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NHC-Catalyzed Metathesis and Phosphorylation Reactions of Disulfides: Development and Mechanistic Insights

Reece D. Crocker,[a] Mohanad A. Hussein,[a] Junming Ho*[b] and Thanh V. Nguyen*[a]

Abstract: The development of efficient methods for the metathesis and phosphorylation reactions of disulfide compounds is of widespread interests due to their important synthetic utility in polymer, biological, medicinal and agricultural chemistry. Herein, we demonstrate the use of N-heterocyclic carbenes (NHCs) as versatile organocatalysts to promote these challenging reactions under mild conditions. This metal-free oxidant-free protocol is operationally simple with very short reaction times. The interplay between the nucleophilicity and basicity of NHCs in these reactions were also elucidated by NMR studies and high-level *ab initio* calculations.

Sulfur-transfer chemical transformations play pivotal roles in biological processes and synthetic chemistry.[1] Despite sulfur being an abundant element of the chalcogen group, organic reactions involving organosulfur compounds are relatively under-investigated compared to their oxygen counterparts.[2] The development of efficient metathesis[3] and phosphorylation[4] reactions of disulfides are of particular interest due to their synthetic values in polymer, medicinal, agricultural and catalytic chemistry.[3,5] Recently, these reactions have also become versatile tools for dynamic combinatorial[6] and diversity-oriented chemistry[7] as they can rapidly generate molecular libraries for various applications.[6a,8] Traditional methods for these reactions normally require harsh conditions or involve toxic or unstable reagents and catalysts with limitations in scope.[9] Herein, we report a novel and efficient N-heterocyclic carbene (NHC)-catalyzed procedure to promote both the disulfide metathesis reaction and the synthesis of phosphorothiolates via phosphite-disulfide coupling reaction (Scheme 1). High-level *ab intio* studies were carried out to propose plausible mechanisms for these reactions. This work opens up new possibilities in NHC-mediated organic synthesis,[10] as the catalytic activity of NHCs on organosulfur and organophosphorus substrates has been inadequately studied.[5a,11]

The disulfide bond is one of the most interesting covalent bonds in dynamic covalent/combinatorial chemistry (DCC) for drug discovery and chemical biology studies.[6,12] The readily exchangeable -S-S- linkage[13] can be utilized in metathesis reactions to rapidly access diverse libraries of heterodimeric analogues from a small number of disulfide building blocks.[8,14]

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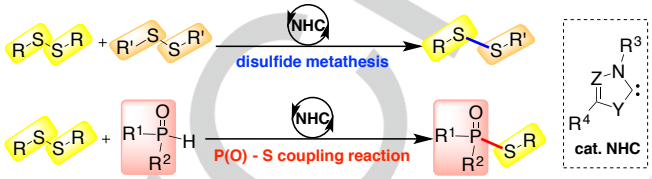
[**] The Supporting Information is available: Experimental and computational de-tails, analytical data, NMR spectra, and Cartesian coordinates of M06-2X optimized geometries are provided.



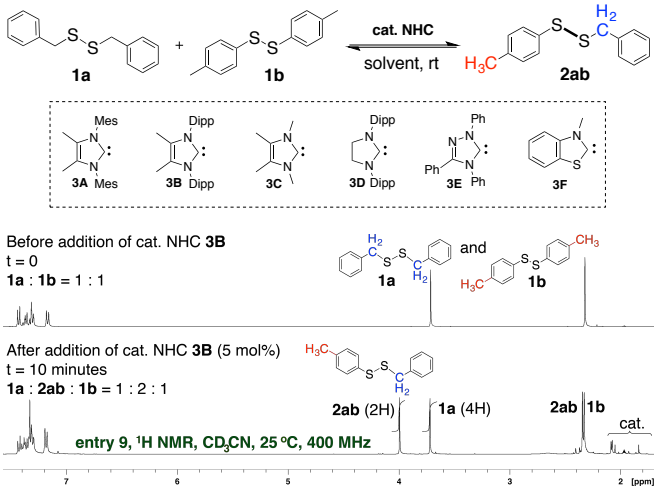
Scheme 1. NHC-catalyzed reactions of disulfides.

Several methods have been recently developed to facilitate the disulfide metathesis reactions using phosphine catalysts[15] or mechano-[9a,16] and photochemical processes.[17] However, it is still an ongoing challenge to address the limitations in substrate scope, equilibration time and the precision of these methods. Given the fact that thiolates or phosphines can heterolytically cleave disulfide bond via nucleophilic attack,[9a,18] we envision that the highly nucleophilic NHCs could act as effective organocatalyst for this reaction. Indeed, our study demonstrated that disulfide metathesis reactions proceeded smoothly in the presence of NHC catalysts under mild conditions with excellent efficiency.

Our first test reaction on the metathesis of Bn-S-S-Bn (**1a**) and *p*Tol-S-S- *p*Tol (**1b**, Table 1) using the standard ^{Me}IMes NHC **3A** (10 mol %) catalyst was met with instant success. The reaction was initially carried out in CD_3CN where NMR and GC-MS analyses clearly showed that the equilibrium to Bn-S-S-*p*Tol (**2ab**) was reached within 10 minutes without any side reaction. The product **1a**:**2ab**:**1b** ≈ 25:50:25 ratio is in good agreement with the theoretical yields of this statistical equilibrium reaction. These favorable preliminary results, with up to 10-fold reduction in reaction time compared to known methods,[9a,15a,17] encouraged us to fully optimize this NHC-promoted disulfide metathesis reaction (Table 1). Among the pool of six NHC catalysts tested, imidazolylidenes **3A**-**3C** gave similar results with shorter reaction times than imidazolinylidene, triazolylidene and thiazolylidene catalysts (**3D**-**3E**), which is in good agreement with the nucleophilicity of these catalysts.[19] Acetonitrile proved to be the best solvent (entries 2,7,8, Table 1) hinting at a polar transition state for these reactions. The catalyst loading could be reduced to 5 mol% without affecting the equilibrium outcomes (entries 2 and 9-11, Table 1). In the absence of NHC catalysts, no disulfide **2ab** was found even after a prolonged reaction time (entry 12, Table 1). Disulfide exchange by homolytic cleavage of the S-S bond[9b] is ruled out as the use of BHT as a radical scavenger still led to good conversion (entry 15, Table 1).[20]

The optimized conditions were then used for dynamic metathesis reactions between a range of disulfides (Scheme 2). Most of them underwent rapid and clean cross metathesis with each other to give a library of unsymmetrical disulfides. There was negligible discrepancy in reaction outcomes for primary

Table 1. Optimization of disulphide metathesis reaction



Entry[a]	Catalyst, mol%	Solvent	Time[b]	2ab[c]
1	**3A**, 10	CD_3CN	<10	50%
2	**3B**, 10	CD_3CN	5	50%
3	**3C**, 10	CD_3CN	<10	50%
4	**3D**, 10	CD_3CN	90	50%
5	**3E**, 10	CD_3CN	240	50%
6	**3F**, 10	CD_3CN	240	50%
7	**3B**, 10	CD_2Cl_2	90	50%
8	**3B**, 10	$C_6D_5CD_3$	720	5%
9	**3B**, 5	CD_3CN	<10	50%
10	**3B**, 2.5	CD_3CN	360	20%
11	**3B**, 1.3	CD_3CN	720	5%
12	No catalyst	CD_3CN	1440	-
13	NaSBn, 10	CD_3CN	120	22%
14	KHMDS, 10[d]	CD_3CN	720	12%
15	**3B**, 10 and BHT (1.0 equiv)[20]	CD_3CN	120	35%

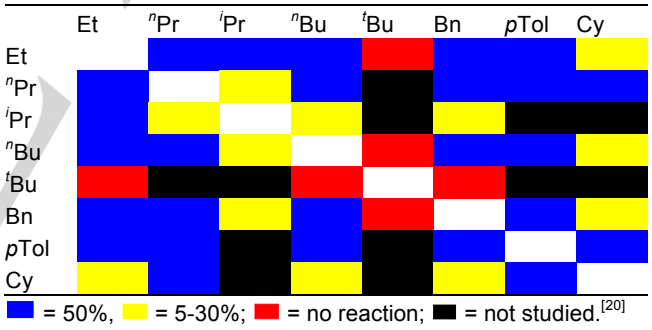
[a] Reaction conditions: NHC catalyst **3** in solvent (1.0 mL) then a mixture of disulfide **1a** (0.5 mmol) and **1b** (0.5 mmol) in solvent (1.0 mL). [b] Time (in minute) to reach equilibrium. [c] Conversion by NMR or GC/LCCMS. [d] 10 mol% BnSH was also added.

alkyl disulfides or aryl disulfides. However, bulky substrates such as diisopropyl, dicyclohexyl or di(*tert*-butyl)disulfides only reacted sluggishly to afford the products in poor to moderate yields (Scheme 2a). To the best of the authors' knowledge, this is the first example of NHC-catalyzed disulfide metathesis, and it is of interest to understand the mechanism of these reactions. However, mechanistic studies of these reactions is challenging due to the short reaction times, as even at – 40 °C, the equilibria were reached within 10-30 minutes.

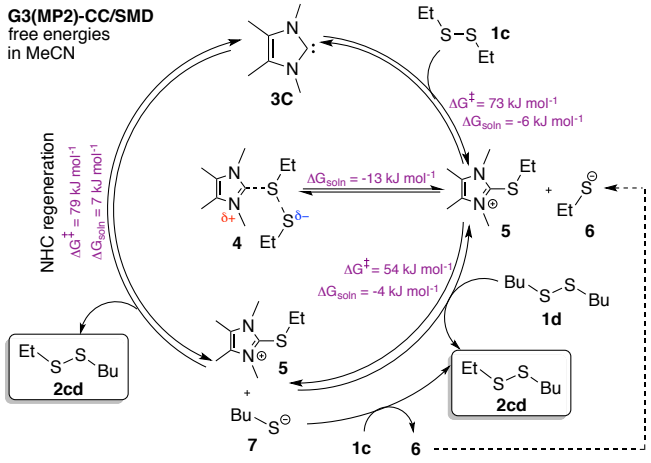
In combination with high-level *ab initio* calculations,[21] we proposed possible mechanistic pathways for this type of reaction with disulfides **1c** and **1d** (Scheme 2b). NHC **3C** presumably acted as a *nucleophilic* initiator to form thio-imidazolium cation **5** and thiolate **6**, which then attacks a disulfide and regenerates a sulfide anion each time. The initiation step has a significantly higher (ca. 20 kJ mol^{-1}) barrier, and is consistent with reaction times correlating inversely with nucleophilicity of the NHCs (Table 1). Control experiments (entries 13-14 in Table 1) where the benzylthiolate or KHMDS/BnSH are introduced directly into the reaction mixture resulted in significantly longer reaction times (*c.f.* entry 3).[20] The relatively small thermodynamic driving force (-6 kJ mol^{-1}) and barrier (70 kJ mol^{-1}) associated with the initial/regeneration step indicates that a small but non-negligible amount of free NHC (*ca.* 10% of the total amount of NHC-derived species, based on calculated ΔG) is present throughout the reaction, which is consistent with NMR observations.[20] Presumably, this small fraction of charge-neutral NHC catalyst diffuses more rapidly than thiolates in acetonitrile,[22] initiating the reaction at distal sites that would explain the observed rate enhancement. As such, the NHC also plays a minor catalytic role in the metathesis reactions.

With the establishment of this NHC-promoted disulfide metathesis protocol, we turned our attention to the synthesis of phosphorothiolates from disulfide-phosphite coupling reactions. These organo-phosphorus-sulfur compounds serve as valuable intermediates in organic chemistry and precursors for important

(a) Substrate scope

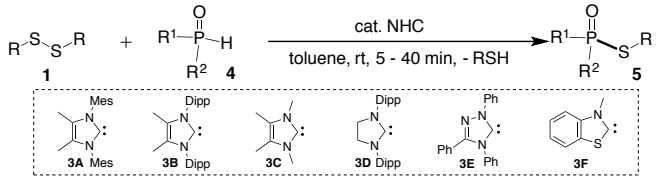


(b) Proposed mechanism and computational studies



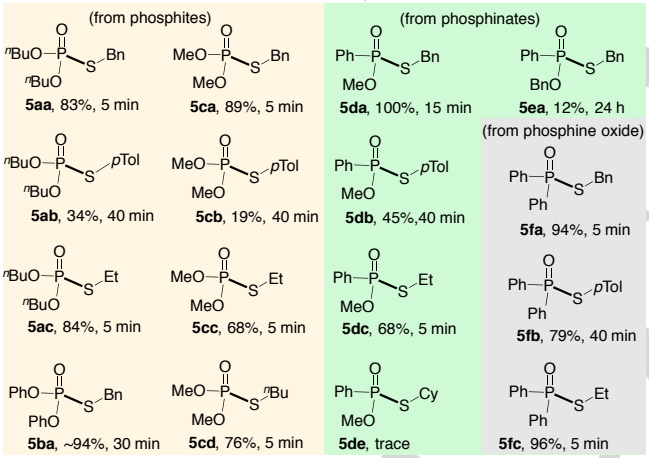
Scheme 2. NHC-catalyzed disulfide metathesis.

Table 2. P(O)-S coupling reactions[a]



Entry[a]	Product	Catalyst	Cat. loading	Yield[b]
1	**5aa**	-	10 mol%	-
2	**5aa**	**3A**	10 mol%	74%
3	**5aa**	**3B**	10 mol%	83%
4	**5aa**	**3C**	10 mol%	56%
5-7	**5aa**	**3D-F**	10 mol%	traces-20%
8	**5aa**	**3B**	5 mol%	17%
9	**5aa**	**3B**	10 mol%[c]	70%
10[d]	**5aa**	**3B**	10 mol%	65%
11	**5aa**	**NaSBn**	10 mol%	14%
12	**5aa**	**DBU**	10 mol%	23%

with 10 mol% catalyst **3B**



[a] Reaction conditions: NHC catalyst **3** in solvent (6.0 mL) then a mixture of disulfide **1** (0.55 mmol) and phosphite **4** (0.50 mmol) in solvent (1.0 mL) at rt. [b] Yield of isolated product. [c] 10 mol% water was added to the reaction. [d] MeCN was used as solvent.

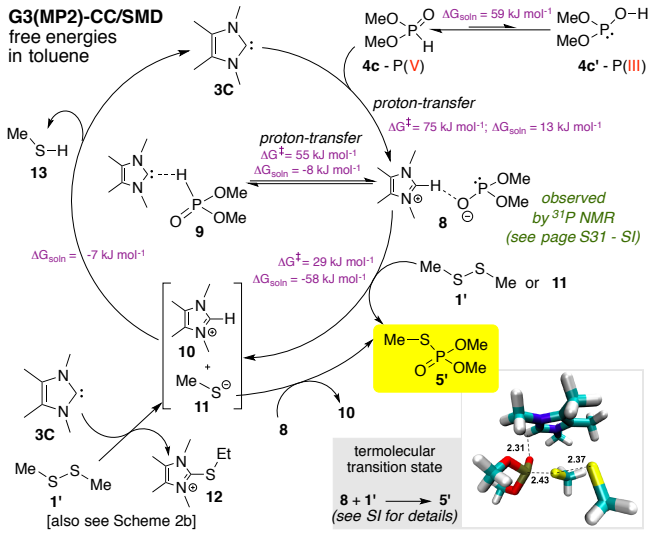
medicinal agents and agrochemicals.[4,9b] Current methods to produces these compounds normally involve toxic and moisture-sensitive reagents or catalysts.[4,9b,23] NHC organocatalysts were previously known to also activate phosphites for a number of (1,ω)-hydrophosphonylation to carbonyl compounds.[11b,11i,24] Hence, it seems likely that NHCs should also act as effective catalysts for the P(O)-S coupling reactions between disulfides and P(O)H substrates.

We focused our initial investigation on the reaction between Bn-S-S-Bn and $(BuO)_2P(O)H$ (entries 1-10, Table 2). It was encouraging to note that the reaction proceeded smoothly and cleanly at room temperature with excellent yields within very short reaction times. The solvent effect was found to be slightly different from the disulfide metathesis reaction where toluene gave better reaction outcomes than acetonitrile (entries 3 and 10, Table 2). Imidazolylidene catalysts **3A**, **3B** again gave the best outcomes for this P(O)-S coupling reaction (entries 1-7, Table 2). The optimization of catalyst loading stalled at 5 mol% for catalyst **3B** (entries 3 and 8 Table 2).

With these optimal conditions, we were able to promote the coupling reactions between a range of disulfides and organophosphorus compounds to afford phosphorothiolate products in good to excellent yields for most cases studied (**5aa**-**5fc**, Table 2). Thiol derivatives of the disulfide substrates were always isolated in comparable yields to the main products. This NHC-catalyzed reaction worked well for all three different types of P(O)-H substrates, namely phosphites (**5aa**-**5cd**), phosphinates (**5da**-**5ea**) and phosphine oxide (**5fa**-**5fc**). The limitation actually arose from less reactive disulfide substrates where steric hindrance might be at play (**5ab**, **5cb**, **5db**, **5de**, **5ea**, also see Scheme 2a).[20] In light of its overall good performance, this method could serve as a convenient and efficient organocatalytic alternative[4] for the synthesis of synthetically valuable phosphorothiolates.

Interestingly, ^{31}P NMR studies[20] in combination with computational modelling[20] suggest that the reaction did not proceed through the activation of disulfide substrate like the S-S metathesis reaction discussed earlier (see pages S32/33 – SI).[20] In this proposed mechanism (Scheme 3), NHC **3C** acts as a Brønsted base catalyst to activate the phosphorus center of substrate **4c** via a proton-transfer to form an ion-pair intermediate **8**. This is also the rate-limiting step for the reaction, as confirmed by kinetic studies (see page S34 in the SI). The nucleophilic phosphorus center readily reacts with the disulfide **1'** (with a barrier height of 27 kJ mol^{-1}) to form the phosphorothiolate product **5'** via a termolecular transition state (inset in Scheme 3). The higher catalyst loading (10 mol%) needed in these reactions is attributed to competing reaction between the NHC and the disulfide substrate to form the thiolates (Scheme 2b). The proposed mechanism also agrees well with the experimental observation that species with weak basicity (**3D**-**F**, entries 5-7, Table 2) to drive the proton transfer could not promote the reaction efficiently.

In support of the proposed mechanism, we note that there is a direct correlation between basicity and reaction outcome. Computed relative p*K*a values in toluene, as well as experimental *aqueous* values for structurally related NHCs indicate that catalysts A-C are the most basic amongst the present set of NHCs (See page S50 in the SI).[25] Additionally, replacement of NHC catalyst (p*K*a in DMSO *ca.* 24)[26] by the weakly basic NaSBn (p*K*a in DMSO *ca.* 10.3)[27] resulted in 14% yield (entry 11 Table 2), whilst DBU[28] (p*K*a in DMSO *ca.* 12) provided a slight improvement (entry 12). The calculations also indicate that **4c'**-P(III) is not likely to be an active species since **4c**-P(V) to **4c'**-P(III) tautomerization[29] (Scheme 3) is thermodynamically disfavored (ΔG *ca.* 60 kJ mol^{-1}).[30] Notably,



Scheme 3. Proposed mechanism for the P(O)-S coupling reactions

addition of a catalytic amount of water (entry 9) or using a more polar solvent (entry 10), known to enhance the formation of P(III) tautomer,[28] both led to lower reaction efficiency.

In conclusion, we have developed novel NHC-catalyzed methods to efficiently promote the disulfide metathesis as well as the phosphite-disulfide coupling reactions under very mild conditions and short reaction times. These metal-free protocols were operationally simple but computational studies suggest that they might be mechanistically more complex with interesting activation modes. The computational studies provide mechanistic insights into how the nucleophilicity/basicity of NHCs can be exploited to enhance the two aforementioned synthetic procedures. These reactions could serve as versatile tools to rapidly generate diverse molecular libraries for applications in synthetic and medicinal chemistry. This work also opens up new opportunities in NHC-mediated chemistry of organosulfur and organophosphorus compounds. Studies to expand the scope of these methodologies in stereoselective synthesis of bioactive compounds are on-going and will be reported in due course.

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Keywords: N-heterocyclic carbene • organocatalysis • disulfide • phosphorylation • high-level ab initio calculations

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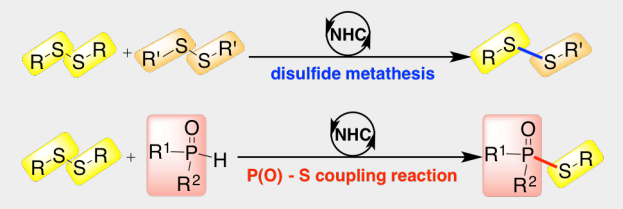

Instant reactions: N-heterocyclic carbenes (NHCs) served as versatile organocatalysts to promote disulfide exchange and phosphite-disulfide coupling reactions under mild conditions. This metal-free oxidant-free protocol is operationally simple and highly efficient with very short reaction times.

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Page No. – Page No.

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