd}=1.040 g cm^{-3}; μ=0.071 mm^{-1}; no absorption correction was applied; Z=16; tetragonal; space group *I*41/a, λ=0.71073 Å; T=123(2) K; ω and ϕ scans; 49596 reflections collected; 9043 independent (R_{int}=0.1487); completeness to θ=25.25°: 96.0%; 551 refined parameters, R^1=0.0786, wR^2=0.1960; largest difference peak and hole: 0.293 and −0.395 e Å^{-3}.

Compound 7h (*anti,anti,syn*): R_f=0.24 (85% cyclohexane/ethyl acetate); m.p. 198–199°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.12 (s, 27H), 2.76–2.80 (m, 6H), 4.57–4.63 (m, 6H), 7.55 (s, 6H), 7.71 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=24.3, 34.2, 40.6, 49.3, 100.2, 123.1, 124.5, 134.0, 148.7; MS (ESI+): *m/z*: 836.4 [*M*+Na]$^+$; HRMS: *m/z* calcd for $C_{45}H_{51}N_9NaO_6$: 836.3860 [*M*+Na$^+$]; found: 836.3855.

Compound 6i (*all-syn*): R_f=0.12 (30% cyclohexane/ethyl acetate); m.p. 157–158°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.09 (s, 27H), 1.72–1.75 (m, 6H), 2.14–2.18 (m, 6H), 3.26–3.30 (m, 6H), 4.59 (s, 3H), 6.26–6.28 (m, 3H), 6.47–6.50 (m, 3H), 7.29–7.32 (m, 3H), 7.65 (s, 6H), 8.00–8.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.3, 24.6, 31.3, 40.5, 42.1, 99.5, 106.5, 112.6, 124.1, 124.6, 137.6, 147.7, 149.2, 158.6; MS (ESI+): *m/z*: 932.5 [*M*+H]$^+$; HRMS: *m/z* calcd for $C_{57}H_{68}N_6O_6$: 932.5200 [*M*+H$^+$]; found: 932.5164.

Compound 7i (*anti,anti,syn*): R_f=0.21 (30% cyclohexane/ethyl acetate); m.p. 130–131°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.05 (s, 27H), 1.65–1.72 (m, 6H), 2.10–2.16 (m, 6H), 3.21–3.25 (m, 6H), 4.53 (s, 3H), 6.17–6.23 (m, 3H), 6.42–6.44 (m, 3H), 7.22–7.28 (m, 3H), 7.61 (s, 6H), 7.97–8.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=22.2, 24.6, 31.2, 40.6, 42.0, 99.7, 106.5, 112.7, 124.1, 124.7, 137.4, 147.8, 149.1, 158.5; MS (ESI+): *m/z*: 931.5 [*M*+H]$^+$; HRMS: *m/z* calcd for $C_{57}H_{67}N_6O_6$: 931.5122 [*M*+H$^+$]; found: 931.5117.

X-ray crystallography: CCDC-749439 (**6h**) and 749440 (**7d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[18] The templated **2a** is a black-greenish powder which quickly decomposes. Switching to a solvent other than dichloromethane promotes degradation of templated **2a**.

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[20] The distances between the central N atoms of the triazole units are 13.107(5), 12.104(5), and 10.672(5) Å.

[21] The molecular solid-state structure of **7d** features another independent molecule in the asymmetric unit. The corresponding values are 6.0(2), 12.1(2), and −16.5(2) pm. The negative sign denotes a distance in the opposite direction of the least-squares plane in comparison to the other distances.

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