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Dialkyl Dicyanofumarates as New Oxidizing Reagents for the Conversion of Thiols into Disulfides and Selenols into Diselenides

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Dedicated 'In Memoriam' to Professor Jerzy Suwiński (1939-2017) (TU Gliwice, Poland)

Abstract

Both aliphatic and aromatic thiols react smoothly with dialkyl dicyanofumarates in CH_2Cl_2 at r.t. to give the corresponding disulfides in excellent yields. Aliphatic 1,2-, 1,3- and 1,4-dithiols afford cyclic disulfides. Analogous reaction courses were observed starting with selenols and the required diselenides were also formed in nearly quantitative yields. In all reactions, dialkyl dicyanosuccinates, formed as a 1:1-mixture of diastereoisomers, were the only second product. Cysteamine (2-mercaptoethylamine) behaved differently and the Michael addition of the primary amino group led to complete consumption of the dicyanofumarate, and the formation of the disulfide containing the enamine motive occurred without formation of dicyanosuccinate.

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KEYWORDS

Disulfides, Diselenides, Dialkyl dicyanofumarates, SET mechanism, Michael addition

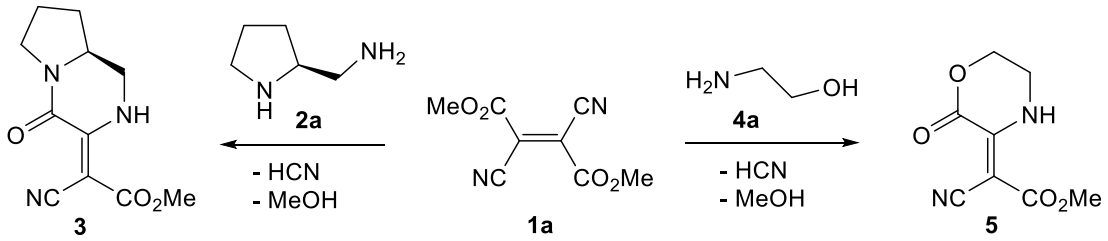
Introduction

Organic disulfides constitute a most relevant class of organic sulfur compounds with great importance not only in organic synthesis, but also in biological, polymer and materials chemistry.[1] Moreover, the formation and dissociation of the S–S bond is of central importance in life sciences.[2] Disulfides play also an important role in medicinal chemistry, especially in peptide-based therapeutics.[3] Different methods are known for their preparation, but the most important is the oxidation of thiols by treatment with diverse oxidizing agents, and the use of iodine offers the most popular approach.[1b,4a] Other methods have to be applied to obtain non-symmetrical disulfides and they have been summarized in a recent review.[4b] The formation of symmetrical disulfides can also be achieved efficiently by using electron deficient reagents such as azodicarboxylates[5] or 4-phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione.[6] In these systems, the addition of the thiol onto the activated N=N unit is proposed as the initial step of the reaction. Subsequent nucleophilic attack of the second molecule of thiol on the activated S-atom leads to the formation of the S–S bond.

Electron deficient ethenes were also used in reactions with thiols, and in some instances the formation of disulfides was observed side by side with other products. For example, the reaction of tetracyanoethene (TCNE) with a 3-mercapto-1,2,4-triazine derivative gave, among other products, the corresponding disulfide in 46% yield.[7] In another example, the disulfide derived from diethyl dithiophosphonate was formed after treatment with TCNE. In this case, TCNE was reduced to 1,1,2,2-tetracyanoethane without fragmentation.[8]

In a series of recent publications, reactions of electron deficient dialkyl dicyanofumarates with primary amines[9] as well as with diverse dinucleophiles such as 2-aminoalcohols[10] and 1,2-diamines[11] were described. In all studied reactions, the initial step was the nucleophilic addition of the amino group, followed by spontaneous elimination of HCN. The enamines formed thereby underwent secondary conversions leading to cyclic products (heterocyclizations). For example, the reaction of dimethyl dicyanofumarate (DCFM, **1a**) with (*S*)-prolinamine (**2a**) afforded bicyclic

piperazine derivatives **3**[11] (Scheme 1). A similar reaction with 2-aminoethanol (**4a**) led to the morpholinone derivative **5**.[10]

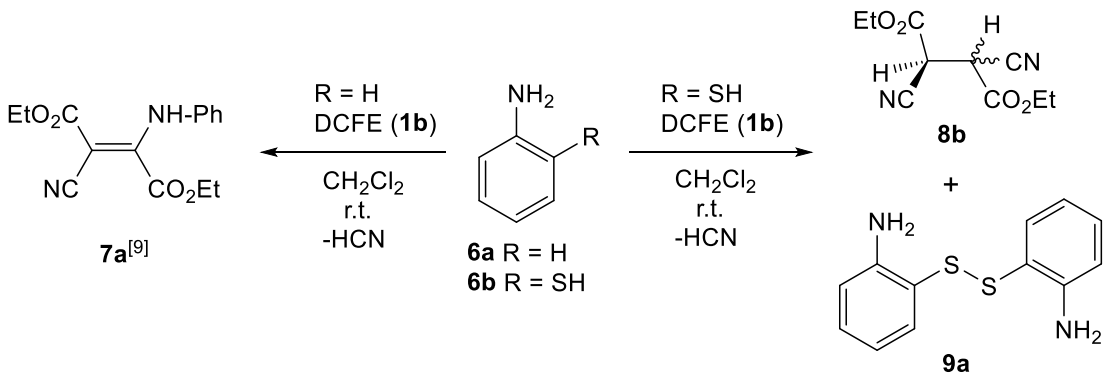


Scheme 1. Reactions of DCFM (**1a**) with dinucleophiles **2a** and **4a**.

In the present study, reactions of 2-aminothiols as another class of dinucleophiles should be examined in reactions with dialkyl dicyanofumarates **1**. Thiols are known as reactive nucleophiles[12] and Michael donors.[13] For that reason the comparison of the reactivity of 2-aminothiols with 2-aminoalcohols and 1,2-diamines toward **1** would supplement the previous studies. It is also worth of mentioning that aminothiols are important compounds from the biological point of view, and the cytoprotective functions are of special interest.[14a,b] In addition, mercaptoalcohols and mercaptoselenols are important building blocks for the preparation of sulfur and selenium containing organic compounds with diverse functional groups.[14c]

Results and Discussion

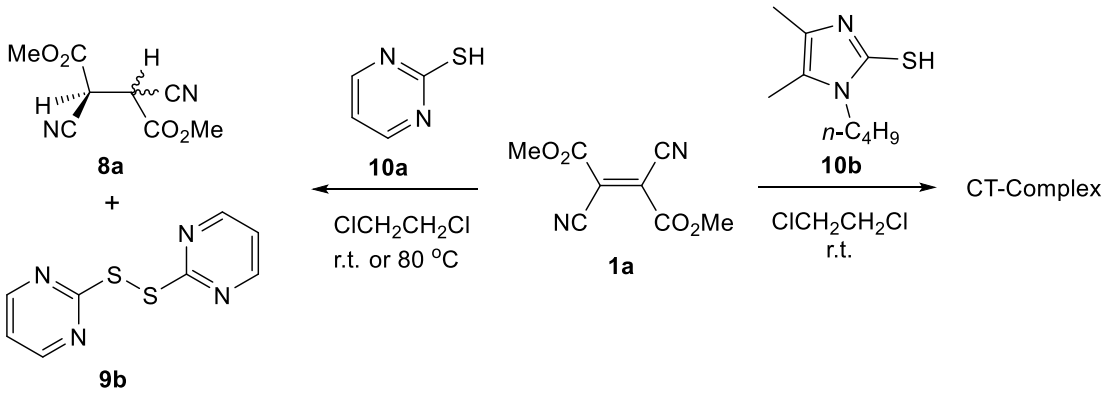
Aniline (**6a**) reacts smoothly with diethyl dicyanofumarate (DCFE, **1b**), and dimethyl (*Z*)-2-cyano-3-phenylaminoethene-1,2-dicarboxylate (**7a**) was obtained as sole product.[9] In the analogous experiment with 2-mercaptoaniline (**6b**), the ^{1}H NMR spectrum of the crude reaction mixture showed, along with the signals of aromatic H-atoms and Et groups, two characteristic singlets at 4.24 and 4.18 ppm. After chromatographic separation, two products were isolated, and the more polar one showed these two singlets as well as two triplets and two quartets for two ethoxy moieties. By comparison with original samples,[15] the isolated material was indentified as 1:1-mixture of *dl*- and *meso*-diethyl 2,3-dicyanosuccinate (**8b**, Scheme 2).



Scheme 2. Different pathways in reactions of DCFE (**1b**) with aniline (**6a**) and 2-mercaptoaniline (**6b**).

The second product, isolated as yellow crystals (m.p. 88–90 °C) from the less polar fraction, was identified as 2,2'-diaminodiphenyldisulfide (**9a**).[16a] This unexpected result prompted us to test 2-mercaptopyrimidine (**10a**) and 1-butyl-2-mercapto-4,5-dimethylimidazole (**10b**)[16b] in the reaction with DCFM (**1a**). Whereas in the case of **10a** a slow formation of **8a** and disulfide **9b**[16c] (Scheme 3) was observed at r.t., no disulfide was formed in the case of **10b**, neither at r.t. nor in boiling $ClCH_2CH_2Cl$ (80 °C). In the latter case, a violet charge-transfer complex was formed, which decomposed after evaporation of the solvent.

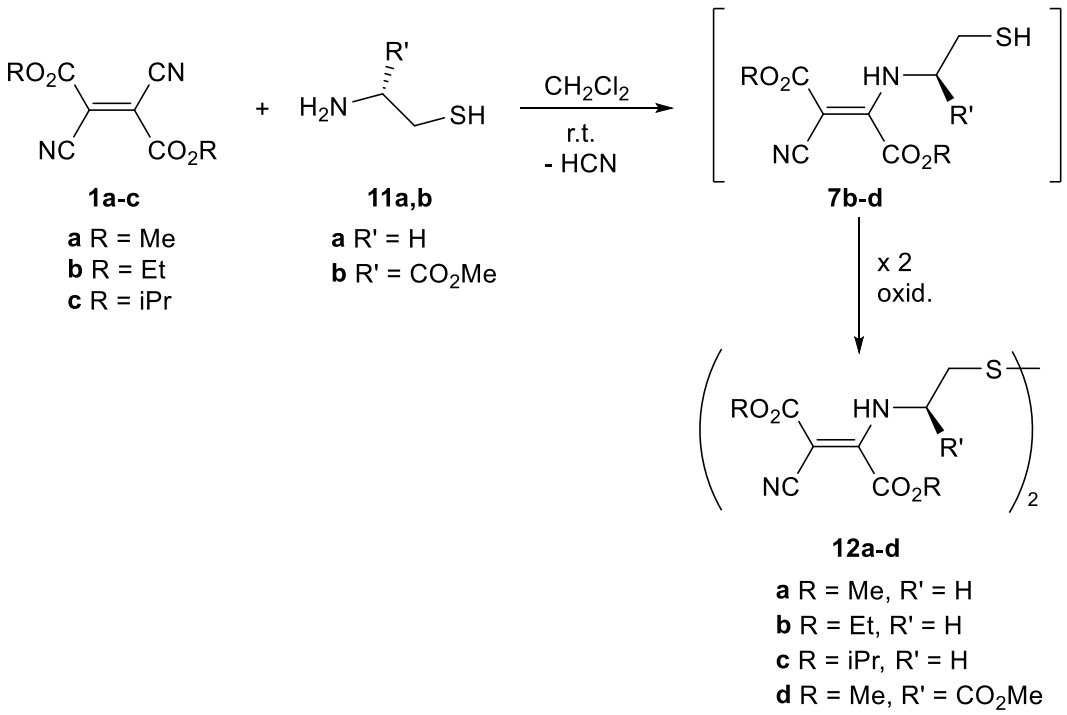
It is worth mentioning that 4-mercaptoaniline and other aromatic thiols are reported to react at r.t. with DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) in CH_2Cl_2 solutions forming charge transfer complexes with absorption bands located between 440 and 800 nm; in these systems no redox reactions leading to the formation of the corresponding diaryl disulfides were observed.[16d]



Scheme 3. Reactions of DCFM (**1a**) with 2-mercaptopyrimidine (**10a**) and 2-mercaptoimidazole derivative **10b**.

In our study, preliminary experiments were also performed with sterically crowded thiols, but the attempted syntheses of disulfides starting either with tritylthiol or *tert*-butylthiol and **1a** (molar ratio 2:1) were unsuccessful, and after 24 h at r.t. only non-converted substrates were detected in the ^{1}H NMR spectra. These results point out the influence of the steric hindrance on the studied redox processes.

In the next step of the study, selected binucleophiles such as β-amino thiols, β-mercapto alcohols, and β-hydroxy selenols should be tested in reactions with dialkyl dicyanofumarates. Firstly, the reactivity of cysteamine (**11a**) should be compared with that of the aromatic analogue **6b**. Equimolar amounts of **11a** and DCFE (**1b**) were reacted in CH_2Cl_2 at r.t. After 10 min, the reaction was complete, and the initially formed blue color of the intermediate charge transfer complex practically vanished. The ^{1}H NMR spectrum of the crude mixture showed, unexpectedly, that in contrast to the reaction with **6a** no diethyl succinate **8b** was formed. The chromatographic separation gave one product only, which in the ^{1}H NMR spectrum showed signals for structural fragments of both **11a** and **1b**. The only new signal was a triplet at 9.64 ppm (J = 6.0 Hz), which could be attributed to a CH_2-N**H**-C=C unit. Furthermore, the ^{13}C NMR spectrum revealed three signals at low field for CN (116.0 ppm) and two C=O groups (160.9 and 161.0 ppm). In addition, signals located at 167.9 and 72.2 ppm suggest the presence of an enamine of type **7**. On the other hand, no indication of a SH group could be found neither in the ^{1}H NMR nor in the IR spectra. Finally, the HRMS showed a peak at m/z = 565.1393, which corresponds with the molecular formula $C_{22}H_{30}N_4NaO_8S_2$ of disulfide **12b** ($[M+Na]^+$). An analogous reaction course was observed in the reactions of **11a** with DCFM (**1a**) and diisopropyl dicyanofumarate (DCFP, (**1c**). In both cases, the corresponding disulfides **12a** and **12c** were obtained as the only products, and no formation of dicyanosuccinates was observed.



Scheme 4. Reactions of cysteamine (**11a**) and L-cysteine methyl ester (**11b**) with dialkyl dicyanofumarates **1** leading to disulfides **12** with enamine units.

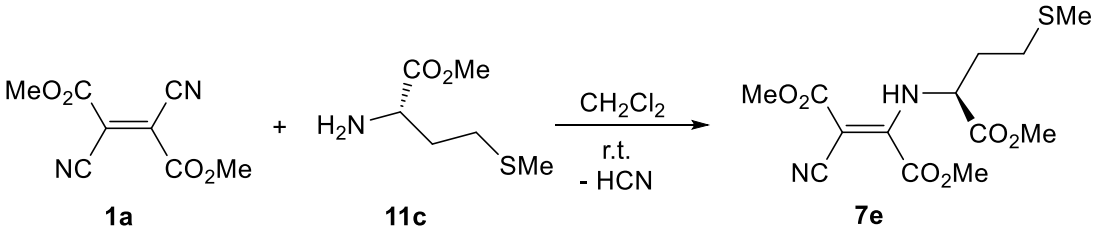
The reaction of freshly prepared L-cysteine methyl ester (**11b**), liberated from its hydrochloride, with DCFM (**1a**) was performed using equimolar amounts of both reagents. Also in this case, the reaction solution showed an intense blue coloration, which disappeared after *ca.* 10 min. In analogy to the experiment with cysteamine (**11a**), the ^{1}H NMR analysis of the crude mixture did not reveal the presence of dimethyl dicyanosuccinates. Chromatographic separation gave a product as an oily fraction, formed side by side with minor admixtures of some non-identified components. Based on spectroscopic data and comparison with the product **12a** obtained in the reaction of **1a** with **11a**, the isolated product was identified as the analogous disulfide **12d** containing the characteristic enamine moiety.

The absence of dicyanosuccinates in the reactions with cysteamine (**11a**) and L-cysteine methyl ester (**11b**) points out that these reactions follow a different course. The observed initial blue coloration of the reaction solution suggests that the first step of the reaction with a *β*-aminothiol unit is the formation of a reactive charge-transfer complex, which undergoes further transformations, *e.g.*, the Michael addition of the primary amino group followed by elimination of HCN to give enamine **7**. Therefore,

dicyanofumarate **1** is completely consumed, and the subsequent oxidation leading to the disulfide **12** results from the presence of air oxygen or it is formed via an unknown reaction mechanism. In contrast, the formation of disulfides **9** is governed by a SET mechanism, and the initiating step is the electron transfer from the SH group to the electron-deficient C=C bond of **1**. Dicyanofumarates are well known as powerful one-electron acceptors,[17a,b] and therefore they may act as oxidizing agents for thiols via a SET mechanism.

The presented results obtained in reactions of **11a** and **11b** with dimethyl dicyanofumarate (**1a**) differ drastically from those reported for **11a** and typical Michael acceptors, like *α*-methylidene lactones[17c,d] and *α,β*-unsaturated esters.[17e] In all these cases, the –SH group reacted as Michael donor and the initial formation of the corresponding sulfides was observed with no exception.

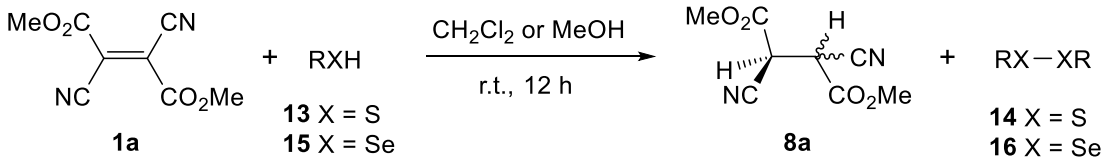
In our study, in an additional experiment, L-methionine methyl ester (**11c**) was treated with dimethyl dicyanofumarate (**1a**) at room temperature, and after short reaction time (5 min) the expected, stable enamine **7e** was isolated in 52% yield (Scheme 5).



Scheme 5. Reaction of L-methionine methyl ester (**11c**) with dimethyl dicyanofumarate (**1a**) leading to enamine **7e**.

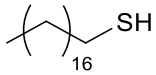
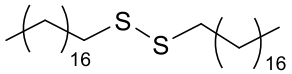
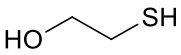
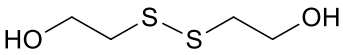
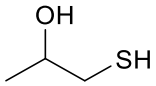
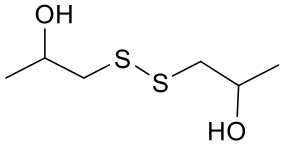
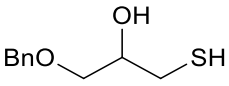
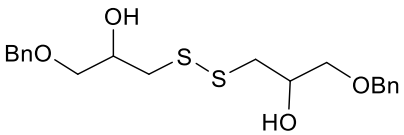
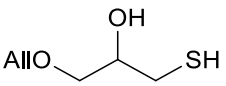
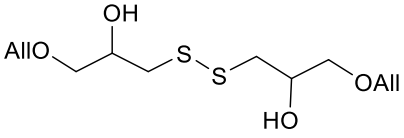
Based on the results obtained with 2-mercaptoaniline (**6a**) and 2-mercaptopyrimidine (**10a**), the study was extended by the involvement of thiophenol (**13a**), octadecane-1-thiol (**13b**), propane-1,3-dithiol (**13k**) and ethane-1,2-dithiol (**13n**, Table 1). All these thiols were efficiently oxidized with equimolar amounts of DCFM (**1a**). The products obtained from **13a** and **13b** were identified as disulfides **14a** and **14b**, respectively (Scheme 6, Table 1). In the reactions with dithiols **13k** and **13n**, cyclic disulfides **14k** and**14n**, respectively, were obtained in high yields. Whereas 1,2-dithiolane **14k** is formed via an intramolecuar oxidative ring closure of

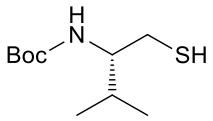
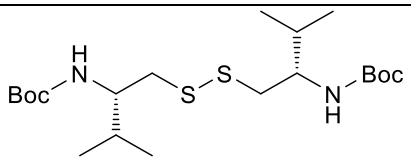
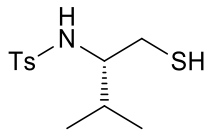
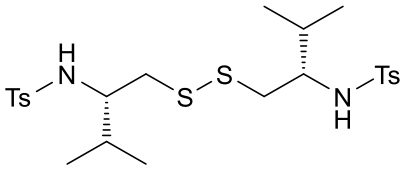
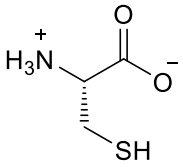
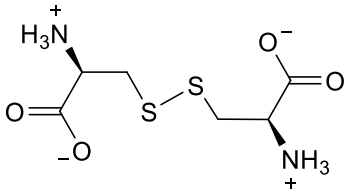
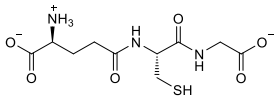
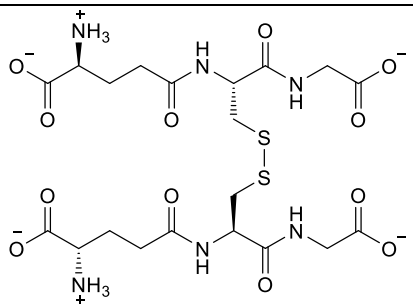
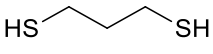
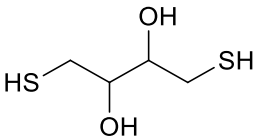
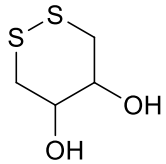
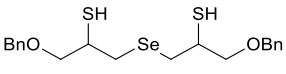
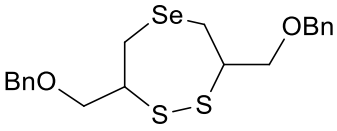
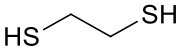
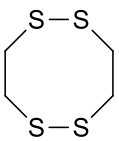
13k, 1,2,5,6-tetrathiocane (**14n**) is the product of an oxidative dimerization. In all these reactions, the expected mixture of diastereoisomers of dimethyl dicyanosuccinate (**8a**) was obtained in *ca.* equimolar amounts.



Scheme 6. Reactions of thiols **13** and selenols **15** with **1a** to give disulfides **14** and diselenides **16** (see Table 1 and 2).

Table 1. Reactions of methyl dicyanofumarate (DCFM, **1a**) with thiols **13**.

Entry	Thiol	**13**	Disulfide	**14**	Yield (%)[a)]
1	PhSH	**a**	PhSSPh	**a**[18]	98
2		**b**		**b**[18]	96
3		**c**		**c**[18]	96
4		**d**		**d**[19]	97
5		**e**		**e**	95
6		**f**		**f**	94

7		**g**		**g**[20]	92
8		**h**		**h**[21]	94
9		**i**		**i**[22]	98
10		**j**		**j**[22]	98
11		**k**		**k**[23]	89
12		**l**		**l**[24]	98
13		**m**		**m**[25]	96
14		**n**		**n**[26]	82

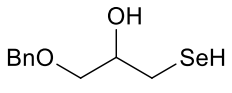
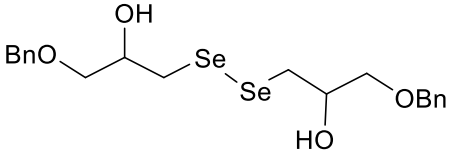
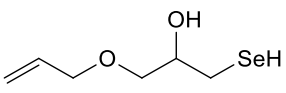
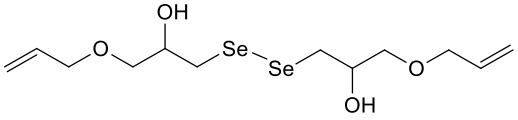
[a)] Yield of isolated product.

Another group of thiols examined in reactions with DCFM (**1a**) involved mercaptoalcohols **13c**–**f** and **13l**. Whereas substrates **13c**–**f** delivered linear disulfides **14c**–**f**, the latter afforded, in analogy to **13k**, 4,5-dihydroxy-1,2-dithiane **14l** *via* intramolecular reaction. Another cyclic disulfide, **14m**, was formed in excellent yield from 3,3'-selenobis[1-(benzyloxy)propane]-2-thiol (**13m**, Table 1).

In two cases of enantiopure *N*-protected aminothiols, **13g** and **13h**, smooth formation of the expected disulfides **14g** and **14h**, respectively, was observed. Finally, cystein (**13i**) and the tripeptide glutathione (**13j**) were used as substrates for the transformation into disulfides. In full agreement with the other thiols **13**, the expected products **14i** and **14j** were obtained in nearly quantitative yields (Table 1). In these two cases, the primary amino groups exist as ammonium ions and therefore are completely inactive toward the activated C=C bond of **1a**.

In order to establish the scope of the application of the presented oxidative disulfide formation, selected selenols were evaluated whether the diselenide bond can be formed *via* a SET mechanism. Thus, the treatment of phenylselenol (**15a**) with DCFM (**1a**, Scheme 6) was as efficient as in the case of **13a**, and the known diphenyldiselenide **16a** was isolated in 98% yield (Table 2). Similar results were obtained in three other experiments with aliphatic selenols **15b**–**d**.

Table 2. Reactions of methyl dicyanofumarate (**1a**) with selenols **15**.

Entry	Selenol	**15**	Diselenide	**16**	Yield (%)[a)]
1	PhSeH	**a**	PhSeSePh	**a**[27]	98
2		**b**		**b**[28]	95
3		**c**		**c**[28]	96

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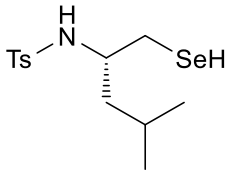
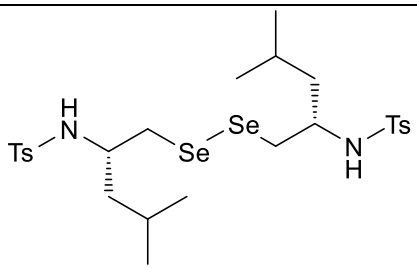
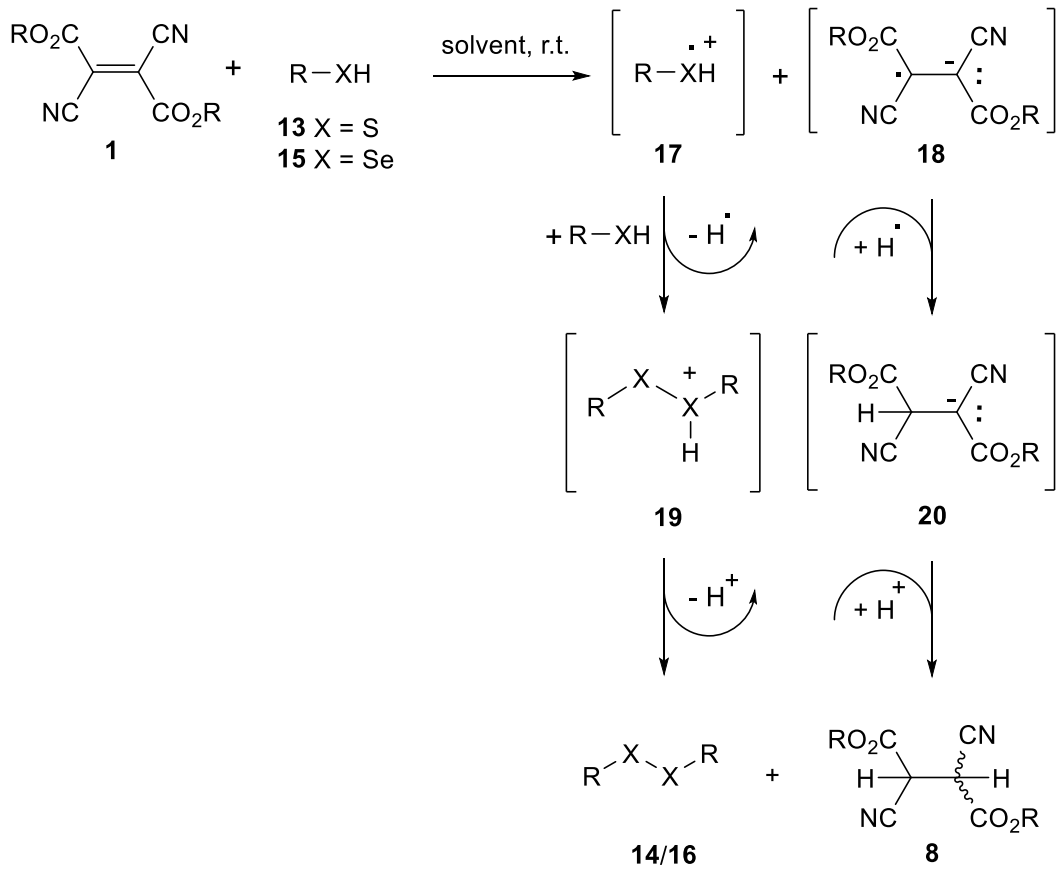
4		**d**		**d**[28]	97

[a)] Yield of isolated product.

Dialkyl dicyanofumarates and dicyanomaleates are known as prone one-electron acceptors,[17a,b] and for that reason the presented conversions of thiols or selenols into disulfides and diselenides, respectively, can be explained by the assumption that the initiating step of the studied reactions is a single electron transfer (SET) leading to pairs of elusive radical cations **17** and radical anions **18** (Scheme 7). Further interaction of the radical cation **17** with the parent thiol **13** (or selenol **15**) and transfer of an H-atom leads to the ions **19** and **20** and via proton transfer to the respective disulfide **14** (or diselenide **16**) and succinates **8**. No question, the reactions of thiols/selenols with strongly electron deficient alkenes open a new field for discussions about the reaction mechanisms involving chalcogens.

On the other hand, in a very recent publication by other authors, the mechanism of the reaction of ethane-1,2-dithiol with the electron deficient TCNE was explained *via* a stepwise ionic addition-cyclization-elimination route leading to a 1,4-dithiane derivative.[29a]



Scheme 7. Proposed SET mechanism for the formation of disulfides **14** and diselenides **16** from thiols **13** and selenols **14**, respectively, in the presence of dialkyl dicyanofumarates **1**.

However, the presence of the 'free' β-NH_2 group in cysteamine (**11a**) or L-cysteine methyl ester (**11b**) strongly modifies the behavior of the system. Very likely, a fast irreversible Michael addition of the NH_2 group onto the C=C bond of **1**, followed by the fast HCN elimination occurs, consuming the fumarate **1** completely. The subsequent oxidation step occurs *via* H_2 elimination or interaction with the air oxygen without the involvement of dicyanofumarates **1** as oxidizing agents.

Conclusions

The presented studies showed that easily available electron-deficient dialkyl dicyanofumarates can be applied for the efficient oxidation of thiols and selenols leading to disulfides and diselenides, respectively. The reactions occur under mild

conditions and, in general, the yields of the products are excellent. The only product formed side-by-side with disulfides or diselenides is the corresponding dialkyl dicyanosuccinate, obtained as a 1:1-mixture of diastereoisomers, which can easily be separated from the target products by standard chromatographic methods. For all these reasons, the described protocol can be recommended as a practically useful approach to disulfides and diselenides. However, sterically bulky thiols such as tritylthiol and *tert*-butylthiol do not undergo the oxidation reaction leading to the desired disulfides. This is the first observation of an efficient application of fumaric acid derivatives for the oxidative formation of disulfide and diselenide bonds. On the other hand, it should be emphasized that fumaric acid and succinic acid form an important red-ox system operating in biological systems.[30]

It seems likely that the SET mechanism formulated for the formation of dialkyl dicyanosuccinates in the course of the oxidative conversion of thiols into disulfides operates also in the reaction of dialkyl dicyanofumarates with diethyl phosphinate described in our recent publication.[15]

However, the reactions with cysteamine and L-cysteine methyl ester deserve a special comment as in these cases, in contrast to mercaptoalcohols and hydroxyselenols, a competitive Michael addition of the primary amino group is observed. The oxidation of the thiol function occurs without reduction of dicyanofumarate. This amazing effect of the *β*-amino thiol motif cannot be explained by the same interpretation formulated for all other cases studied and requires further mechanistic investigation.

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Experimental Section

General

All reactions were carried out in oven-dried glassware under inert atmosphere (N_2). CH_2Cl_2 and MeOH were dried using a solvent purification system (Pure-Solv™). *β*-

Hydroxy- and β-aminothiols were synthesized according to ref.[29b] Benzeneselenol is commercially available. β-Substituted selenols were prepared through the procedure developed in one of our groups.[31] L-Cysteine methyl ester hydrochloride, L-methionine methyl ester hydrochloride, and cysteamine were purchased from Aldrich and they were used without further purification. Flash column chromatography purifications were performed with silica gel 60 (230-400 mesh). Thin layer chromatography was carried out on TLC plates silica gel 60 F_{254}. NMR spectra were recorded in $CDCl_3$ on a Varian Gemini 200, Varian Mercury 400 or Bruker Avance III 600 spectrometer operating at 200, 400 and 600 MHz (for ^1H), and 50, 100 and 150 MHz (for ^{13}C). NMR signals were referenced to residual non-deuterated solvent signals (7.26 ppm for ^1H, 77.0 ppm for ^{13}C). The abbreviations used are: s (singlet), d (doublet), dd (doublet of doublet), m (multiplet), b (broad). Mass spectra were determined by ESI using a LCQ Fleet™ Thermo Scientific spectrometer, HRMS (ESI) on a Bruker maxis spectrometer. Elemental analysis was carried out with a Perkin–Elmer 2400 series II elemental analyser.

Reaction of 2-mercaptoaniline (6b) and pyrimidine-2-thione (10a) with diethyl dicyanofumarate (1b) – general procedure

Diethyl dicyanofumarate (**1b**, 0.222g, 1 mmol) was added to a solution of 2-mercaptoaniline (**6b**, 0.250 g, 2 mmol) or pyrimidine-2-thione (**10a**, 0.224 g, 2 mmol) in CH_2Cl_2 (4 mL). The mixture was stirred at r.t. for 20 min (for **6b**) or 6 d (for **10a**). Next, the solvent was evaporated and the crude products were purified by PLC using in both experiments a 1:1 mixture of petroleum ether and ethyl acetate. Analytically pure samples were obtained after crystallization from methanol.

*2,2'-Diaminodiphenyldisulfide (**9a**)*: Yellow crystals (220 mg, 99%); m.p. 88–90 °C (ref.[16a], m.p. 94−96 °C). ^1H NMR (600 MHz, $CDCl_3$): δ = 4.33 (bs, 4H; 2 NH_2), 6.57–6.62 (m, 2H; 2 CH), 6.71 (dd, J = 7.8, 1.2 Hz, 2H; 2 CH), 7.14–7.19 (m, 4H; 4 CH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 115.2, 118.2, 131.5, 136.8 (8 CH), 118.8, 148.6 (2 C–N, 2 C–S) ppm; IR (KBr): 458 (m), 472 (m), 673 (m), 699 (m), 746 (vs), 754 (vs), 1157 (m), 11247 (m), 1302 (m), 1311 (m), 1446 (s), 1473 (vs), 1584 (m), 1614 (s), 1625 (s), 3301 (s), 3380 (s) cm^{-1}.

*2,2'-Dipyrimidyldisulfide (**9b**)*: Colorless crystals (after crystallization: 140 mg, 63%); m.p. 139−141 °C (ref.[16b], m.p. 134−137 °C). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.06 (pt, J = 4.8 Hz, $2CH_{arom}$), 8.56 (d, J = 4.8 Hz, $4CH_{arom}$).

Reaction of 1-butyl-2-mercapto-4,5-dimethylimidazole (10b) with dimethyl dicyanofumarate (1a)

To a magnetically stirred solution of **10b** (0.092 g, 0.5 mmol) in 2 mL of CH_2Cl_2, crystalline **1a** (0.097 g, 0.5 mmol) was added and the blue colored reaction solution was stirred overnight at r.t. Then, the blue colored solution was evaporated and a colorless solid residue was obtained after removal of the solvent. The obtained solid was triturated with a portion of Et_2O and filtered off. The crystalline material (m.p. 115–117 °C) obtained thereafter was analysed by running the ^{1}H NMR spectrum, which evidenced its identity with the starting **10b** (ref.[16b], m.p. 134 °C).

Reactions of cysteamine (11a) with dialkyl dicyanofumarates 1a–c – general procedure

To a solution of cysteamine (0.077g, 1 mmol) in CH_2Cl_2 (2 mL), the corresponding dialkyl dicyanofumarate **1** (1 mmol) was added. The mixture was stirred at r.t. for 20 min. After this time, the solvent was evaporated and the crude product was purified by chromatography (silica gel, petroleum ether/ethyl acetate 7:3).

*N,N'-(Dithiodiethylene)bis((Z)-2-amino-3-cyano-2-butenedioic acid dimethyl ester) (**12a**)*: Viscous colorless oil (77 mg, 32%); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.85 (t, J = 6.6 Hz, 4H; 2 CH_2), 3.58–3.63 (m, 4H; 2 CH_2), 3.79 (s, 6H; 2 CH_3O), 3.99 (s, 6H; 2 CH_3O), 9.65 (t, J = 5.4 Hz, 2H; 2 NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 37.3, 44.7 (4 CH_2), 52.2, 53.9 (4 CH_3O), 72.0, 168.1 (2 C=C), 116.1 (2 C–N), 161.0, 161.2 (4 C=O) ppm; IR (KBr): 783 (m), 881 (w), 1062 (m), 1154 (m), 1271 (vs), 1434 (s), 1594 (vs), 1682 (s, C=O), 1746 (s, C=O), 2211 (s, CN), 2961 (m), 3243 (m) cm^{-1}; (+)-HRMS (ESI) (*m/z*): calcd. for $C_{18}H_{22}N_4NaS_2O_8$ 509.07713; found 509.07682.

*N,N'-(Dithiodiethylene)bis((Z)-2-amino-3-cyano-2-butenedioic acid diethyl ester) (**12b**)*: Viscous colorless oil (100 mg, 45%); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.31 (t,

J = 7.2 Hz, 6H; 2 CH_3), 1.42 (t, *J* = 7.2 Hz, 6H; 2 CH_3), 2.85 (t, *J* = 6.6 Hz, 4H; 2 CH_2), 3.61 (q, *J* = 6.6 Hz, 4H; 2 CH_2), 4.24 (q, *J* = 7.2 Hz, 4H; 2 CH_2O), 4.45 (q, *J* = 7.2 Hz, 4H; 2 CH_2O), 9.66 (t, *J* = 6.0 Hz, 2H; 2 NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.7, 14.2 (4 CH_3), 37.4, 44.6 (4 CH_2), 61.3, 63.9 (4 CH_2O), 72.2, 167.9 (2 C=C), 116.0 (2 C–N), 160.9, 161.1 (4 C=O) ppm; IR (KBr): 783 (m), 857 (w), 1058 (m), 1174 (m), 1238 (s), 1270 (vs), 1369 (m), 1457 (m), 1592 (vs), 1675 (s, C=O), 1744 (s, C=O), 2213 (s, CN), 2983 (m), 3237 (m), 3442 (m) cm^{-1}. (+)-HRMS (ESI) (*m/z*): calcd. for $C_{22}H_{30}N_4NaS_2O_8$ 565.13973; found 565.13926.

*N,N'-(Dithiodiethylene)bis((Z)-2-amino-3-cyano-2-butenedioic acid diisopropyl ester) (**12c**)*: Viscous colorless oil (100 mg, 33%); ^1H NMR (600 MHz, $CDCl_3$): δ = 1.29 (d, *J* = 6.6 Hz, 12H; 4 CH_3), 1.42 (d, *J* = 6.6 Hz, 12H; 4 CH_3), 2.86 (t, *J* = 6.6 Hz, 4H; 2 CH_2), 3.60 (q, *J* = 6.6 Hz, 4H; 2 CH_2), 5.04–5.10 (m, 2H; 2 CHO), 5.27–5.32 (m, 2H; 2 CHO), 9.68 (t, *J* = 6.0 Hz, 2H; 2 NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.5, 21.8 (8 CH_3), 37.4, 44.6 (4 CH_2), 69.1, 72.7 (4 CHO), 72.3, 167.6 (2 C=C), 116.1 (2 C–N), 160.5, 161.2 (4 C=O) ppm; IR (KBr): 783 (m), 1100 (s), 1274 (vs), 1591 (vs, C=C−N), 1670 (vs, C=O), 1739 (vs, C=O), 2214 (s, C≡N), 2984 (s), 3234 (m), 3332 (m), 3443 (m) cm^{-1}. (–)-HRMS (ESI) (*m/z*): calcd. for $C_{26}H_{37}N_4S_2O_8$ 597.20583; found 597.20646.

Reaction of L-cysteine methyl ester (11b) with dimethyl dicyanofumarate (1a)

A magnetically stirred solution of commercial L-cysteine methyl ester hydrochloride (0.189 g, 1.1 mmol) in MeOH (5 mL) was neutralized with a portion of potassium carbonate (0.455 g, 3.3 mmol). After 15 min the solid material was filtered off and the methanolic solution of free **11b** was evaporated to dryness. The oily residue was dissolved in 2 mL of CH_2Cl_2. Then, crystalline **1a** (0.194 g, 1.0 mmol) was added in small portions. The solution was stirred magnetically at r.t. for 15 min and subsequently a portion of CH_2Cl_2 was added. The precipitate was filtered off and the clear filtrate was evaporated yielding 198 mg of a viscous material, which was analyzed by ^1H NMR spectroscopy, showing the absence of isomeric dimethyl dicyanosuccinates. Subsequent chromatographic separation on preparative plates (SiO_2, 7:3 mixture of petroleum ether and ethyl acetate) led to an oily fraction (100 mg) with R_f = 0.5 as the only product. The isolated product did not solidify while storing in a refrigerator over several days.

*N,N'-(Dithiodi[(R)-(1-methoxycarbonyl)ethylene])bis((Z)-2-amino-3-cyano-2-butenedioic acid dimethyl ester) (**12d**)*: Viscous colorless oil (100 mg, 30 %); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.12 (m, 4H; 2 CH_2), 3.79, 3.80 (2s, 12H; 4 CH_3O), 3.96 (s, 6H; 2 CH_3O), 4.49 (m, 2H; 2 CH), 10.03 (d, ^{3}J = 8.4 Hz, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 33.4 (2 CH_2), 36.5 (2 CH), 52.4, 53.3, 53.9 (6 CH_3O), 57.3, 169.1 (2 C=C), 115.7 (2 C≡N), 159.0, 161.1, 167.9 (6 C=O) ppm; IR (KBr): 723 (m), 777 (m), 1008 (m), 1090 (m), 1280 (broad, vs), 1436 (s), 1587 (vs, C=N), 1679 (s, C=O), 1746 (vs, C=O), 2217 (s, CN), 2958 (m), 3240 (m, NH) cm^{-1}; Elemental analysis: calcd for $C_{22}H_{26}N_4O_{12}S_2$ (602.59): C 43.85%, H 4.35%, N 9.30, S 10.64; found: C 43.86%, H 4.56%, N 9.07, S 10.52.

Reaction of L-methionine methyl ester (11c) with dimethyl dicyanofumarate (1a)

A magnetically stirred solution of commercial L-methionine methyl ester hydrochloride (0.204 g, 1.1 mmol) in MeOH (5 mL) was neutralized with a portion of potassium carbonate (0.455 g, 3.3 mmol). After 15 min, the solid material was filtered off and the methanolic solution of free **11c** was evaporated to dryness. The oily residue was dissolved in 2 mL of CH_2Cl_2, and crystalline **1a** (0.194 g, 1.0 mmol) was added in small portions. The solution was stirred magnetically at r.t. for 15 min and subsequently the solvent was evaporated in vacuum. The crude product was analyzed by ^{1}H NMR spectroscopy, showing the absence of isomeric dimethyl dicyanosuccinates **8a**. Chromatographic separation on preparative plates (SiO_2, 7:3 mixture of petroleum ether and ethyl acetate) led to an oily fraction (100 mg) with R_f = 0.4 as the only product. The isolated material did not solidify while storing in a refrigerator over several days.

*Dimethyl (Z)-N-((1'-methoxycarbonyl-3'-methylsulfanyl)propan-1'-yl]-2-amino-3-cyano-2-butenedioate (**7e**)*: Viscous colorless oil (100 mg, 32%); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.05−2.12 (m, 1H, CH), 2.10 (s, 3H, CH_3S), 2.15−2.22 (m, 1H, CH), 2.49−2.54, 2.55−2.61 (2m, 2H, CH_2), 3.80, 3.83, 3.98 (3s, 9H, 3 CH_3O), 4.37−4.43 (m,1H, CH), 9.84 (d, J = 8.2 Hz, NH) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.1 (SCH_3), 29.4, 32.3 (2 CH_2), 52.2, 52.9, 53.8 36.5 (3 CH_3O), 56.8 (CH), 73.3, 160.9 (C=C), 115.7 (C≡N), 159.8, 167.9, 170.1 (3 C=O) ppm; IR (KBr): 732 (m), 786 (m), 913 (w), 1024 (m), 1100 (m), 1239 (broad, vs), 1439 (s), 1594 (vs, C=C-N), 1679 (s, C=O), 1746 (vs, C=O), 2214 (s, C≡N), 2920 (w), 2958 (m), 3144 (m, NH), 3229 cm^{-}

^{1}; Elemental analysis: calcd for $C_{13}H_{18}N_2O_6S$ (330.36): C 47.26%, H 5.49%, N 8.48, S 9.71; found: C 47.36%, H 5.51%, N 8.45%, S 9.60% $[\alpha]_D^{25}$ = –31.1 (*c* 0.25, $CHCl_3$).

Reactions of dimethyl dicyanofumarate (1a) with chalcogenols – general procedure

To a solution of a thiol or selenol (0.4 mmol (2 equiv.) or 0.2 mmol (1 equiv.) in the case of dithiols and *β*-mercaptoselenols) in 1 mL of CH_2Cl_2 or MeOH (for Cys (**13i**), GSH (**13j**) and **13l**), **1a** (39 mg, 0.2 mmol, 1 equiv.) was added at 0 °C. The mixture was stirred for 12 h at r.t., the solvent was evaporated under vacuum, and the crude material was purified by flash chromatography (petroleum ether/ethyl acetate 3:1). Conversion of **1a** and thiols or selenols into the corresponding dicyanosuccinate **8a** and disulfides **14** or diselenides **16** was almost quantitative (>96%, Tables 1 and 2). In experiments performed with tritylthiol and *tert*-butylthiol intense odor detected even after 24h and the registered ^{1}H NMR spectra of crude mixtures revealed the presence of unconverted substrates; characteristic singlet for two MeO groups of DCFM was found at δ ($CDCl_3$) = 4.05 ppm. Yields of known disulfides **14a**−**c**,**k**,**n** and were determined based on the ^{1}H NMR analysis of the crude reaction mixtures with weighted portion of xylene added as a concentration standard.

Diphenyldisulfide (1,2-diphenyldisulfane)[18] ***(14a**, Table 1, entry 1)*: Colorless oil (98%).

1,2-Dioctadecyldisulfane[18] ***(14b**, Table 1, entry 2)*: Glossy white solid (96%).

2,2'-Disulfandiyldiethanol[18] ***(14c**, Table 1, entry 3)*: Colorless oil (96%).

1,1'-Disulfanediylbis(propan-2-ol)[19] ***(14d**, Table 1, entry 4)*: Colorless oil (97%).

*3,3'-Disulfanediylbis[1-(benzyloxy)propan-2-ol] (**14e**, Table 1, entry 5)*: Following the general procedure, 1-(benzyloxy)-3-mercaptopropan-2-ol (**13e**, 0.4 mmol, 80 mg) and **1a** (39 mg, 0.2 mmol) gave after purification the corresponding disulfide **14e** (75 mg, 95%) as a 1:1 mixture of diastereoisomers. Yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* = 7.28–7.38 (m, 20H), 4.05–4.11 (m, 4H, C**H**OH), 3.60 (bdd, *J* = 3.9, 9.6

Hz, part of an ABX system, 4H, CH_2O), 3.59 (bdd, J = 3.9, 9.5 Hz, part of an ABX system, 4H, CH_2O), 3.52 (bdd, J = 6.1, 9.5 Hz, part of an ABX system, 4H, CH_2O), 3.51 (bdd, J = 6.5, 9.6 Hz, part of an ABX system, 4H, CH_2O), 2.89–2.94 (m, 4H, CH_2S), 2.83 (dd, J = 7.4, 12.8 Hz, 4H, CH_2S), 2.69 (bs, 4H, OH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.4, 129.1, 128.5, 128.4 (Ph), 74.1 (O**C**H_2Ph), 73.2 (CH**C**H_2O), 69.9 (CHOH), 69.8 (CHOH), 43.1 (CH_2S) ppm; MS (ESI positive) (*m/z*): 417 [*M*+Na]$^+$, (100). Elemental analysis: calcd for $C_{20}H_{26}O_4S_2$ (394.55): C 60.88%, H 6.64%; found: C 60.82%, H 6.67%.

*3,3'-Disulfanediylbis[1-(allyloxy)propan-2-ol] (**14f**, Table 1, entry 6)*: Following the general procedure, 1-(allyloxy)-3-mercaptopropan-2-ol (**13f**, 0.4 mmol, 59 mg) and **1a** (39 mg, 0.2 mmol) gave after purification the corresponding disulfide **14f** (55 mg, 94%) as a 1:1 mixture of diastereoisomers. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80–5.99 (m, 4H), 5.15–5.32 (m, 8H), 3.99–4.05 (m, 8H), 3.87–3.96 (m, 4H, C**H**OH), 3.40–3.55 (m, 8H), 2.87 (bs, 4H, OH), 2.78 (dd, J = 4.9, 13.9 Hz, part of an ABX system, 4H, CH_a**H$_b$**S), 2.65 (dd, J = 7.3, 13.9 Hz, part of an ABX system, 4H, C**H$_a$**H$_b$S) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.3 (=CH), 117.4 (=CH_2), 72.5, 72.4, 72.3 (CH_2O), 69.2, 69.1 (CHOH), 42.5, 42.4 (CH_2S) ppm; MS (ESI positive) (*m/z*): 317 [*M*+Na]$^+$, (100). Elemental analysis: calcd for $C_{12}H_{22}O_4S_2$ (294.43): C 48.95%, H 7.53%. Found: C 49.01%, H 7.51%.

*Di(tert-butyl) [(2S,2'S)-disulfanediylbis(3-methylbutane-2,1-diyl)]dicarbamate[20] (**14g**, Table 1, entry 7)*: White solid (92%).

*N,N'-[(2S,2'S)-Disulfanediylbis(3-methylbutane-2,1-diyl)]bis(4-methylbenzenesulfonamide)[21] (**14h**, Table 1, entry 8)*: White solid (94%).

*(2S,2'S)-3,3'-Disulfanediylbis(2-aminopropanoic acid) (cystine)[22] (**14i**, Table 1, entry 9)*: White solid (98%).

*Glutathione disulfide (GSSG)[22] (**14j**, Table 1, entry 10)*: White solid (98%).

*1,2-Dithiolane[23] (**14k**, Table 1, entry 11)*: Yellowish oil (89%).

1,2-Dithiane-4,5-diol[24] (***14l***, *Table 1, entry 12)*: White solid (98%).

3,7-Bis[(benzyloxy)methyl]1,2,5-dithiadelenepane[25] (***14m***, *Table 1, entry 13)*: Yellowish oil (96%).

1,2,5,6-Tetrathiocane[26] (***14n***, *Table 1, entry 14)*: Yellowish oil (82%).

Dipenyldiselenide (1,2-diphenyldiselene)[27] (***16a***, *Table 2, entry 1)*: Yellow solid (98%).

3,3'-Diselanediylbis[1-(benzyloxy)propan-2-ol[28] (***16b***, *Table 2, entry 1)*: Yellowish oil (95%).

3,3'-Diselanediylbis[1-(allyloxy)propan-2-ol[28] (***16c***, *Table 2, entry 1)*: Yellowish oil (96%).

N,N'-[(2S,2'S)-Diselanylbis(4-methylpentane-2,1-diyl)]bis{4-methylbenzenesulfonamide)[28] (***16d***, *Table 2, entry 4)*: Yellow solid (97%).

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Dialkyl dicyanofumarates act as efficient hydrogen acceptors towards diverse thiols and selenols yielding the desired disulfides and diselenides, respectively; aliphatic dithiols form cyclic disulfides. In most cases yields are high to excellent. The only side products are isomeric dicyanosuccinates formed in a 1:1 ratio. A SET mechanism offers a likely explanation of the reaction course.

Graphical abstract: