Phosphine-catalyzed disulfide metathesis†

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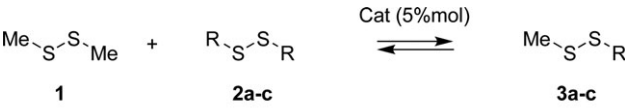
The reaction between disulfides and phosphines generates a reversible disulfide metathesis process.

Disulfide formation and exchange remain central in a wide range of biological and chemical systems, enabling reversible access to stabilized structures, and regulating functions and properties of disulfide containing entities.[1] For example, the reversible property of the disulfide bridge has recently become an important tool in Constitutional Dynamic Chemistry (CDC) and Dynamic Combinatorial Chemistry (DCC) protocols, used for efficient generation of molecular diversity in different applications.[2,3] A variety of exchange methods have over time been developed,[3–5] most of which rely on a balance between free thiolate and disulfide and generally requiring extended reaction times of up to several days to reach equilibrium. However, only very few examples in the literature describe this reaction when only disulfides are used as starting materials in a metathesis system.[4] Harsher conditions, such as elevated temperatures, strong acid and/or transition-metals are then generally required to accelerate the exchange, and the ability to perform the interchange reaction at ambient conditions in short time still remains to be addressed. In the present study, a novel and efficient method of disulfide metathesis under mild conditions using phosphines as catalysts is described, and its application in DCC demonstrated.

Reactions between phosphines and disulfides have been studied extensively,[6–8] and it is well known that phosphines act as reducing agents with disulfides forming the corresponding phosphine oxides and thiols in water.[7] It has also been reported that particularly aminophosphines lead to desulfurization of the starting disulfide.[8] In the present study, alkyl and aryl phosphines were initially chosen as catalysts for the disulfide metathesis reaction of model aliphatic and aromatic disulfides (Table 1). The reactions were carried out in $CDCl_3$, and ^{1}H NMR spectroscopy was conveniently used to analyze the exchange reaction. Mixing dimethyl disulfide **1** and diethyl disulfide **2a** in $CDCl_3$ with triphenylphosphine (PPh_3, 5 mol%) led to the formation of **3a** (53%) and to the recovery of **1** and **2a** (23.5%) (Table 1, entry 1). After considerable optimization, it could be concluded that PPh_3 indeed catalyzes the metathesis reaction, although rather inefficiently (Table 1, entries 1, 2 and 3). However, the slow equilibration rate allowed the comparison of the structural effects of the disulfide. The exchange reaction between alkyl–alkyl disulfides was thus found to proceed at a higher rate than alkyl–aryl disulfides. In both cases, no desulfurization product was observed after 68 h. Furthermore, no thiolate intermediates could be observed during the exchange reaction, even when a higher concentration of catalyst was used (50 mol%), thus indicating a metathesis-type reaction mechanism with a rate-determining first step.

Table 1 Phosphine-catalyzed disulfide metathesis[a]



Entry	RSSR	Catalyst	**1**[b] (%)	**2**[b] (%)	**3**[b] (%)	*t*/h
1	**2a**	PPh_3	23.5	23.5	53	44
2	**2b**	PPh_3	22.5	22.5	55	24
3	**2c**	PPh_3	36	36	28[c]	68
4	**2a**	PCy_3	24.5	24.5	51	0.28
5	**2b**	PCy_3	24	24	52	1
6	**2c**	PCy_3	26	26	48	68
7	**2a**	$PCyPh_2$	27	27	46[c]	68
8	**2b**	$PCyPh_2$	40	40	20[c]	68
9	**2c**	$PCyPh_2$	34	34	32[c]	68
10	**2a**	PCy_2Ph	27	27	46[c]	68
11	**2b**	PCy_2Ph	27.5	27.5	45[c]	68
12	**2c**	PCy_2Ph	37.5	37.5	25[c]	68
13	**2a**	$P(BiPh)Cy_2$	45	45	10[c]	68
14	**2b**	$P(BiPh)Cy_2$	45	45	10[c]	68
15	**2c**	$P(BiPh)Cy_2$	41	41	18[c]	68
16	**2a**	$P(OEt)_3$	47.5	47.5	5[c]	68
17[d]	**2a**	$P(NEt_2)_3$	22.5	22.5	50	0.13
18[e]	**2a**	$OPCy_3$	50	50	0	68
19[e]	**2a**	—	50	50	0	68

[a] All experiments were performed with 5 mol% of catalyst at room temperature and 350 mM of each disulfide. [b] Yields are based on the methyl group. [c] The exchange reaction did not proceed to completion. [d] 5% of the final mixture corresponds to products from the desulfurization process. [e] No exchange was observed.

In order to accelerate the reaction rate, an aliphatic phosphine, tricyclohexylphosphine (PCy_3), was subsequently tested. In contrast to PPh_3, PCy_3 is very sensitive to oxidation and rapidly transforms into the corresponding phosphine oxide in the presence of oxygen. Our intention was however to avoid an inert atmosphere for practical convenience, and air exposed PCy_3 was initially probed in the reaction. The degree of oxidation was determined by ^{31}P NMR, revealing that the phosphine was partially oxidized (46% tricyclohexylphosphine oxide, $OPCy_3$). A comparison of the efficiency of the partially oxidized and the non-oxidized catalyst was performed, showing that the reaction was slightly faster (1.5×) under inert conditions, as expected. The experiments were

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nevertheless carried out using air-exposed phosphine without further restrictions.

The resulting effects were in this case highly conspicuous. Mixing **1** and **2a** with PCy_3 (5 mol%) led to almost the same product ratio (53% of **3a** and recovery of 23.5% of **1** and **2a**, respectively) as with PPh_3, but the equilibration rate was considerably higher (Table 1, entries 4, 5 and 6). Under these conditions, the metathesis reaction between **1** and **2a** was completed in 17 min compared to 44 h for PPh_3. Control experiments using only the oxide form were performed in order to probe its catalytic efficiency, where no exchange was observed (Table 1, entry 18). The reversibility of the system was verified by adding a third disulfide (**2b**) to the reaction between **1** and **2a** after equilibrium formation (*cf.* ESI†). A new equilibrium was then observed, in agreement with a reversible process.

To further probe the effect of the catalyst structure, a series of cyclohexyl containing phosphines were tested; cyclohexyldiphenylphosphine ($PCyPh_2$), dicyclohexylphenylphosphine (PCy_2Ph), and (2-biphenyl)dicyclohexylphosphine ($P(BiPh)Cy_2$), the latter of which shown to be very stable towards oxidation.[9] In this series, PCy_3 remained the best catalyst and aromatic groups generally retarded the reaction rate. In addition, $P(BiPh)Cy_2$ proved less efficient than PCy_2Ph, likely due to steric effects. In search for further improvements of the system, triethylphosphite ($P(OEt)_3$) (Table 1, entry 16) and a phosphoramide derivative ($P(NEt_2)_3$) (Table 1, entry 17), were subsequently envisaged. The exchange reaction however proceeded very slowly in presence of $P(OEt)_3$ as catalyst and only 5% of mixed disulfide **3a** was generated within 68 h. In the case of $P(NEt_2)_3$ on the other hand, the disulfide exchange occurred faster than with PCy_3, and the exchange between **1** and **2a** was completed in 8 min. Irreversible desulfurization was also observed with this catalyst, but the desulfurization generally proved slower than the exchange reaction, indicating that this is a viable route to disulfide metathesis albeit with consumption of a small amount of disulfide.

Further kinetic studies of mixtures of disulfides **1** and **2a** were carried out using different concentrations of PCy_3 in $CDCl_3$ (Fig. 1). In this case, when the reaction was performed using a phosphine concentration higher than 3.7 mol%, small differences in rates were observed, and the disulfide exchange still occurred with a high equilibration rate ($t_{1/2} < 8$ min). However a significant difference appeared when less than 2.5 mol% of PCy_3 was used ($t_{1/2} = 24$ min).

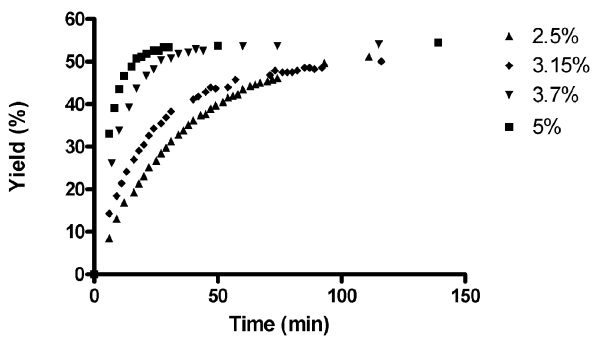


Fig. 1 Formation of **3a** at different phosphine concentrations. Experimental conditions: methyl disulfide **1** (350 mM), ethyl disulfide **2a** (350 mM), r.t., $CDCl_3$.

Table 2 Equilibration times in different solvents[a]

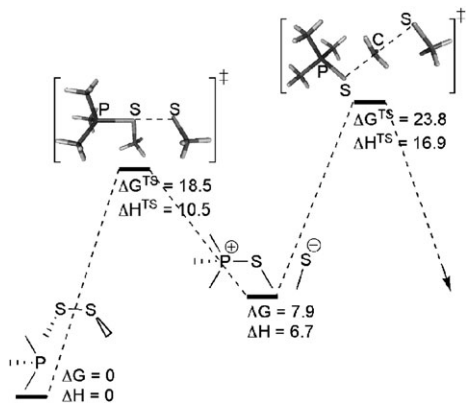
Solvent	ε_r[b]	E_T[b]	Time
C_6D_6	2.3	0.111	11 d
$CDCl_3$	4.9	0.259	17 min
CD_3CN	35.9	0.460	<5 min
DMSO-d_6	46.4	0.404	<5 min

[a] Methyl disulfide **1** (350 mM), ethyl disulfide **2a** (350 mM), PCy_3 (5 mol%), r.t. [b] Values from ref. 10, non-deuterated solvents.

The system was subsequently investigated for solvent effects (Table 2). Disulfides **1** and **2a** were treated together with PCy_3 (5 mol%) in a range of solvents and the equilibration monitored. From these studies, strong solvent effects were clearly observed. Low polarity solvents, such as benzene, led to low reaction rates (11 d), while solvents with higher polarity, such as acetonitrile and DMSO resulted in very short equilibration times (<5 min, the same reaction without catalyst did not give any exchange after a time of 24 h). No difference in the exchange rates of alkyl–alkyl disulfides and aryl–aryl disulfides could be discerned in DMSO and acetonitrile under these conditions. Furthermore, 1 mol% of PCy_3 was sufficient to equilibrate the exchange reaction in <5 min in DMSO.

A proposed mechanism utilizing PMe_3 as catalyst is depicted in Scheme 1, together with computed free energies of reaction and activation. All structures were optimized at the B3LYP/6-31G(d) level in acetonitrile using the default PCM solvation model of Gaussian.[11] Vibrational analysis was performed at the same level of theory. Energies were obtained at the B2PLYP/aug-cc-pVTZ level with the COSMO solvation model, employing the ORCA program suite.[12] The results indicate that the rate-determining step is the nucleophilic attack of PMe_3 on **1**, forming thiolate and the Me_3P^+–SMe cation. The reverse reaction, which reforms the catalyst, is rapid and explains the observed disulfide exchange. The charge-localized nature of the transition state is consistent with the observed solvation effects. Desulfurization through S_N2-attack of thiolate on the SMe-carbon of the Me_3P^+–SMe cation, is not likely to occur in the modeled scenario due to high energy of the corresponding transition state.

In order to demonstrate the convenience of the phosphine catalyzed metathesis process, the generation of a larger dynamic



Scheme 1 Quantum chemical studies of the phosphine-catalyzed reaction in acetonitrile. Energies have been calculated for 298 K and 1 M and are given in kcal mol^{-1}.

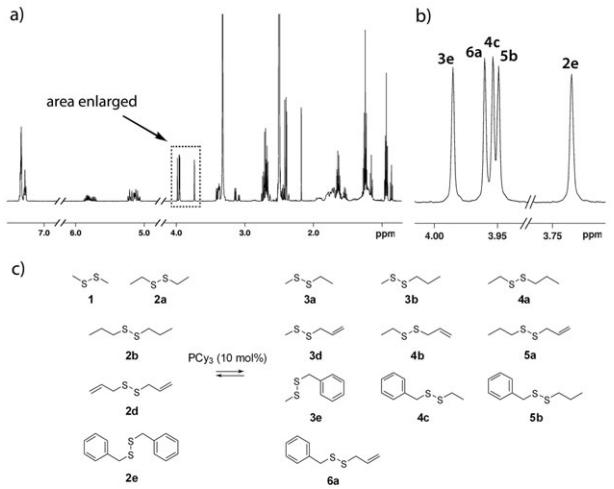


Fig. 2 Disulfide metathesis in dynamic system generation: (a) ^{1}H NMR spectrum of the reaction mixture after equilibration of the library; (b) enlarged area displaying the resulting benzyl disulfides; (c) library reaction formation. Experimental conditions: Disulfides **1**, **2a–2e** (5 mM each), PCy_3 (10 mol%), r.t., DMSO.

system at lower concentration was addressed. Five aliphatic disulfides were thus chosen as initial compounds (total disulfide concentration: 20 mM), and equilibration was performed in DMSO using PCy_3 as catalyst. As expected, rapid equilibrium generation occurred (55 min), efficiently producing a dynamic system composed of 15 different disulfides (Fig. 2). This demonstrates the potential of using phosphine-catalyzed disulfide metathesis in the generation of larger dynamic systems.

In conclusion, we have described a novel and efficient method to catalyze disulfide metathesis *via* the use of phosphines. The reaction proceeds very fast under mild conditions in polar solvents, efficiently catalyzed by PCy_3 and $P(NEt_2)_3$. This new catalytic process can for example be used as a very powerful tool for dynamic system generation.

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