Organocatalysis

International Edition: DOI: 10.1002/anie.201911793
German Edition: DOI: 10.1002/ange.201911793

Umpolung Strategy for α-Functionalization of Aldehydes for the Addition of Thiols and other Nucleophiles

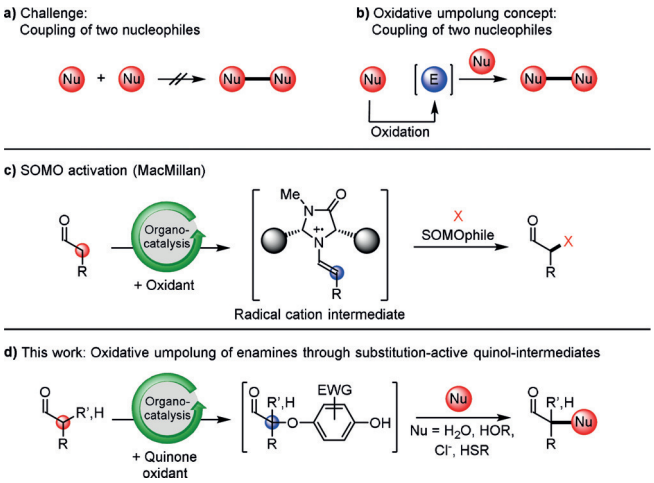
*Jakob Blom, Gabriel J. Reyes-Rodríguez, Henriette N. Tobiesen[+], Johannes N. Lamhauge[+], Marc V. Iversen[+], Casper L. Barløse, Niels Hammer, Matilde Rusbjerg, and Karl Anker Jørgensen**

Abstract: *Nucleophile–nucleophile coupling is a challenging transformation in organic chemistry. Herein we present a novel umpolung strategy for α-functionalization of aldehydes with nucleophiles. The strategy uses organocatalytic enamine activation and quinone-promoted oxidation to access O-bound quinol-intermediates that undergo nucleophilic substitution reactions. These quinol-intermediates react with different classes of nucleophiles. The focus is on an unprecedented organocatalytic oxidative α-thiolation of aldehydes. The reaction scope is demonstrated for a broad range of thiols and extended to chemoselective bioconjugation, and applicable to a large variety of aldehydes. This strategy can also encompass organocatalytic enantioselective coupling of α-branched aldehydes with thiols forming quaternary thioethers. Studies indicate a stereoselective formation of the intermediate followed by a stereospecific nucleophilic substitution reaction at a quaternary stereocenter, with inversion of configuration.*

Introduction

A reaction between a nucleophile and an electrophile forming a covalent bond is a fundamental transformation in chemistry. In contrast, the bond formation between two nucleophiles is much more challenging as their electronic nature makes them inherently incompatible (Scheme 1 a). To overcome this, an oxidative umpolung strategy can be applied by which an in situ oxidation inverts the electronic properties of one of the nucleophiles (Scheme 1 b).

The reactivity of the α-position of a carbonyl functionality is typically determined by its nucleophilic nature, traditionally as an enol/enolate intermediate, however, it can be converted into an activated electrophile. Recently, an increasing interest in umpolung strategies in combination with organocatalysis has evolved. In particular, umpolung of enamines has broadened the scope of conventional enamine catalysis.[1]



Scheme 1. a) Incompatible coupling of two nucleophiles. b) The oxidative umpolung concept for the coupling of two nucleophiles. c) SOMO activation by radical-cation intermediates. d) This work: Quinone-mediated oxidation of enamines to facilitate umpolung of the α-position of aldehydes.

Based on a single-electron transfer oxidation, MacMillan et al. introduced the concept of SOMO activation, where an enamine is oxidized in situ generating a radical-cation intermediate (Scheme 1 c). This activation principle has provided attractive strategies for α-alkylations, α-allylations, α-vinylations, α-alkynylations, and α-arylations of aldehydes.[2] However, its applicability towards functionalizations with classical polar nucleophiles is limited.[2f] Recently, we have turned our attention towards oxidative umpolung strategies of enamines and dienamines and disclosed various oxidants for such approaches.[3]

A particularly interesting class of oxidants are the 1,4-benzoquinones which have been used as oxidative promoters of both carbon–carbon and carbon–heteroatom bonds.[4,5] An important aspect of the quinone-mediated oxidative transformations is the formation of covalent quinone adducts, which have been proposed as crucial intermediates in for example, dehydrogenation reactions.[5] A major challenge in generating covalent quinone intermediates is the diverse reactivity of the quinones, allowing for formation of various regioisomers. Studies have shown that several quinone adducts can co-exist as intermediates, each of which may give access to different reaction pathways.[6] Mayr et al.

[*] J. Blom, Dr. G. J. Reyes-Rodríguez, H. N. Tobiesen,[+] J. N. Lamhauge,[+] M. V. Iversen,[+] C. L. Barløse, Dr. N. Hammer, M. Rusbjerg, Prof. Dr. K. A. Jørgensen
Department of Chemistry, Aarhus University
Langelandsgade 140, 8000 Aarhus C (Denmark)
E-mail: kaj@chem.au.dk
H. N. Tobiesen[+]
Research Chemistry, Global Research Technologies
Novo Nordisk A/S
Novo Nordisk Park, 2760 Maaloev (Denmark)
[+] These authors contributed equally to this work.
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/anie.201911793.

investigated the product distribution in reactions of π-nucleophiles (primarily silyl-enol ethers) with quinone derivatives and found that product mixtures of *C*- and *O*-bound adducts were obtained.[7] Regiocontrol can be enforced, but requires a perfect match between steric and electronic properties of both quinone and nucleophile, as well as kinetic versus thermodynamic control of the reaction. Recently List et al. disclosed an unexpected formation of *O*-bound quinol-adducts resulting from a phosphoric acid catalyzed functionalization of α-substituted cyclic ketones with unactivated 1,4-benzoquinones.[8] These *O*-bound quinol-adducts were found to be persistent enough to allow for isolation and were isolated in moderate yields. Notably, *O*-bound quinol-intermediates are generally considered deleterious and of no synthetic utility due to their reported inability to facilitate dehydrogenation transformations.[5,6] In the following, we will demonstrate that these intermediates are more useful than what is the general conception in quinone-mediated oxidations and that their potential for further functionalization have been overlooked. Furthermore, we will disclose the development of a novel umpolung strategy for α-functionalization of aldehydes based on quinone-mediated oxidation of enamines (Scheme 1 d). Early exploration of its mechanistic aspects led to the discovery of α-substituted quinone-aldehyde adducts and allowed us to identify *O*-bound quinol adducts as unprecedented reactive intermediates in α-functionalizations of aldehydes. It will be shown that these *O*-bound adducts provide access to reactions that are not possible with outer-sphere oxidants, and that α-substituted *O*-bound quinol-aldehyde adducts present conceivable potential as electrophilic intermediates for substitution reactions.[9,10]

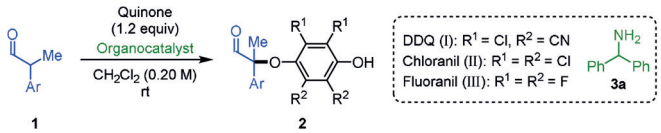
In comparison to the single-electron oxidative approach of SOMO activation, using *O*-bound quinol adducts as electrophilic intermediates offers a novel complementary reactivity. The single-electron oxidation of the enamine in SOMO activation generates a radical-cation as the reactive umpolung intermediate which reacts with SOMOphiles as single-electron donors. However, with the use of an *O*-bound quinol adduct, classical polar substitution reactivity can be obtained, allowing for the use of simple and readily available nucleophiles. The potential of these intermediates in coupling reactions is demonstrated with thiol nucleophiles, which are normally incompatible with oxidative conditions. The reaction is general for a very broad range of thiols and aldehydes forming tertiary and quaternary stereocenters, as well as tolerant towards biologically relevant thiols such as cysteine derivatives and a peptide. Furthermore, this novel reactivity opens up for an enantioselective organocatalytic protocol providing optically active α-functionalized aldehydes with thiol nucleophiles. An important aspect of the present work is the transfer of chiral information. It has been found to occur by an aminocatalyzed formation of an enantioenriched *O*-bound quinol-intermediate, and a subsequent stereospecific nucleophilic displacement on a quaternary center with inversion of configuration.[11] Finally, some key mechanistic insights are discussed.

Results and Discussion

We set out to investigate the potential formation of *O*-bound quinol-intermediates generated by reaction of aldehydes **1a–e** with quinones (Table 1). 2-(6-Methoxynaphthalen-2-yl)propanal **1a** underwent full conversion into the quinol-intermediate **2aI** in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) and absence of benzhydrylamine **3a** as the aminocatalyst (entry 1). Aldehydes which were found to be less activated, such as **1b**,**c**, required prolonged reaction times and provided moderate conversions, while 2-phenylpropanal **1d**, as well as the electron-poor aldehyde **1e** gave low conversion to the corresponding quinol-intermediates (entries 2–5). Employing quinones with lower reduction potentials, such as tetrachloro-*p*-benzoquinone (chloranil) and tetrafluoro-*p*-benzoquinone (fluoranil) failed to provide sufficient reactivity, even in combination with the most reactive aldehyde **1a** (entries 6,7). We were pleased to find the application of aminocatalyst **3a** promoted the oxidation of aldehyde **1d** and allowed for use of less-activated quinones as oxidants (entries 8–10). The use of a phosphoric acid catalyst also provided the desired quinol-intermediate from aldehyde **1d**, albeit in lower conversion (entry 11, see below). For the screening of other organocatalysts, such as secondary and tertiary amines, see the Supporting Information.

During the development of the reaction concept, we were pleased to realize that we were able to isolate and character-

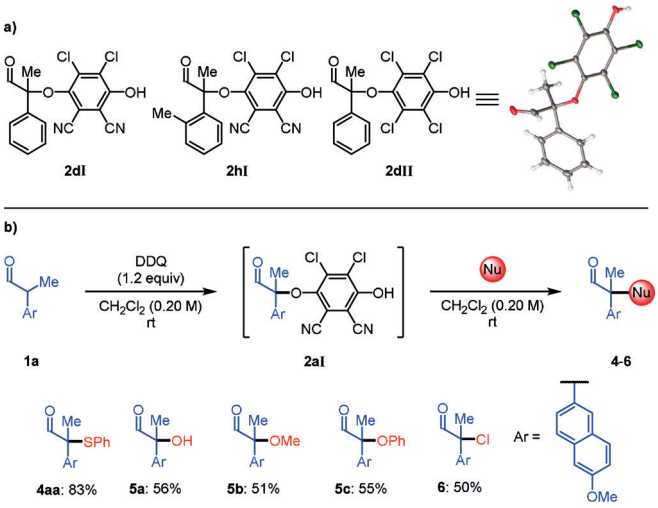
Table 1: Reaction of aldehydes with quinones under various reaction conditions.



Entry	Aldehyde Ar	Quinone	Catalyst (mol%)	Time (h)	Conv. (%)[a]	Yield (%)[a]
1	6-MeO-Naphth (**1a**)	DDQ	–	1	>95	**2aI**, 85
2	Naphth (**1b**)	DDQ	–	20	70	**2bI**, 48
3[b]	*p*-MeOPh (**1c**)	DDQ	–	20	64	**2cI**, 20
4	Ph (**1d**)	DDQ	–	20	6	**2dI**, 6
5	*p*-NO_2Ph (**1e**)	DDQ	–	20	8	**2eI**, 6
6	6-MeO-Naphth (**1a**)	chloranil	–	20	n.r.	**2aII**, –
7	6-MeO-Naphth (**1a**)	fluoranil	–	7	7	**2aIII**, <5
8	Ph (**1d**)	DDQ	**3a** (10)	1	>95	**2dI**, 85
9	6-MeO-Naphth (**1a**)	chloranil	**3a** (10)	23	>95	**2aII**, 27
10	6-MeO-Naphth (**1a**)	fluoranil	**3a** (10)	3	>95	**2aIII**, 81
11	Ph (**1d**)	DDQ	$(PhO)_2PO_2H$ (10)	21	49	**2dI**, 34

Performed on 0.10 mmol scale. [a] Conversion and yields measured by ^{1}H NMR of the crude reaction mixture relative to an internal standard (methyl 4-methyl-3-nitrobenzoate). [b] Performed on 0.05 mmol scale.

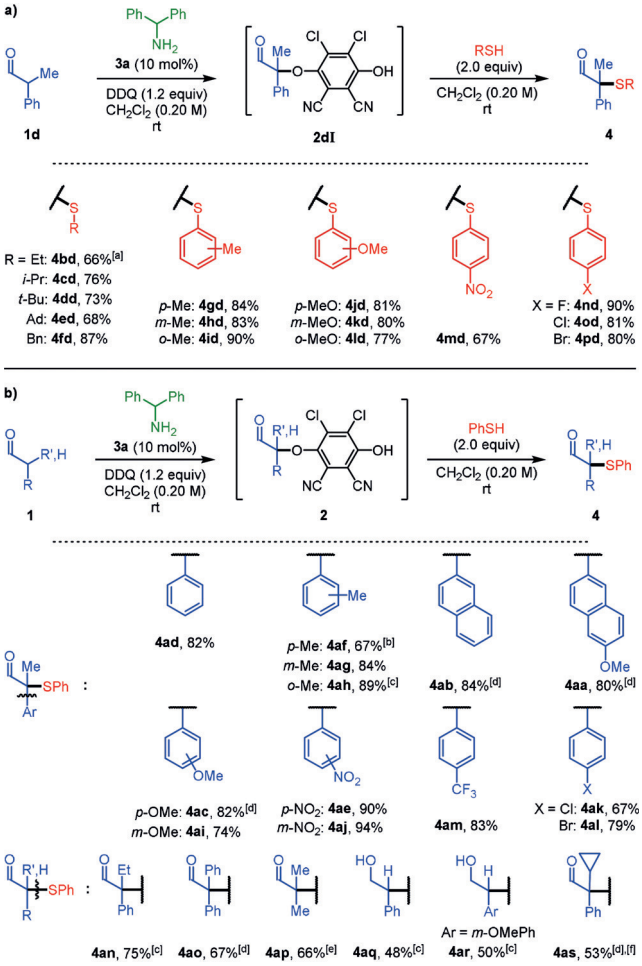
ize the *O*-bound quinol-intermediates **2dI**,**hI**,**dII**. The structure of the intermediates were confirmed by X-ray analysis of **(±)-2dII** (Scheme 2a, see the Supporting Information). This demonstrates that the former nucleophilic α-carbon in the enamine is selectively converted into an activated electrophile by an overall two-electron oxidation upon reaction with the quinone.



Scheme 2. a) Isolated *O*-bound quinol-intermediates applying different aldehydes and quinones in the presence of aminocatalyst, and single-crystal X-ray structure of **(±)-2dII** (thermal ellipsoids drawn at 50% probability).[19] b) Reactions of *O*-bound quinol-intermediate **2aI** with nucleophiles. Performed on 0.20 mmol scale.

As shown in Table 1, 2-(6-methoxynaphthalen-2-yl)propanal **1a** underwent full conversion into the *O*-bound quinol-intermediate **2aI** in the absence of benzhydrylamine **3a**. Attempts to isolate **2aI** were unsuccessful due to the inherent reactivity of the compound. Encouraged by this, **2aI** was reacted with simple nucleophiles to provide the corresponding coupling products (Scheme 2b). We were pleased that thiophenol reacted smoothly forming **4aa** in 83% yield. Introducing other nucleophiles such as water, methanol, phenol and chloride also afforded the corresponding α-functionalized products **5**,**6** in moderate yields under unoptimized reaction conditions. It is worthwhile to reiterate that oxidative umpolung strategies are typically restricted to nucleophilic coupling partners that are not prone to oxidation. The presented one-pot procedure allows for coupling of nucleophiles known to be incompatible with oxidants such as DDQ (e.g. phenols and thiols). It is also noteworthy that the reaction concept allows the presence of oxidant in tandem with nucleophiles that are not prone to oxidation by DDQ. While the presented methodology permits the coupling of several nucleophiles, we have decided to focus on thiols. A general oxidative thiolation based on readily available thiols is a valuable goal given the ubiquity and importance of the thioether functionality in nature.[12] Traditionally, organocatalytic methodologies available for the preparation of α-sulfur-functionalized carbonyl compounds have been reactions involving electrophilic sulfenylation reagents.[12] Therefore, these have been restricted to classical enamine-electrophile couplings, limiting the thioether moiety to the nature of electrophilic sulfur reagents. Thus, it has a significant impact if one can overcome the incompatibility of thiols to oxidative conditions as this allows the coupling of thiols inaccessible using sulfenylation strategies.

To examine the potential of quinol-intermediates as electrophilic synthons for an α-thiolation strategy, various thiols were tested (Scheme 3a). Quinol-intermediate **2dI**, derived from aminocatalyzed DDQ-promoted oxidation of 2-phenylpropanal **1d**, was chosen as the coupling partner to generate a scope using only commercially available reagents. Aliphatic thiols such as ethylthiol gave thioether **4bd** in 66% yield. Sterically demanding aliphatic thiols also reacted and led to formation of **4cd**–**ed** in similar yields, while benzyl thiol provided **4fd** in 87%. It was observed that the thiolation rate decreases and prolonged reaction times are needed to ensure full consumption of the quinol-intermediate as the steric bulk of the thiol is increased (see the Supporting Information).

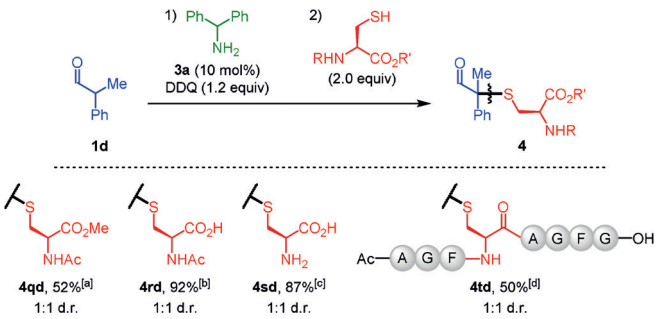


Scheme 3. a) Oxidative coupling of 2-phenylpropanal **1d** with thiols. Performed on 0.20 mmol scale. [a] 3.0 equiv of ethylthiol were used. b) Oxidative coupling of aldehydes **1** with thiophenol. Performed on 0.20 mmol scale. [b] 20 mol% of **3a** were used. [c] (±)-3,3-Dimethyl-1-morpholinobutane-2-amine, **(±)-3b**, was used as the aminocatalyst. [d] Fluoranil was used as the oxidant. [e] Thiophenol was added in two portions. [f] 20 mol% of **(±)-3b** were used.

Substituted thiophenols afforded the desired thioether products **4gd–pd** in good to high yields (67–90%). *Ortho*-, *meta*-, and *para*-substituted thiophenols were tolerated and gave similar yields (compare **4gd–id** and **4jd–ld**). Both electron-rich and electron-poor thiophenols also reacted, though lower reactivity was observed for the more electron-poor variants (**4kd** and **4md–pd**), suggesting an electronic influence on the nucleophilic displacement step. To summarize, both aliphatic and aromatic, as well as very sterically hindered thiols reacted smoothly under these organocatalytic oxidative coupling conditions with aldehyde **1d**.

Next, we turned our attention toward exploring the aldehyde scope using thiophenol as the standard nucleophile (Scheme 3b). Unsubstituted 2-phenylpropanal **1d** smoothly provided 2-phenyl-2-(phenylthio)propanal **4ad** in 82% yield. A library of 2-arylpropanals containing electron-donating and withdrawing groups was tested under the reaction conditions. Substituents in *ortho*-, *meta*-, and *para*-positions were tolerated, as demonstrated with Me-substituted aldehyde derivatives **1f–h** which afforded the thioethers **4af–ah** in 67–89% yield. Both electron-poor and electron-rich aryl substituents gave the desired products **4aa–am** in 67–94% yield. In the case of the electron-rich aldehyde derivatives **1a–c**, the DDQ quinol-intermediates were found to undergo undesired dehydrogenations affording α,β-unsaturated aldehydes as byproducts due to their increased reactivity. This undesired reactivity was suppressed by employing the less activated quinone fluoranil, which still provided substitution-active intermediates **2aIII-cIII** and formation of thioethers **4aa–ac** in 80–84% yield. The α-thiolation strategy can also be applied to a broader class of acetaldehydes. 2-Phenylbutanal **1n** smoothly underwent conversion and gave thioether **4an** in 75% yield. Diaryl- and dialkyl-substituted acetaldehydes, such as diphenylacetaldehyde **1o** and isobutyraldehyde **1p**, also afforded products **4ao** and **4ap** in 67% and 66% yield. Furthermore, phenylacetaldehyde **1q** and 2-(3-methoxyphenyl)acetaldehyde **1r** gave the desired tertiary substituted thioethers. However, it was necessary to implement a one-pot $NaBH_3CN$ reduction following the thiophenol addition due to the instability of the thioethers. This provided alcohols **4aq** and **4ar** in 48% and 50% yield, respectively. As a part of the mechanistic investigation, cyclopropyl acetaldehyde **1s** was included in the scope and tested under the reaction conditions. It is notable, that the coupling occurred without ring-opening of the cyclopropyl moiety to afford thioether **4as** in 53% yield, indicating a non-radical intermediate (see below). To summarize, both aliphatic and aromatic, as well as α-branched and linear aldehydes provided all the desired thioethers in good to high yields under the standard reaction conditions.

Encouraged by the broad tolerance towards the various thiols, we envisioned that the methodology might allow for functionalization of biologically relevant thiols, such as cysteine derivatives (Scheme 4). *N*-Acetyl-L-cysteine methyl ester reacted smoothly to give the cysteine-coupled product. To ease the purification, a one-pot $NaBH_3CN$ reduction was employed to give alcohol **4qd** in an overall 52% yield and 1:1 d.r. Inspired by this, protected and unprotected cysteine derivatives were also tested and both *N*-acetyl-L-cysteine and



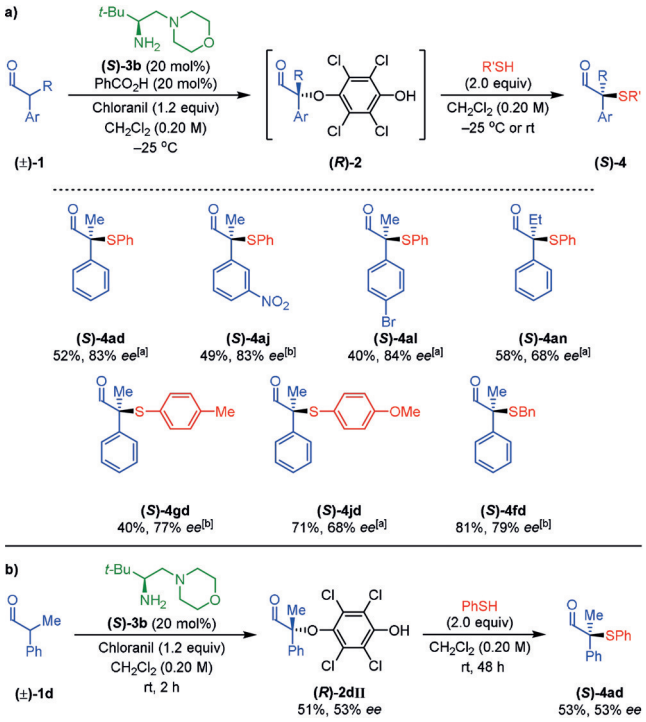
Scheme 4. Oxidative coupling of 2-phenylpropanal **1d** with cysteine derivatives and a peptide. [a] Yield was determined after $NaBH_3CN$ reduction and purification of the corresponding alcohol. d.r. was determined on the crude reaction mixture prior to reduction. [b] Yield and d.r. were measured by ^{1}H NMR analysis of the crude reaction mixture relative to an internal standard (1,3,5-tris(trifluoromethyl)benzene). [c] After full consumption of **1d**, the reaction mixture was concentrated and redissolved in TFA prior to addition of the cysteine derivative; yield and d.r. were measured by ^{1}H NMR analysis of the crude reaction mixture relative to an internal standard (methyl 4-methyl-3-nitrobenzoate). [d] Octapeptide was used as limiting reagent, and added after the crude reaction mixture was redissolved in TFA; yield and d.r. were measured by ^{1}H NMR analysis of the crude reaction mixture relative to an internal standard (methyl 4-methyl-3-nitrobenzoate).

L-cysteine underwent the oxidative coupling chemoselectively affording **4rd** and **4sd**. We were pleased, that the reaction concept could be extended to afford bioconjugates, as exemplified by the coupling of an octapeptide (**4td**).

In light of the developed aminocatalyzed oxidative thiolation strategy, we aimed to demonstrate that the concept might have the potential to also proceed as an enantioselective variant.

Nucleophilic substitution at a quaternary stereocenter is a major synthetic challenge and only very few enantioselective examples have been reported with thiols, despite the importance of quaternary thioethers in biological and medicinal chemistry.[13] To the best of our knowledge, no one-pot enantioselective α-thiolation of racemic carbonyl compounds has been disclosed.[11,14] Screening of aminocatalysts and quinones provided reaction conditions (see the Supporting Information) that afforded moderate to high enantioselectivities for the formation of various thioethers **4** using aminocatalyst (*S*)-3,3-dimethyl-1-morpholinobutan-2-amine, **(*S*)-3b**, chloranil as the oxidant, and a benzoic acid additive (Scheme 5a). We were pleased to find that aldehydes **(±)-1d,j,l,n** allowed for the formation of optically active thioethers **(*S*)-4ad,aj,al,an,fd,gd,jd** in 40–81% yield and 68–84% *ee*. The stereochemistry of **(*S*)-4ad** was assigned by X-ray crystallography, and the remaining thioethers were assigned by analogy (see the Supporting Information).[19]

In order to obtain further insight into the thiolation step, we focused the attention on isolating the enantiomeric enriched quinol-intermediates formed by chloranil promoted oxidation of aldehydes **(±)-1** in the presence of aminocatalyst **(*S*)-3b**. We were pleased that quinol-intermediate **(*R*)-2dII** could be isolated in practical quantities. The absolute configuration of **(*R*)-2dII** was assigned based on calculated



Scheme 5. a) Enantioselective organocatalytic procedure for the synthesis of optically active thioethers **4**. Performed on 0.20 mmol scale, and *ee* was determined by chiral stationary phase ultra performance convergence chromatography (UPC^2). [a] Thiol addition was performed at −25 °C. [b] Thiol addition was performed at rt. b) Stereospecific transformation of isolated *O*-bound quinol-intermediate **(*R*)-2dII** to thioether **(*S*)-4ad**. *ee* was determined by chiral stationary phase UPC^2.

electronic circular dichroism (ECD) spectra and compared with experimental results (see the Supporting Information). The reactivity of isolated quinol-intermediate **(*R*)-2dII** was evaluated under the reaction conditions and treated with thiophenol in the absence of catalyst **(*S*)-3b** (Scheme 5b). This led to formation of the thioether **(*S*)-4ad** in 53% yield. Interestingly, the substitution was stereospecific as the enantiomeric excess of **(*R*)-2dII** (53% *ee*) was maintained in **(*S*)-4ad** (see the Supporting Information for specific details). This demonstrates that the enantioselectivity originates from the formation of **2dII** and is transferred in the subsequent thiolation event, thus under these reaction conditions, the substitution step does not involve stereoinduction by the aminocatalyst.

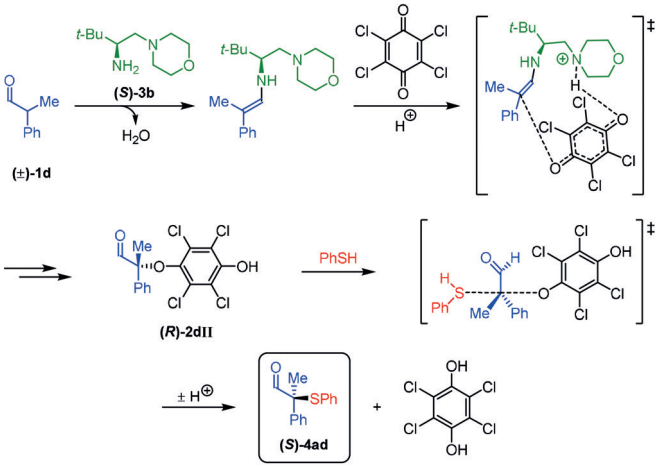
In an attempt to understand the mechanism and the stereochemical implications, further investigations were performed. Key empirical observations reveal insights into the reaction mechanism. Single-electron oxidation processes accountable for previously disclosed couplings[3a,c] were limited to electron-rich aldehydes whereas the present work also proceeds very well for electron-poor aldehydes. For example, oxidation of enamines derived from 2-arylpropanals **1d–n** and isobutyraldehyde **1p** proceeds smoothly in the presence of DDQ and at comparable rates of formation. Thus varying the electronic nature of the aldehyde has a limited effect on the extent of oxidation. In fact, these aldehydes were incapable of product formation in the aforementioned single-electron oxidation couplings, indicating that a different oxidation pathway may be operational when using quinones as oxidants. Evidence in favor of a two-electron pathway includes, specifically, the formation of covalent *O*-bound quinol-intermediates prior to the nucleophilic coupling. As for the thiolation event, isolated *O*-bound quinol-intermediates **2dI**,**hI**,**dII** react with thiophenol to afford the corresponding thioether products **4ad**,**ah** in the absence of additives. This observation suggests that the aminocatalyst is not essential for the substitution step (Scheme 5b). In addition, as the steric bulk of the thiol is increased, the thiolation rate decreases and prolonged reaction times are needed to ensure full consumption of the quinol-intermediates. Similar decrease in reactivity is observed when comparing electron-rich thiophenols to electron-poor analogues (see above). Prolonged reaction times were also observed when decreasing the equivalents of thiol indicating a non-zero order dependence of the thiol nucleophile (see Figure S5, p. 37 in the Supporting Information). These observations indicate a dependence of both steric and electronic properties, as well as concentration of thiol, on the rate of substitution. Furthermore, we have demonstrated that the conversion of isolated quinol-intermediate **(*R*)-2dII** to thioether **(*S*)-4ad** conserved the enantiomeric excess of the intermediate, thus pointing to a stereospecific transformation independent of the aminocatalyst. On the basis of these experimental results, the thiol substitution appears to proceed via an unusual bimolecular pathway with inversion of configuration.

Multiple mechanistic scenarios can be envisioned. Given the ability of bulky thiols, such as *tert*-butyl thiol and 1-adamantanethiol, to displace the quinol moiety, led us to consider a radical-type substitution reaction. These have previously been observed for substitution of quaternary benzylic and α-carbonyl positions.[15,16] To probe for potential radical pathways, common inhibitors of such reactivities[16] were tested by forming quinol-intermediate **2dI** under the general reaction conditions and monitoring the thiolation in the presence of various inhibitors (see the Supporting Information). Most challenging is the inherent reactivity of the thiols towards commonly employed radical trapping reagents, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), galvinoxyl and O_2, which makes in situ studies of the thiolation event biased in their presence.

In the absence of light, the addition of thiophenol to the *O*-bound quinol-intermediate **2dI** underwent smoothly, thus excluding light promoted radical propagation to account for the reactivity. Reactions in CH_2Cl_2 saturated with O_2 and under an O_2 atmosphere proceeded well, albeit with slightly prolonged reaction time. Addition of *p*-dinitrobenzene, a strong electron acceptor, and the radical trap galvinoxyl, did not suppress the thiolation. The thiolation also proceeded smoothly in the presence of 3,5-di-*tert*-butyl-4-hydroxytoluene (BHT). Attempted trapping of intermediate **2dI** by addition of TEMPO, in the absence of excess DDQ and thiophenol did not afford any consumption of **2dI**. Finally, cyclopropyl derivative **1s** afforded the corresponding quinol-intermediate **2sIII** and underwent thiolation without ring-opening of the cyclopropyl moiety (see above). In summary, all attempts to trap a radical species as the reactive

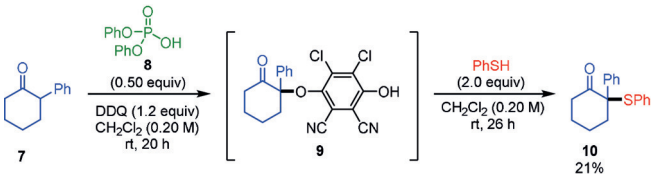
intermediate proved inconclusive since no trapping adducts were observed, and the thiolation was not inhibited by the presence of known radical inhibitors, regardless of minor rate attenuations.

The formation of thioethers from thiol addition to the *O*-bound quinol-intermediates points to a rare event: a nucleophilic bimolecular substitution at a quaternary stereocenter with inversion of configuration. Leaving groups at quaternary centers adjacent to carbonyls are known to be activated and have previously been described to undergo stereospecific nucleophilic substitution, albeit very few examples are reported.[11,14,17] The activation of quaternary α-substituted carbonyl compounds towards nucleophilic substitution is a fundamental discussion addressed by several authors.[18] Based on this, several key characteristics in the presented concept make an S_N2-type displacement feasible. The electron-withdrawing effect of the aldehyde moiety deactivates the intermediate towards S_N1 reactivity, as well as increasing the electrophilic character of the α-position, and the planarity of the carbonyl may better accommodate the sterically demanding transition state required for an S_N2 displacement compared to classic quaternary centers. As for the initial interaction between the thiol and quinol-intermediate, multiple scenarios may be envisioned. Depending on the substrate, electrostatic as well as covalent interactions with the carbonyl substituent have been postulated to account for the increased activation of quaternary α-substituted carbonyl compounds towards nucleophilic substitution.[18] It is uncertain if such interactions are promoters of this unprecedented thiolation reaction and we can not exclude, that the reaction might proceed by a nucleophilic attack to the carbonyl carbon atom, followed by a 1,2-shift to the achieve substitution at the quaternary carbon.[18b] To account for the experimentally observed stereochemistry, a mechanistic proposal for **(*S*)-3b**-promoted oxidation of **(±)-1d** to give quinol-intermediate **(*R*)-2dII**, and sequential thiolation to provide **(*S*)-4ad**, is outlined in Scheme 6.



Scheme 6. Proposed mechanism for the stereoselective formation of **(*S*)-4ad**. Reaction model to account for the enantioselective, enamine-promoted oxidation of **(±)-1d** and the observed stereospecific inversion in the thiolation of quinol-intermediate **(*R*)-2dII**.

In light of the recent phosphoric acid catalyzed formation of *O*-bound quinol-adducts from α-substituted cyclohexanones and unactivated quinones, disclosed by List et al.,[8] we were encouraged to investigate ketone substrates. Curiously, the authors did not observe the desired quinol-adduct when using DDQ as oxidant. However, we found that 2-phenylcyclohexanone **7** can be oxidized in the presence of DDQ and phosphoric acid catalyst **8**, and sequential addition of thiophenol provided the desired thioether **10** in 21% yield (Scheme 7). This result highlights the potential of the presented quinone-promoted umpolung strategy since it can be extended to other organocatalytic HOMO-raising strategies, thus enabling α-functionalization on a broader class of substrates.



Scheme 7. Reaction performed on 0.20 mmol scale (unoptimized conditions, see the Supporting Information).

Conclusion

In summary, we have disclosed a new oxidative strategy based on enamine catalysis merged with quinones as oxidants to access α-substituted *O*-bound quinol adducts as substitution-active intermediates allowing for coupling of nucleophiles. The approach is simple and enables a general α-thiolation of a broad selection of aldehydes in moderate to high yields. The study underscores a stereoselective oxidation and subsequent transfer of chirality by nucleophilic displacement at a quaternary center, accounting for the observed enantioselectivities. We are confident that the methodology bears great potential for a variety of functionalizations and for the development of their asymmetric variants, as well as an alternative approach for bioconjugation.

Acknowledgements

This work was made possible by generous support from Carlsberg Foundation "Semper Ardens", FNU, Aarhus University. K.A.J. was funded by a Villum Investigator grant (no. 25867) from The Villum Foundation. H.N.T. thanks Novo Nordisk for a PhD grant. We thank Frank Jensen for guidance on computational ECD analysis as well as Jacob Overgaard and Mathias Kirk Thøgersen for performing X-ray analysis.

Conflict of interest

The authors declare no conflict of interest.

Keywords: bioconjugation · enantioselective α-thiolation · organocatalysis · oxidative thiolation · umpolung

How to cite: *Angew. Chem. Int. Ed.* **2019**, *58*, 17856–17862
Angew. Chem. **2019**, *131*, 18020–18026

[1] L. Zhu, D. Wang, Z. Jia, Q. Lin, M. Huang, S. Luo, *ACS Catal.* **2018**, *8*, 5466–5484.

[2] a) T. D. Beeson, A. Mastracchio, J. B. Hong, K. Ashton, D. W. C. MacMillan, *Science* **2007**, *316*, 582–585; b) H. Y. Jang, J. B. Hong, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2007**, *129*, 7004–7005; c) T. H. Graham, C. M. Jones, N. T. Jui, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 16494–16495; d) H. Kim, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2008**, *130*, 398–399; e) J. E. Wilson, A. D. Casarez, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 11332–11334; f) M. Amatore, T. D. Beeson, S. P. Brown, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2009**, *48*, 5121–5124; *Angew. Chem.* **2009**, *121*, 5223–5226; g) J. M. Um, O. Gutierrez, F. Schoenebeck, K. N. Houk, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 6001–6005; h) N. T. Jui, J. A. O. Garber, F. G. Finelli, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2012**, *134*, 11400–11403.

[3] a) L. Næsborg, L. A. Leth, G. J. Reyes-Rodríguez, T. A. Palazzo, V. Corti, K. A. Jørgensen, *Chem. Eur. J.* **2018**, *24*, 14844–14848; b) L. Næsborg, V. Corti, L. A. Leth, P. H. Poulsen, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2018**, *57*, 1606–1610; *Angew. Chem.* **2018**, *130*, 1622–1626; c) L. A. Leth, L. Næsborg, G. J. Reyes-Rodríguez, H. N. Tobiesen, M. V. Iversen, K. A. Jørgensen, *J. Am. Chem. Soc.* **2018**, *140*, 12687–12690; d) N. M. Rezayee, V. H. Lauridsen, L. Næsborg, T. V. Q. Nguyen, H. N. Tobiesen, K. A. Jørgensen, *Chem. Sci.* **2019**, *10*, 3586–3591.

[4] a) M. Lemaire, J. Doussot, A. Guy, *Chem. Lett.* **1988**, *17*, 1581–1584; b) M. Bouquet, A. Guy, M. Lemaire, J. P. Guette, *C. R. Acad. Sci. Ser. II* **1984**, *299*, 1389–1390; c) A. Guy, A. Lemor, D. Imbert, M. Lemaire, *Tetrahedron Lett.* **1989**, *30*, 327–330; d) A. Guy, J. Doussot, M. Lemaire, *Synthesis* **1991**, 460–462.

[5] A. E. Wendlandt, S. S. Stahl, *Angew. Chem. Int. Ed.* **2015**, *54*, 14638–14658; *Angew. Chem.* **2015**, *127*, 14848–14868.

[6] a) A. Bhattacharya, L. M. Dimichele, U. H. Dolling, A. W. Douglas, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1988**, *110*, 3318–3319; b) A. Bhattacharya, L. M. DiMichele, U. H. Dolling, E. J. J. Grabowski, V. J. Grenda, *J. Org. Chem.* **1989**, *54*, 6118–6120.

[7] a) X. Guo, H. Mayr, *J. Am. Chem. Soc.* **2013**, *135*, 12377–12387; b) X. Guo, H. Mayr, *J. Am. Chem. Soc.* **2014**, *136*, 11499–11512.

[8] G. A. Shevchenko, B. Oppelaar, B. List, *Angew. Chem. Int. Ed.* **2018**, *57*, 10756–10759; *Angew. Chem.* **2018**, *130*, 10916–10919.

[9] For the first proposal of an *O*-bound quinol adduct as electrophilic intermediate in a substitution reaction (no experimental evidence of such an intermediate was disclosed) see: H.-D. Becker, *J. Org. Chem.* **1965**, *30*, 989–994.

[10] V. S. Batista, R. H. Crabtree, S. J. Konezny, O. R. Luca, J. M. Praetorius, *New J. Chem.* **2012**, *36*, 1141–1144.

[11] Shibatomi et al. recently disclosed a two-step procedure where α-chloro-β-keto ester products were isolated form a Cu^{II} catalyzed α-chlorination. A subsequent nucleophilic substitution of the chloride by nucleophiles provided α-functionalized-β-keto esters, albeit the concept was limited to azide, fluoride, and only two examples of alkyl thiols: K. Shibatomi, Y. Soga, A. Narayama, I. Fujisawa, S. Iwasa, *J. Am. Chem. Soc.* **2012**, *134*, 9836–9839.

[12] P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.* **2014**, *114*, 8807–8864.

[13] J.-S. Yu, H.-M. Huang, P.-G. Ding, X.-S. Hu, F. Zhou, J. Zhou, *ACS Catal.* **2016**, *6*, 5319–5344.

[14] J. Clayden, P. MacLellan, *Beilstein J. Org. Chem.* **2011**, *7*, 582–595.

[15] G. A. Russell, F. Ros, *J. Am. Chem. Soc.* **1985**, *107*, 2506–2511.

[16] W. R. Bowman, *Chem. Soc. Rev.* **1988**, *17*, 283–316.

[17] a) E. J. Corey, T. H. Lowry, *Tetrahedron Lett.* **1965**, *6*, 793–801; b) J. E. Green, D. M. Bender, S. Jackson, M. J. O'Donnell, J. R. McCarthy, *Org. Lett.* **2009**, *11*, 807–810; c) J. D. Weaver, D. K. Morris, J. A. Tunge, *Synlett* **2010**, 470–474.

[18] a) J. W. Thorpe, J. Warkentin, *Can. J. Chem.* **1973**, *51*, 927–935; b) M. Hannaby, S. Warren, *J. Chem. Soc. Perkin Trans. 1* **1989**, 303–311.

[19] Crystallographic data for the structures of **(±)-2dII** and **(*S*)-4ad** are available free of charge from The Cambridge Crystallographic Data Centre under references CCDC 1916306 and 1916307, respectively.

Manuscript received: September 15, 2019
Revised manuscript received: October 2, 2019
Accepted manuscript online: October 9, 2019
Version of record online: October 24, 2019

