Trithioorthoester Exchange and Metathesis: New Tools for Dynamic Covalent Chemistry

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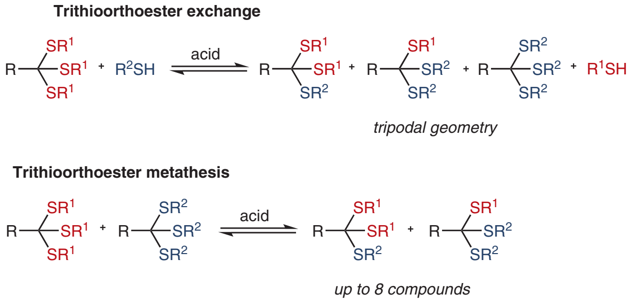

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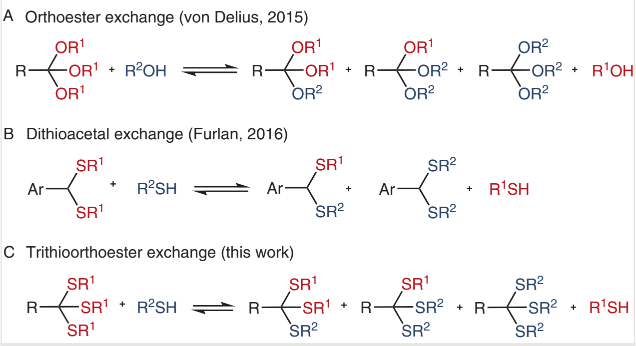
Abstract To expand the toolbox of dynamic covalent and systems chemistry, we investigated the acid-catalyzed exchange reaction of trithioorthoesters with thiols. We found that trithioorthoester exchange occurs readily in various solvents in the presence of stoichiometric amounts of strong Brønsted acids or catalytic amounts of certain Lewis acids. The scope of the exchange reaction was explored with various substrates, and conditions were identified that permit clean metathesis reactions between two different trithioorthoesters. One distinct advantage of *S,S,S*-orthoester exchange over *O,O,O*-orthoester exchange is that the exchange reaction can kinetically outcompete hydrolysis, thereby making the process less sensitive to residual moisture. We expect that the relatively high stability of the products might be beneficial in future supramolecular receptors or porous materials.

Key words transesterification, trithioorthoesters, thiols, exchange reaction, metathesis, dynamic covalent chemistry

Dynamic covalent chemistry (DCC)[1] has emerged in the last two decades as an area that combines the best attributes of organic chemistry (synthesis of stable compounds) with those of supramolecular chemistry (error correction).[2] At the heart of DCC are robust and reliable chemical reactions that, at least in the presence of suitable catalysts,[3] lead to the formation of equilibrium mixtures under relatively mild conditions. Typical examples include the exchange of disulfides with thiols,[4] and the reversible condensation reactions of imines,[5] hydrazones,[6] and oximes.[7] However, in the light of new applications of DCC, especially in the synthesis of porous materials[8] and in the life sciences,[9] there is unabated interest in the development of new dynamic covalent reactions.

To this end, the groups of von Delius and of Furlan recently reported investigations of *O,O,O*-orthoester exchange[10] and dithioacetal exchange reactions,[11] respectively (Scheme 1). Both reactions share similarities, such as a requirement for acid catalysis in organic solvents[12] and their widespread use in protective-group chemistry.[13] The tripodal nature of orthoesters makes them uniquely suited for the self-assembly of cage-type architectures.[14,15] Also, orthoester exchange gives rise to a remarkable level of molecular diversity, because by mixing one orthoester with one alcohol, an equilibrium mixture consisting of four different orthoesters is obtained (Scheme 1A). In contrast, dithioacetal exchange produces fewer products (Scheme 1B) and is more suited to the preparation of cyclic hosts.[16] This exchange can be connected to that of disulfides and thioesters to generate multilevel dynamic systems.[17] Compared with orthoesters, dithioacetals are less susceptible to hydrolysis and they demand more-acidic media for exchange.



Scheme 1 Exchange reactions of (A) orthoesters, (B) dithioacetals, and (C) trithioorthoesters

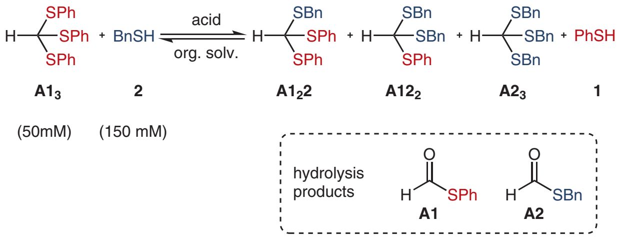
In this study, we focus on trithioorthoester exchange, an area of chemical space that, from the perspective of topology and reactivity, lies between orthoester exchange and dithioacetal exchange (Scheme 1C). Trithioorthoesters[18] can be obtained from, inter alia, *O,O,O*-orthoesters,[19] chloroform,[20] orthothioformates,[21] or dithioacetals,[22,23] and trithioorthoester groups have been used primarily as protective groups, especially when the product is required to be more stable toward acid hydrolysis than its oxygen counterpart.[13] Here, we present a comprehensive investigation of the conditions required for trithioorthoester exchange and for trithioorthoester metathesis, in the hope that these transformations will prove useful in areas where the advantages of thermodynamic control can be harnessed.[8e,24]

We started by testing the feasibility of trithioorthoester exchange under conditions similar to those used for the activation of *O*,*O*,*O*-orthoesters[10] or dithioacetals.[11] To this end, trifluoroacetic acid (TFA; 1 or 10 equiv) was added to a chloroform-*d* solution containing tris(phenylthio)methane (**A1$_3$**; 50 mM, 1 equiv) and phenylmethanethiol (**2**; 3 equiv) at room temperature (Table 1). All solvents were dried over molecular sieves before use to minimize the irreversible hydrolysis of trithioorthoesters to thioesters. The compositions of the reaction mixtures were analyzed by ^{1}H NMR spectroscopy after one hour and 24 hours. The use of ten equivalents of TFA led to equilibration of the mixture within one hour of reaction time. The apparent bias toward trithioorthoesters rich in building block **2** (Table 1, entry 1) can be rationalized in terms of differences in steric demand. The undesired hydrolysis reaction led to ≤2% of thioesters **A1** and **A2** with respect to the initial trithioorthoesters. A tenfold decrease in the amount of TFA was possible, but led to slower exchange, as indicated by the dominance of starting material **A1$_3$** after 24 hours of reaction time (Table 1, entry 2). The harsh Brønsted acidic conditions, which are required to equilibrate trithioorthoesters within a reasonable timespan, are similar to those giving rise to dithioacetal exchange, whereas *O*,*O*,*O*-orthoester exchange proceeds under much milder conditions.

A range of parameters was next investigated to better understand the reaction. First, various solvents were tested by using TFA in a standard amount of ten equivalents. In benzene-d_6, equilibrium was reached after one hour of reaction (Table 1, entry 3), whereas in acetonitrile-d_3 the exchange was slow and the composition after 24 hours was still far from equilibrium (Table 1, entry 4). No exchange products were observed in DMSO-d_6 or THF-d_8. When stronger Brønsted acids were compared in acetonitrile-d_3 (for solubility reasons), a correlation between the pK_a value[25] and the reaction kinetics was observed. Slow exchange was observed with TFA (pK_a = 12.7) or methanesulfonic acid (pK_a = 10.0) (entries 4 and 5), whereas the mixtures with *p*-toluenesulfonic acid (pK_a = 8.0) or sulfuric acid (pK_a = 7.2) equilibrated after 24 hours (entries 6 and 7). Only the mixture with trifluoromethanesulfonic acid (pK_a = 2.6) equilibrated after one hour of reaction (entry 8). Trifluoromethanesulfonic acid turned out to be a less effective catalyst in DMSO-d_6, whereas THF-d_8[26] was unstable in the presence of this acid [see the Supplementary Information (SI)]. Stoichiometric or excess Brønsted acids were shown to be useful for promoting trithioorthoester exchange. These conditions were used in exchange experiments initiated from various starting materials,[1c,27] which confirmed the reversibility of the reaction (Figures S1–S3, SI).

In the hope of identifying milder and truly catalytic (substoichiometric) conditions, we proceeded to investigate some representative Lewis acids.[28] For reasons of solubility, we chose CD_3CN as a solvent to investigate $FeCl_3$, $AlCl_3$, and $BF_3{\cdot}OEt_2$, whereas $CDCl_3$ was used in combination with $SnCl_4$, $TiCl_4$, and $FeCl_3$. We found that one equivalent of each of the Lewis acids $FeCl_3$, $AlCl_3$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ led to equilibration after roughly one hour; experiments with 0.1 equivalent of these Lewis acids showed that they can indeed be regarded as catalysts for this reaction (Table 1, en-

Table 1 Scope of Trithioorthoester Exchange[a]



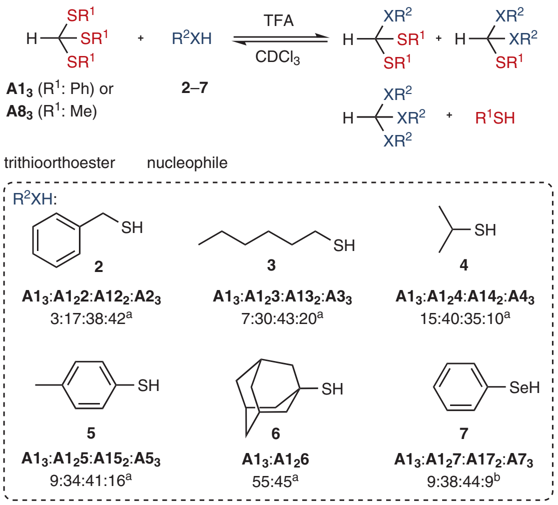
Entry	Acid (Equiv)	Solvent	Reaction time (h)	$A1_3/A1_22/A12_2/A2_3/(A1 + A2)$[b]
1	TFA (10)	$CDCl_3$	1 24	**3:17:38:42:–** **2:16:38:43:1**
2	TFA (1)	$CDCl_3$	1 24	97:3:–:–:– 46:30:16:8:–
3	TFA (10)	C_6D_6	1 24	**8:17:33:42:–** **3:17:39:41:–**
4	TFA (10)	CD_3CN	1 24	98:2:–:–:– 66:22:8:4:–
5	MsOH (1)	CD_3CN	1 24	97:3:–:–:– 56:26:13:5:–
6	PTSA (1)	CD_3CN	1 24	60:24:1:5:– **2:11:37:50:–**
7	H_2SO_4 (1)	CD_3CN	1 24	73:18:6:3:– **4:14:39:43:–**
8	TfOH (1)	CD_3CN	1 24	**1:18:42:39:–** **2:19:43:36:–**
9	$FeCl_3$ (0.1)	CD_3CN	1 24	35:26:23:16:– **3:15:39:43:–**
10	$AlCl_3$ (0.1)	CD_3CN	1 24 48	92:8:–:–:– 24:21:26:29:– **14:15:29:42:–**
11	$BF_3{\cdot}OEt_2$ (0.1)	CD_3CN	1 24 48	78:18:4:–:– **9:14:33:44:–** **4:15:38:43:–**
12	$FeCl_3$ (0.1)	$CDCl_3$	1	**3:17:40:40:–**

[a] Reaction conditions: **A1$_3$** (37.5 μmol), **2** (112.5 μmol), TFA (375 μmol), $CDCl_3$ (V_{total}: 750 μL), r.t.
[b] Product ratios were determined by integration of ^{1}H NMR signals. Equilibrium mixtures are highlighted in bold face; '–' indicates not detected. For full spectra, see Figures S4–S25 in the Supplementary Information.

tries 9–12) with the following reactivity trend: $FeCl_3$ > $BF_3{\cdot}OEt_2$ > $AlCl_3$. In addition, the use of Lewis acids in $CDCl_3$ was found to be promising. When 0.1 equivalent of $FeCl_3$ in $CDCl_3$ was tested, equilibrium was attained after one hour (entry 12). Although the equilibrium position seems to be unaffected by the presence of the iron cation, signal broadening was observed, which increased with reaction time, preventing accurate integration after 24 hours of reaction. These results show that Lewis acids require a lower catalyst loading than do Brønsted acids. Future work might focus on Lewis acid catalysis in $CDCl_3$ to achieve shorter reaction times when using substoichiometric amounts of catalyst. To this end, alternative analytical tools such as HPLC might be helpful in avoiding interference by the paramagnetic effects induced by metal cations.

To explore the scope of the reaction, we studied the effects of the nucleophile on the kinetics and thermodynamics of exchange. To this end, trithioorthoester **A1$_3$** was combined with thiols **2**–**6** in the presence of TFA (10 equiv) (Scheme 2). Primary thiols such as phenylmethanethiol (**2**) or hexane-1-thiol (**3**) gave compositions shifted toward trithioorthoester products containing more-exchanged units. Secondary and aromatic thiols, such as propane-2-thiol (**4**) and 4-methylbenzenethiol **5**, respectively, led to nearly symmetrical statistical distributions of trithioorthoesters. The use of bulky adamantane-1-thiol (**6**) led to the formation of only a single exchange product containing one building block **6**. The exchange kinetics were not noticeably affected by thiol structures, because all the mixtures were equilibrated after one hour of reaction time. Comparable equilibrium distributions were obtained after 24 hours when **A1$_3$** was exposed to the nucleophiles in CD_3CN in the presence of $FeCl_3$ (0.1 equiv) as catalyst (see SI). These results are in agreement with those observed in *O*,*O*,*O*-orthoester exchange, in which the equilibrium position, but not the equilibration kinetics, depends on the size of the nucleophile.[10] Finally, inspired by recent studies on (crossed) dichalcogenide exchange reactions,[29] we investigated the reaction of trimethyl trithioorthoformate **A8$_3$** with benzeneselenol **7**. After one hour, four signals in the diagnostic trithioorthoester range were observed; these appeared in a statistical proportion, showing the feasibility and the reversibility of the reaction (after 24 hours, selenol oxidation dominates the reaction outcome). To our knowledge, this is the first example of selenol/trithioorthoester exchange.

While keeping the ratio of trithioorthoester **A1$_3$** to thiol **2** at 1:3, and with a constant total amount of TFA, we next investigated the effect of the trithioorthoester concentration (Figure S37). We found that a tenfold decrease in the concentration of **A1$_3$** from 50 mM to 5 mM did not affect the equilibrium position. This indicates that trithioorthoester exchange might well be suited to experiments requiring low concentrations of reactants. However, a simultaneous decrease in the concentration of TFA to 10 equivalents (50 mM) slowed the exchange reaction considerably (96% of **A1$_3$** was present after 1 h).



Scheme 2 Effect of the structure of the nucleophile on the distribution of trithioorthoesters at equilibrium. *Reaction conditions*: **A1$_3$** or **A8$_3$** (37.5 µmol), nucleophile (112.5 µmol), TFA (375 µmol), $CDCl_3$ (V_{total}: 750 µL), r.t. Product ratios were determined by integration of ^1H NMR signals after 1 h. Hydrolysis was negligible (<2%) in all cases except for thiol **6** (7%). ^{a} Exchange performed with **A1$_3$** ($CDCl_3$ or CD_3CN). ^{b} Exchange performance with **A8$_3$** ($CDCl_3$). For full spectra, see Figures S26–S36 (SI).

To take advantage of the low boiling point of methanethiol (6 °C), **A8$_3$** was treated with 4-methylbenzenethiol (**5**) in the presence of excess TFA (10 equiv) under a smooth nitrogen stream while the temperature was increased from r.t. to 40 °C and then to 60 °C to shift the equilibrium completely towards trithioorthoesters containing exchanged side chains.[30] The composition could indeed be shifted almost completely toward the formation of exchange product **A5$_3$** (Figure S38). This straightforward method might be useful whenever a complete shift in the equilibrium toward the product side is desired.

In a comparative study, we examined the hydrolytic stability of trimethyl trithioorthoformate [(*S*,*S*,*S*)-**A8$_3$**], its oxygen-containing counterpart trimethyl orthoformate [(*O*,*O*,*O*)-**A9$_3$**], and the dithioacetal bis(methylthio)methane (**AH8$_2$**).[31] Increasing amounts of TFA were added to solutions containing each compound with one equivalent of water, and the samples were analyzed by ^1H NMR spectroscopy after one hour of reaction (Figure 1; note the logarithmic scale of the *x*-axis).

As expected, the trithioorthoester compound was considerably more stable to hydrolysis than was the orthoester, but was less stable than the dithioacetal. We found that the addition of ten equivalents of TFA led to complete hydrolysis of (*O*,*O*,*O*)-**A9$_3$**, whereas (*S*,*S*,*S*)-**A8$_3$** and **AH8$_2$** were mostly stable. The addition of 100 equivalents of TFA was neces-

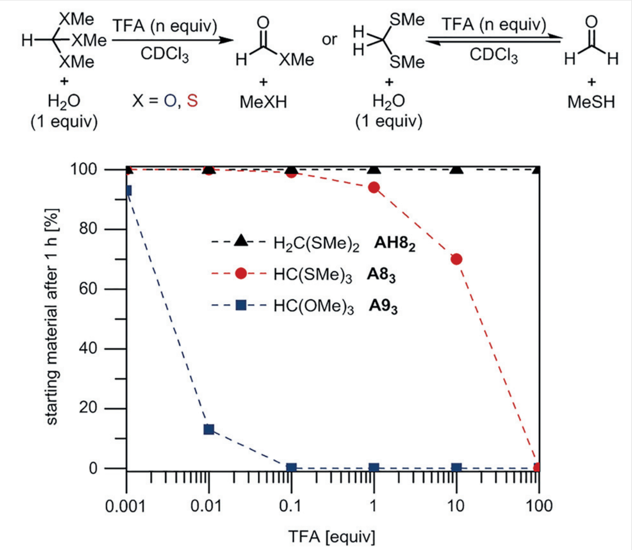


Figure 1 Effects of increasing amounts of TFA on the hydrolysis of orthoester (*O*,*O*,*O*)-**A9$_3$**, trithioorthoester (*S*,*S*,*S*)-**A8$_3$**, and dithioacetal **AH8$_2$**. *Reaction conditions*: **A9$_3$** or **A8$_3$** or **AH8$_2$** (37.5 μmol), increasing amounts of TFA [from 37.5 nmol (50 μM) to 3.75 mmol (5.0 M)], CDCl$_3$ (V_{total}: 750 μL), r.t., 1 h; internal standard: toluene. For full spectra, see Figures S39–S56 in the SI.

sary to hydrolyze(*S*,*S*,*S*)-**A8$_3$** completely, whereas **AH8$_2$** remained stable under these conditions. These findings indicate that in terms of hydrolytic stability, the trithioorthoester compound is located at an intermediate position between the orthoester and dithioacetal compounds. Most importantly, the results point towards faster exchange versus slower hydrolysis kinetics of trithioorthoesters: over a one hour period, treatment of (*S*,*S*,*S*)-**A8$_3$** with ten equivalents of TFA led to complete equilibration (Figure S57), but only to 30% hydrolysis. This observation explains why the rigorous exclusion of water is not as essential for (*S*,*S*,*S*)-orthoester exchange as it is for the (*O*,*O*,*O*)-orthoester variant. When trimethyl trithioorthoacetate (**C8$_3$**) was hydrolyzed with ten equivalents of TFA, the hydrolysis ratio after one hour was 93%, indicating that the same electronic effects as previously reported account for differences in hydrolytic stability (Figure S58).[15e] The observed differential susceptibility to hydrolysis of orthoesters, trithioorthoesters, and dithioacetals is relevant for the selective removal of protective groups.

In light of the shuttle catalysis concept,[32] there has recently been an increase in interest in exchange reactions between molecules having the same kind of functional group, i.e. Type 1 metathesis.[33] Among the Type 1 metathesis reactions that have been studied from the perspective of dynamic covalent/combinatorial chemistry are disulfide,[4,34] trithiocarbonate,[35] thiazolidine,[36] acetal,[37] orthoester,[10] and dithioacetal exchange.[17a] We therefore wondered whether a direct metathesis reaction between two trithioorthoesters might be possible.

To answer this question, a set of trithioorthoesters suitable for crossover experiments were synthesized.[38–41] Treatment of compounds **A1$_3$** and **B8$_3$** with TFA (10 equiv) led to a Type I metathesis, as indicated by the appearance in the ^{1}H NMR spectrum of a set of signals corresponding to the eight expected trithioorthoesters (Figure 2 and Table 2, entry 1). As in the case of related orthoester metathesis,[10] we believe that the generation of small quantities of free thiol[42] is responsible for the observed reactivity.

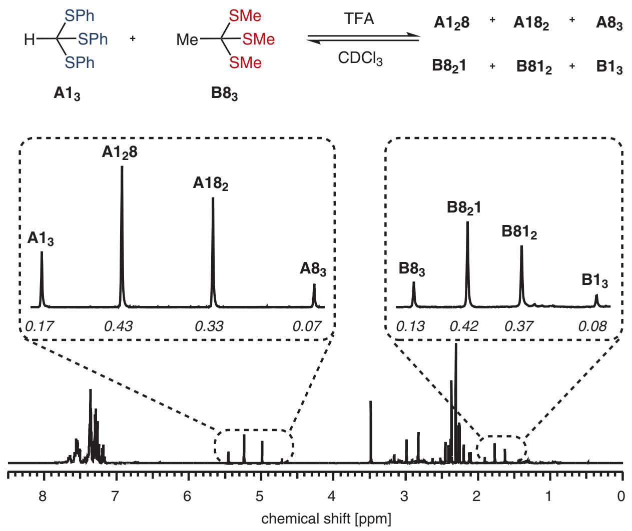
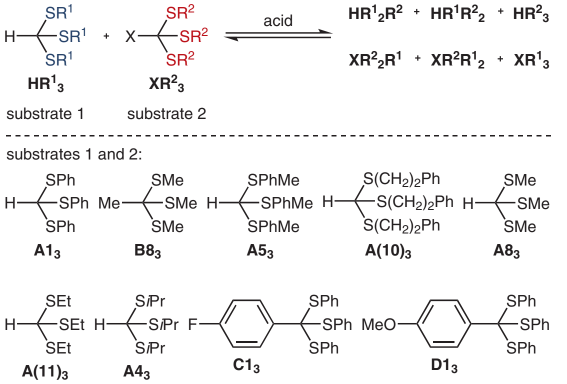


Figure 2 Trithioorthoester metathesis between **A1$_3$** and **B8$_3$** (top) and ^{1}H NMR spectrum measured after one hour (bottom). The two dashed boxes show the corresponding formate and acetoxy hydrogen atoms of trithioorthoesters formed from **A1$_3$** and **B8$_3$**. *Reaction conditions*: **A1$_3$** (37.5 μmol), **B8$_3$** (37.5 μmol), TFA (375 μmol), CDCl$_3$ (V_{total}: 750 μL), r.t., 1 h. Product distributions are given by normalized integral values below the corresponding peaks for both sets. See also Table 2, entry 1 and the full spectra in Figure S59 in the SI.

To explore the generality of this finding, additional metathesis reactions were carried out with other pairs of trithioorthoesters. Combinations of trithioorthoesters containing different aromatic substituents on sulfur (Table 2, entry 2) or aromatic and primary alkyl substituents (entries 3–5) led to statistical distributions, whereas trithioorthoesters containing aromatic and secondary thiol side chains (entry 6) led to a slightly biased composition favoring the starting aromatic trithioorthoester. These experiments can also be regarded as competitive hydrolysis experiments: throughout our investigations, we found that hydrolysis of trithioorthoesters with alkyl residues on sulfur is faster than that for aromatic ones (compare Figure S60 with Figures S61–S64; SI). Next, we investigated the influence of electron-withdrawing and electron-donating substituents on trithioorthoester metathesis by conducting metathesis reactions between tris(ethylthio)methane [**A(11)$_3$**] and trithioorthoesters **C1$_3$** and **D1$_3$**, containing electron-withdrawing and electron-donating groups, respectively (Figures S65 and S66). After one hour, similar equilibrium distributions for the formate species and a comparable degree of hydrolysis were observed in both cases (entries 7 and 8). However, in the case of **D1**$_3$, degradation of the starting material, presumably by ether cleavage[43] occurred, representing a notable limitation of this method. Finally, several attempts were made to carry out crossed metathesis reactions between (*S*,*S*,*S*)-**A1**$_3$ and (*O*,*O*,*O*)-**A9**$_3$; these were unsuccessful due to instantaneous hydrolysis of *O*,*O*,*O*-orthoester, further confirming the previously observed differences in stability (Figure S67).

In summary, we have described a methodological investigation of the exchange reaction between trithioorthoesters and thiols, as well as the direct trithioorthoester metathesis reaction. These reactions have two appealing properties in the context of other reversible covalent reactions. First, the tripodal structure of *S*,*S*,*S*-orthoesters provides an elegant entry to sulfur-rich three-dimensional architectures with possible applications in the removal of heavy-metal ions. Second, the harsh conditions necessary to initiate these exchange reactions might be advantageous for applications in materials science, such as the (solvothermal) synthesis of porous materials.

Table 2 Metathesis between Different Trithioorthoesters



Entry	Substrate 1 HR$^1_3$	Substrate 2 XR$^2_3$	Reaction outcome HR$^1_3$/HR$^1_2$R^2/HR^{1}R$^2_2$/HR$^2_3$/ thioesters (hydrolysis)[a]
1[b]	**A1**$_3$	**B8**$_3$	17:43:33:7:–
2[c]	**A1**$_3$	**A5**$_3$	13:36:36:13:2
3[c]	**A5**$_3$	**A(10)**$_3$	13:35:36:13:3
4[d]	**A1**$_3$	**A8**$_3$	10:36:37:11:6
5[b]	**A1**$_3$	**A(11)**$_3$	12:34:33:10:12
6[c]	**A5**$_3$	**A4**$_3$	18:28:30:12:12
7[b]	**A(11)**$_3$	**C1**$_3$	3:21:42:28:6
8[b]	**A(11)**$_3$	**D1**$_3$	ether cleavage

[a] Product ratios were determined by integration of ^{1}H NMR signals after 1 h of reaction; '–' indicates not detected. For full spectra, see Figures S60–S67 in the SI.

[b] Reaction conditions: **HR**$^1_3$ (37.5 μmol), **XR**$^2_3$ (37.5 μmol), TFA (375 μmol), CDCl$_3$ (V_{total}: 750 μL), r.t.

[c] Reaction conditions: **HR**$^1_3$ (15 μmol), **XR**$^2_3$ (15 μmol,), H$_2$SO$_4$-saturated CDCl$_3$, (V_{total}: 500 μL), r.t.

[d] Reaction conditions: **HR**$^1_3$ (37.5 μmol), **XR**$^2_3$ (37.5 μmol), FeCl$_3$ (3.75 μmol), CD$_3$CN (V_{total}: 750 μL), r.t.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690992.

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(38) Tris[(4-methylbenzene)thio]methane (**A5$_3$**), tris(isopropylthio)methane (**A4$_3$**), and tris[(2-phenylethyl)thio]methane [**A(10)$_3$**] were synthesized by a modified version of the reported procedure; see Ref. 20.

Tris[(4-methylbenzene)thio]methane (A5$_3$); Typical Procedure

$CHCl_3$ (1.48 g, 12.4 mmol, 1.0 equiv), DBU (9.79 g, 64.3 mmol, 5.2 equiv), and 4-methylbenzenethiol (6.14 g, 49.4 mmol, 4.0 equiv) were dissolved in anhyd THF (10 mL), and the mixture was heated to 100 °C for 24 h under N_2 in a pressure tube. The mixture was cooled, H_2O (30 mL) was added, and the resulting mixture was extracted with Et_2O (2 × 50 mL). The combined organic phases were washed with brine (50 mL), dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator. The residue was purified by column chromatography [silica gel, PE–CH_2Cl_2 (100:0 to 80:20)]. Subsequent crystallization (CH_2Cl_2) gave **A5$_3$** as a white solid; yield: 2.10 g (44%, 5.48 mmol); R_f = 0.3 (silica gel, PE–CH_2Cl_2, 80:20, UV_{254}).

^1H NMR (400 MHz, 298 K, $CDCl_3$): δ = 7.43–7.41 (m, 6 H), 7.17–7.15 (m, 6 H). 5.32 (s, 1 H), 2.37 (s, 9 H). ^{13}C NMR (100 MHz, 298 K, $CDCl_3$): δ = 138.5, 133.4, 130.4, 129.6, 65.9, 21.2. Anal. calcd for $C_{22}H_{22}S_3$: C, 69.07; H, 5.80; S, 25.14. Found: C, 69.00; H, 5.93; S, 25.22.

(39) **Synthesis of 1,1,1-Tris(methylthio)ethane (B8$_3$)**

This was synthesized by a modified version of the reported procedure.[21] Trimethyl trithioorthoformate (**A8$_3$**; 5.28 g, 34.2 mmol, 1.0 equiv) was dissolved in anhyd THF (50 mL) and cooled to –78 °C under N_2. A 2.5 M solution of BuLi in hexane (20.5 mL, 51.3 mmol, 1.5 equiv) was added dropwise and the mixture was stirred for 80 min. MeI (12.13 g, 85.5 mmol, 2.5 equiv) was added dropwise, and the mixture was allowed to slowly warm to r.t. overnight. Et_2O (100 mL) was added and the mixture washed with aq $Na_2S_2O_3$ (50 mL). The combined extracted organic phases were washed with brine (50 mL), separated, dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator. Distillation through a short Vigreux column (oil-bath temperature: 120 °C; pressure: 7 mbar; bp 70 °C) gave a colorless oil; yield: 4.55 g (79%, 27.0 mmol); R_f = 0.7 (silica gel, PE–EtOAc, 95:5, UV_{254}).

^1H NMR (400 MHz, 298 K, $CDCl_3$): δ = 2.16 (s, 9 H), 1.87 (s, 3 H). ^{13}C NMR (100 MHz, 298 K, $CDCl_3$): δ = 64.3, 28.3, 13.6. Anal. calcd for $C_5H_{12}S_3$: C, 35.68; H, 7.19; S, 57.14. Found: C, 37.04; H, 7.26; S, 57.81.

(40) 1-[Bis(phenylthio)methyl]-4-fluorobenzene (**CH1$_2$**) and 1-[bis(phenylthio)methyl]-4-methoxybenzene (**DH1$_2$**) were synthesized by a modified version of the reported procedure; see Ref 23a.

1-[Bis(phenylthio)methyl]-4-fluorobenzene (CH1$_2$); Typical Procedure

Iodine (1.29 g, 5.10 mmol, 0.1 equiv) was added to a solution of 4-fluorobenzaldehyde (6.30 g, 50.8 mmol, 1.0 equiv) and benzenethiol (11.7 g, 107 mmol, 2.1 equiv) in $CHCl_3$ (75 mL), and the resulting solution was stirred overnight at r.t. When the reaction was complete, excess I_2 was quenched with 0.1 M aq $Na_2S_2O_3$ (100 mL). The organic phase was separated, washed with H_2O (100 mL), dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator. Purification by flash column chromatography [silica gel, PE–CH_2Cl_2 (95:5 to 80:20)] and subsequent crystallization from petroleum ether gave **CH1$_2$** as a white solid; yield: 12.8 g (77%, 39.2 mmol). R_f = 0.30 (silica gel, PE–CH_2Cl_2, 80:20, UV_{254}).

^{1}H NMR (500 MHz, 298 K, CD_2Cl_2): δ = 7.42–7.36 (m, 6 H), 7.34–7.28 (m, 6 H), 7.03–6.99 (m, 2 H), 5.53 (s, 1 H). ^{13}C NMR (125 MHz, 298 K, CD_2Cl_2): δ = 162.7 (d, $^1J_{CF}$ = 246.5 Hz), 135.9 (d, $^4J_{CF}$ = 3.2 Hz), 134.5, 132.9, 131.0 (d, $^3J_{CF}$ = 8.3 Hz), 129.3, 128.3, 114.6 (d, $^2J_{CF}$ = 21.8 Hz), 59.6. Anal. calcd for $C_{19}H_{15}FS_2$: C, 69.91; H, 4.63; S, 19.64. Found: C, 70.05; H, 4.84; S, 20.05.

(41) 1-Fluoro-4-[tris(phenylthio)methyl]benzene (**C1$_3$**) and 1-methoxy-4-[tris(phenylthio)methyl]benzene (**D1$_3$**) were synthesized by a modified version of the reported procedure; see Ref 22a.

1-Fluoro-4-[tris(phenylthio)methyl]benzene (C1$_3$); Typical Procedure

Dithioacetal **DH1$_2$** (2.49 g, 7.66 mmol, 1.0 equiv) and TMEDA (2.49 g. 21.4 mmol, 2.8 equiv) were dissolved in anhyd THF (15 mL) under N_2. The solution was cooled to –78 °C and a 2.5 M solution of BuLi in hexane (4.29 mL, 10.7 mmol, 1.4 equiv) was added dropwise. The mixture was stirred for 80 min at –78 °C, a solution of diphenyl disulfide (5.02 g, 23.0 mmol, 3.0 equiv) in anhyd THF (10 mL) was added slowly, and the mixture was allowed to warm to r.t overnight. The mixture was then cooled to 0 °C and the reaction was carefully quenched with several drops of H_2O. The resulting mixture was extracted with Et_2O (2 × 70 mL), washed with H_2O (100 mL) and brine (100 mL), and the organic layer was separated, dried (Na_2SO_4), filtered, and concentrated on a rotary evaporator. Purification by flash column chromatography [silica gel, PE–CH_2Cl_2 (100:0 to 80:20)] and subsequent crystallization from PE–CH_2Cl_2 gave **C1$_3$** as a white solid; yield: 2.30 g (69%, 5.30 mmol); R_f = 0.32 (silica gel, PE–CH_2Cl_2, 80:20, UV_{254}).

^{1}H NMR (500 MHz, 298 K, CD_2Cl_2): δ = 7.68–7.60 (m, 2 H), 7.34–7.18 (m, 15 H), 6.90–6.82 (m, 2 H). ^{13}C NMR (125 MHz, 298 K, CD_2Cl_2): δ = 162.6 (d, $^1J_{CF}$ = 248.0 Hz), 135.7 (d, $^4J_{CF}$ = 3.1 Hz), 135.0, 133.1, 131.2 (d, $^3J_{CF}$ = 8.3 Hz), 129.0, 128.7, 114.9 (d, $^2J_{CF}$ = 21.6 Hz), 76.7. Anal. calcd for $C_{25}H_{19}FS_3$: C, 69.09; H, 4.41; S, 22.13. Found: C, 68.96; H, 4.61; S, 22.11.

(42) In the case of *O,O,O*-orthoesters, hydrolysis is presumably the source of the free nucleophile, whereas with *S,S,S*-orthoesters, our observation of a bright-pink color might indicate that a thiol/thionium pair is formed, even without participation of water.

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