Asymmetric Catalysis

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Formal Asymmetric Catalytic Thiolation with a Bifunctional Catalyst at a Water–Oil Interface: Synthesis of Benzyl Thiols**

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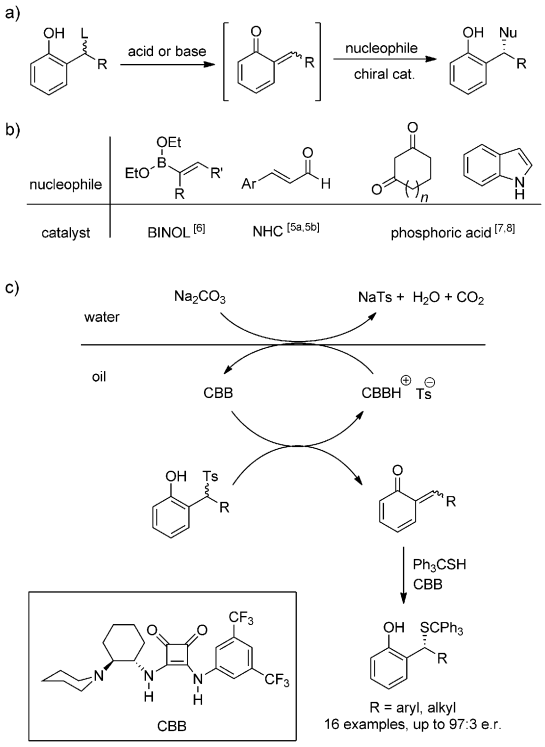
Abstract: *The enantioselective conjugated addition of trityl-thiol to in situ generated ortho-quinone methides (o-QMs) is catalyzed by an acid–base bifunctional squaramide organocatalyst. The transformation proceeds with high yield (up to 99%) and stereoselectivity (up to 97:3 e.r.) using water as solvent under mild conditions. The catalyst system provides a new strategy for the synthesis of optically active benzyl mercaptans. Control experiments suggested that o-QMs are generated by the tertiary amine moiety of the squaramide organocatalyst and that the water–oil biphase is crucial for achieving high reactivity and stereoselectivity.*

Ortho-Quinone methides (*o*-QMs) are important intermediates in a number of biological processes,[1] and have been identified as active species in many chemical reactions.[2] However, despite their broad synthetic utility, only very few catalytic systems have been reported to date on the enantioselective addition to *o*-QMs (Scheme 1). In this context, Sigman and co-workers reported Pd-catalyzed enantioselective dialkoxylation and carboalkoxylation reactions of vinyl phenols through the formation of a quinone methide intermediate.[3] Chiral organocatalysts, including quaternary ammonium salts,[4] N-heterocyclic carbenes,[5] and chiral BINOL,[6] have been employed to activate various nucleophiles for the [4+2] cycloaddition, the [4+3] cycloaddition, and the conjugated addition to *o*-QMs, respectively (Scheme 1). Most recently, chiral phosphoric acids have been used as highly enantioselective bifunctional catalysts for the conjugate addition of β-dicarbonyl compounds[7] and indoles[8] to in situ generated *o*-QMs (Scheme 1). Despite these important advances, a vital issue to most of the reported reaction systems is that the substrate scope of *o*-QMs has generally been limited to either aryl- or alkyl-substituted *o*-QMs. Moreover, the asymmetric catalytic addition of heteroatom nucleophiles to *o*-QMs has been rarely explored.[3] Therefore, it is highly desirable to develop new catalytic systems with broad substrate scope for enantioselective additions to *o*-QMs.



Scheme 1. Asymmetric catalytic reactions with in situ generated *o*-QMs. a) General reaction. b) Previous work on organocatalytic systems. c) This work: chiral organic base catalyzed asymmetric conjugate of thiol to in situ generated *o*-QMs on a water–oil interface. The use of a water–oil diphasic system suppressed the background reaction. CBB = chiral bifunctional base.

In the past years, various chiral organic bases and especially those with hydrogen bond donors (acid–base bifunctional) have emerged as readily available, highly versatile and extremely powerful organocatalysts in asymmetric synthesis.[9] However, to our knowledge, no catalytic system based on a chiral organic base has been reported for the reaction involving *o*-QMs. This may be attributed to the fact that reactive *o*-QMs are often generated in situ from various precursors with the assistance of either acid or base, which are not compatible with catalysts based on organic bases or may provide racemic products as a result of a significant background reaction. As a part of our continuing efforts to develop organocatalytic reactions in aqueous media,[10] we envisioned that an oil–water biphasic reaction system might be advantageous in realizing the spatial separation between a) the organic-base catalyst and reactants in the organic phase, and b) the inorganic base in the aqueous phase, and thus to suppress the racemic background reaction.

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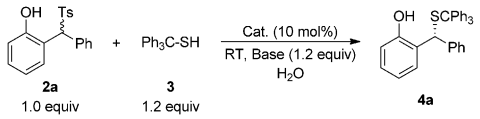
In such a system, an acid–base bifunctional organic catalyst may achieve good chiral induction in the asymmetric reaction of the *o*-QMs through the simultaneous electrophilic activation of *o*-QMs by hydrogen-bonding interactions and activation of the nucleophile by deprotonation by the base (Scheme 1).[11]

With this concept in mind, we envisaged that an asymmetric catalytic reaction of *o*-QMs with sulfur nucleophiles would provide access to chiral α-aryl- or α-alkyl-substituted benzyl mercaptans (Scheme 1). These sulfur-containing structural units are widely found in biologically interesting compounds[12] and in protected reagents for the synthesis of chiral metal clusters.[13] Currently, such thiol compounds are mainly accessible through O–S exchange using chiral benzyl alcohols as the starting materials.[14] This reaction will supply a unique catalytic method for the enantioselective synthesis of both α-aryl- and α-alkyl-substituted benzyl mercaptans, as sulfa-Michael additions,[15] sulfa-1,2 additions,[16] sulfa-allylations,[17] and the kinetic resolution of thiols[18] generally do not afford α-aryl-substituted benzyl mercaptans. We report herein the first conjugate addition of tritylthiol to in situ generated *o*-QMs catalyzed by a chiral organic base with good to excellent enantioselectivities (91:9–97:3 e.r.) using water as the solvent. Moreover, this catalytic system tolerates various substrate precursors in the in situ generation of both aryl- and alkyl-substituted *o*-QMs. The spatial separation between the compounds in the inorganic and organic phase was crucial for achieving the high reactivity and stereoselectivity.

2-(Tosylmethyl)phenols **2** were chosen as the substrates, as they had been employed previously as the precursors for the in situ formation of *o*-QMs under basic conditions.[19] Tritylthiol (**3a**) was chosen as the sulfur nucleophile, because the trityl group in products **4** could be readily cleaved under mild conditions to unmask the thiol functionality. In our initial test, we examined the reaction between 2-(phenyl-(tosyl)methyl)phenol (**2a**) and **3a**, using Na_2CO_3 (1.2 equiv) as the inorganic base and water as the solvent. A trace amount of methylene chloride was added to fully dissolve the substrates. In the absence of an organic base, the reaction proceeded slowly at room temperature to 65% conversion in 48 h (Table 1, entry 1). When a catalytic amount of Et_3N (10 mol%) was added to the reaction system as the organic base, the reaction proceeded to the corresponding racemic product with almost full conversion after 12 h (Table 1, entry 2).

Encouraged by this result, we continued to examine the catalytic potential of some well-established bifunctional organocatalysts (Figure 1), including *Cinchona* alkaloid-derived thiourea (**1a**) and squaramide catalysts (**1b**–**1d**). Quinidine-derived thiourea **1a** exhibited high catalytic activity, completing the reaction in 12 h, but the desired product **4a** was obtained with only a moderate e.r. of 65:35 (Table 1, entry 3). To our delight, quinidine-derived squaramides **1b**–**d** significantly improved the enantioselectivities without loss of activities (Table 1, entries 4–6). Catalyst **1d** with a 3,5-bis(trifluoromethyl)benzene substituent led to an e.r. of 93:7. To further improve the enantioselectivity, chiral (*R*,*R*)-cyclohexane-1,2-diamine-derived thiourea or squaramide catalysts **1e** and **1h**[20] were also evaluated, the latter of which provided

Table 1: Optimization of reaction conditions.[a]



Entry	Cat.	Base	*t* [h]	Conv. [%][b]	e.r.[c]
1	No	Na_2CO_3	48	65	–
2	Et_3N	Na_2CO_3	12	>95	–
3	**1a**	Na_2CO_3	12	>95	65:35
4	**1b**	Na_2CO_3	12	>95	91:9
5	**1c**	Na_2CO_3	12	>95	79:21
6	**1d**	Na_2CO_3	12	>95	93:7
7	**1e**	Na_2CO_3	12	60	77:25
8	**1f**	Na_2CO_3	12	>95	93.5:6.5
9	**1g**	Na_2CO_3	12	>95	84:16
10	**1h**	Na_2CO_3	12	>95	96:4
11	**1h**	$NaHCO_3$	12	75	93.5:6.5
12	**1h**	NaOAc	12	45	91.5:8.5
13	**1h**	NaOH	4	>95	81:19
14	**1h**	Cs_2CO_3	4	>95	95.5:4.5
15[d]	**1h**	Na_2CO_3	36	>95(93)	92.5:7.5

[a] Unless otherwise specified, all reactions were conducted with **2a** (0.1 mmol), tritylthiol (**3a**, 1.2 equiv, 0.12 mmol), and catalyst (0.01 mmol, 10 mol%) in water (1 mL, 50 μL CH_2Cl_2 added to dissolve the substrates) at room temperature. [b] Determined by ^{1}H NMR spectroscopy of the crude mixture; the data in parentheses are the yields of isolated products after column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase (Daicel Chiralpak AD-H column). [d] Catalyst loading: 2 mol%, **2a**: 0.4 mmol.

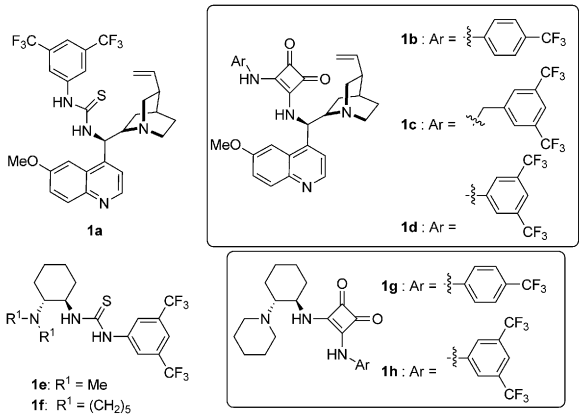
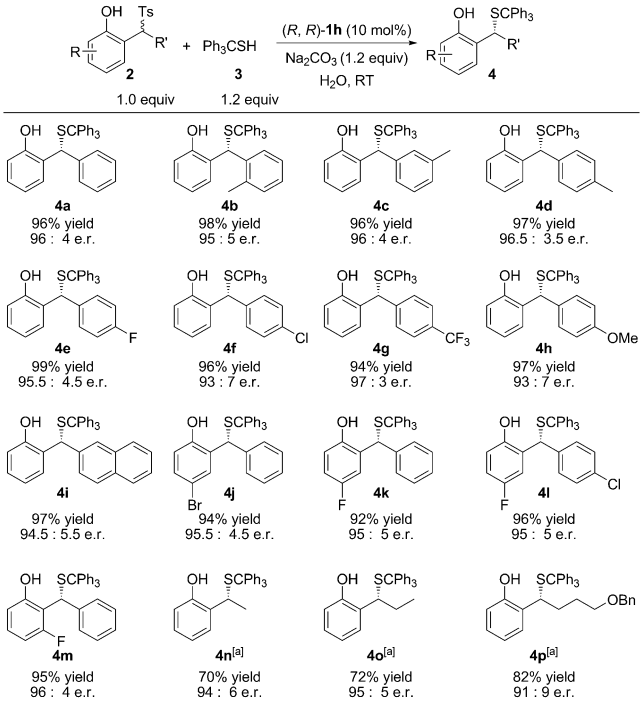


Figure 1. Chiral bifunctional organocatalysts employed in this study.

access to **4a** in 96:4 e.r. (Table 1, entry 10). Several other inorganic bases were then investigated, which displayed a significant effect on the reactivity and enantioselectivity. For example, the reactions using weaker bases, such as $NaHCO_3$ or NaOAc, furnished products with lower reactivities and enantioselectivities (Table 1, entries 11 and 12 versus 10), whereas stronger inorganic bases, such as NaOH and Cs_2CO_3, led to much higher reactivities (full conversion in 4 h), albeit with lower enantioselectivities (Table 1, entries 13 and 14 vs. 10). To further explore the efficiency of this catalytic system, the model reaction was carried out with a reduced catalyst loading (2 mol%), thereby affording **4a** in

93% yield with 85% *ee* by prolonging the reaction time to 36 h (Table 1, entry 15).

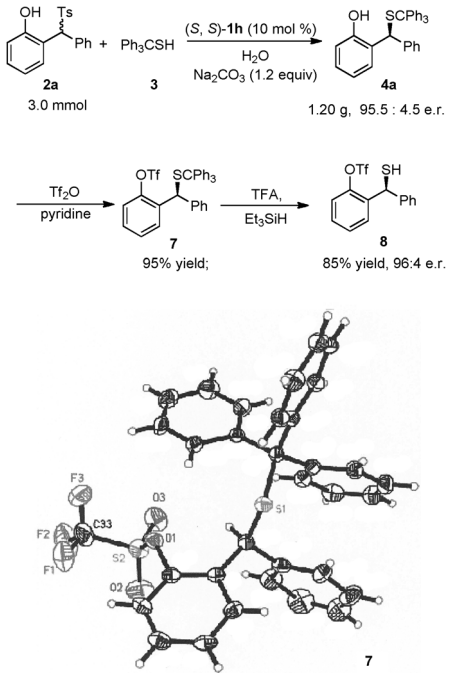
Subsequently, we explored the generality of the organocatalytic asymmetric thiol addition with a variety of in situ generated *o*-QMs. The use of catalyst **1h** was extended to the reactions of **3a** with different 2-(tosylmethyl)phenols **2b–o** under optimized conditions. As shown in Scheme 2, the



Scheme 2. Substrate scope. Reaction conditions: **2** (0.2 mmol), trityl-thiol (**3a**, 1.2 equiv, 0.24 mmol), and catalyst (*R*, *R*)-**1h** (0.02 mmol, 10 mol%) in water (2 mL; 100 μL CH_2Cl_2 added to dissolve the substrates) at RT for 12 h. The yields of isolated products were determined after column chromatography on silica gel. The e.r. was determined by HPLC analysis on a chiral stationary phase. [a] Solvent: 1 mL CH_2Cl_2 and 100 μL H_2O, reaction time: 36 h.

reaction of **3a** with other aryl-substituted 2-(tosylmethyl)-phenols furnished the corresponding products **4b–4i** in excellent yields with up to 97:3 e.r. A methyl substituent at different positions of the phenyl moiety of the 2-(tosylmethyl)phenols had little impact on the enantioselectivity of the reaction, and the corresponding products **4b–d** were obtained with high yields (96–98%) and excellent enantioselectivities (95:5 to 96.5:3.5 e.r.). Regardless of the electron-donating (Me, OMe) or electron-withdrawing (F, Cl, CF_3) nature of the *para* substituent on the phenyl moiety of the 2-(tosylmethyl)phenol substrates, the corresponding products **4d–h** were obtained in up to 99% yield with 93:7 to 97:3 e.r. The reaction of **3a** with 2-(naphthalen-2-yl(tosyl)methyl)-phenol also provides product **4i** with high yield (97%) and excellent enantioselectivity (94.5:5.5 e.r.). Moreover, a substituent at the quinone methide fragment was tolerated as well, and the corresponding adducts **4j–m** were obtained in almost quantitative yields and 95:5 to 96:2 e.r. To our delight, alkyl-substituted 2-(tosylmethyl)phenols were also demonstrated to be acceptors amenable to the reaction protocol, giving rise to the corresponding products **4n–p** with enantioselectivities up to 95:5 e.r.

The synthetic utility of this method was demonstrated by the efficient asymmetric synthesis of chiral benzyl mercaptans, starting from the enantioenriched **4a** obtained through the gram-scale reaction using the above procedure with (*S*,*S*)-**1h** as the catalyst (Scheme 3). Protection of the phenolic



Scheme 3. Synthetic transformations of **4** and crystal structure of **7.**

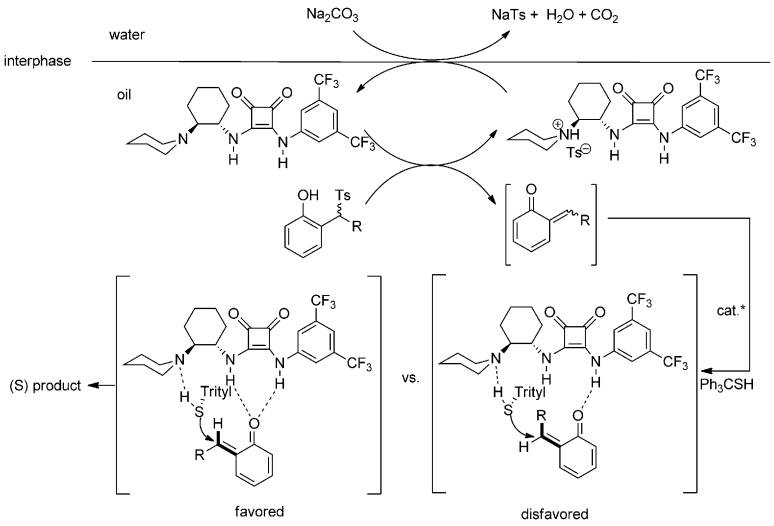
hydroxy group of **4a** with a trifluoromethanesulfonate group, followed by the selective removal of the trityl group, readily delivered chiral benzyl mercaptan **8** in high yield and without loss of enantiopurity. The absolute configuration of compound **7** was unambiguously determined to be (*S*) by X-ray crystallography, thus implying that the absolute configurations of the reaction products shown in Scheme 2 should be *R*.

To clarify the role of water in the reaction, control experiments were performed for the reactions of **2a** and **3a** with catalyst **1h** (Table 2).[21] Using dry methylene chloride as solvent and Na_2CO_3 as the inorganic base, the solid–liquid

Table 2: Control experiments for **1h**-catalyzed asymmetric thiolation of **2a**

Entry	Solvent	Base	Yield [%]	e.r.	State
1	dry CH_2Cl_2	Na_2CO_3	trace	n.d.	solid–liquid biphase
2	H_2O	NaOAc	45	92:8	liquid–liquid biphase
3	H_2O/ CH_2Cl_2	$NaOCOC_{11}H_{23}$	48	61:39	emulsion
4	CH_2Cl_2	Et_3N	98	77:23	homogeneous

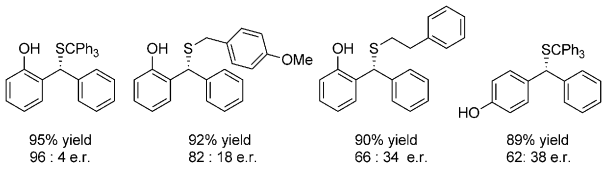
reaction proceeded with much lower reactivity than the one using water as the solvent, thus indicating that water plays an essential role during the reaction. When using sodium laurate as the base instead of Na_2CO_3, an emulsion emerged in the reaction system after the reactants and the catalyst were added and stirred in the mixture of water and methylene chloride. However, the increasing compatibility between the organic phase and sodium laurate facilitated the background reaction that leads to the racemic product. As a result, lower enantioselectivity (61:39 e.r.) was obtained compared with the catalytic result of the liquid–liquid biphasic system when using sodium acetate as the base. These results demonstrated that the use of water as a second phase can effectively realize the spatial separation of the inorganic base from the organic phase. As further evidence to support this concept, the homogeneous reaction of **2a** and **3** catalyzed by **1h** using of Et_3N instead of another inorganic base in methylene chloride led to a moderate enantioselectivity.



Scheme 4. Proposed mechanism of the reaction.

To ascertain which base generates the *o*-QMs, a control experiment was carried out using 1.2 equivalents of **1h** without an inorganic base (see the Supporting Information, page S35). Much higher reactivities than those observed in the reaction using 1.2 equivalents of Na_2CO_3 as base (Table 1, entry 1) indicated that the *o*-QMs might be generated through the deprotonation of the phenolic OH group on substrates **2** by the tertiary amine moiety of **1h**, and that the inorganic base plays a role in regenerating the catalyst. This conclusion was also supported by the reactions between different bases and 2-(tosylmethyl) phenol **2q** derived from sesamol (see the Supporting Information page S35). A higher yield of the stable *o*-QM in the reaction using **1h** as the base compared with the reaction in the presence of Na_2CO_3 as the base confirmed that the *o*-QMs should be generated by the action of tertiary amine **1h**.

On the basis of the above control experiments and the absolute configuration of the products, a plausible reaction mechanism is proposed (Scheme 4). In the organic phase, the *o*-QM is generated by the tertiary amine moiety of **1h**, and the resulting salt reacts with Na_2CO_3 in the aqueous solution, regenerating **1h** in the interfacial region between the aqueous and the organic phase, which may be the rate-determining step. Meanwhile, the acid–base bifunctional catalyst (*S*,*S*)-**1h** activates both the nucleophilic thiol **3** and the (*E*)-*o*-QMs, and **3** attacks the *o*-QMs from the *Si* face (for calculated results, see the Supporting Information, page S34) because of the steric hindrance of the trityl group, thus giving the product *S*-**4a**. To verify the proposed intermediate, thiols with smaller moieties were investigated as nucleophiles in the model reaction (Scheme 5). The thiols bearing larger moieties led to higher enantioselectivities, which demonstrated that a bulky moiety on the thiol plays an important role in the asymmetric induction. Furthermore, the reaction of tritylthiol with *p*-QM afforded poor enantioselectivity (68:23 e.r.), which also proved the rationality of the proposed bifunctional mechanism.



Scheme 5. Control experiments with different thiols.

In conclusion, we developed an enantioselective conjugate addition of thiols to in situ generated aryl- and alkyl-substituted *o*-QMs in good to excellent yields. The reaction is catalyzed by a chiral bifunctional organic base and leads to high enantioselectivities. We also verified that the oil–water interface in our reaction system enabled the spatial separation between the chiral organic components and the inorganic base. We then demonstrated the utility of our process by the efficient synthesis of chiral benzyl mercaptans. This study paves a new route for the reactions involving *o*-QMs, and further extension of this strategy to other nucleophiles are currently in progress in our laboratory.

Keywords: asymmetric catalysis · organocatalysis · *ortho*-quinone methides · thiol addition

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[21] We carried out control experiments with different amounts of water to prove the critical role of the inorganic base in the regeneration of catalyst **1h**. For details, see the Supporting Information, page S36.

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