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Asymmetric Brønsted Acid Catalyzed Substitution of Diaryl Methanols with Thiols and Alcohols for the Synthesis of Chiral Thioethers and Ethers

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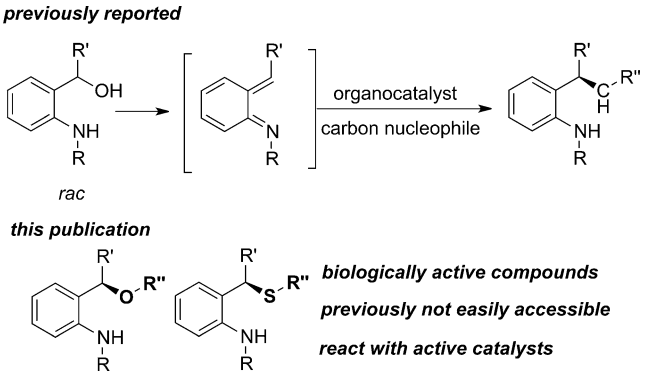
Dedicated to Professor David A. Evans on the occasion of his 75th birthday

Abstract: *An enantioselective addition of thiols and alcohols to aza-ortho-quinone methides, starting from diaryl methanols, was developed. The asymmetric additions occur under mild reaction conditions in the presence of chiral phosphoric acids and furnish the corresponding adducts with excellent yields and enantioselectivities.*

Aza-*ortho*-quinone methides have become an important player in synthetic organic chemistry.[1] The facile access they offer to tetrahydroquinolines and indoles,[2,3] as well as their increasing utilization in complex natural product syntheses (e.g. virantmycin[4] and chartellin[5]), have led to an increased awareness of these scaffolds.[6] Nevertheless, aza-*ortho*-quinone methides, especially compared to their oxygen-containing analogous *ortho*-quinone methides,[7] have not been adequately investigated to date. Particularly in the area of asymmetric synthesis, only a few examples exist.[8]

For the in situ generation of aza-*ortho*-quinone methides various methods have been proven of value, among them the base-induced 1,4-elimination of *ortho*-chloromethyl aniline derivatives,[2–4,9] thermally induced dehydration of benzyl alcohols,[10] and photochemically induced enolizations of *ortho*-carbonyl anilides.[11,12] The variety of possibilities may be surprising; however, in reality it is limited by the predominantly harsh reaction conditions. Many substrates are not compatible with the use of overstoichiometric amounts of base, the exposure to high temperatures (often under flash-vacuum-pyrolysis conditions), or continuous irradiation. Thus often only moderate yields were achieved. Furthermore, numerous reported methods became less attractive due to troublesome substrate syntheses. In this context, the organocatalytic in situ synthesis of aza-*ortho*-quinone methides, starting from diaryl methanols, offers an interesting approach to realize new C–C bond-forming reactions (Scheme 1). Those reactions stand out because of their simple substrate synthesis—benzylic, secondary alcohols can be obtained via Grignard reactions—and the alcohols are prone to very mild dehydration, thereby creating the intermediate aza-*ortho*-quinone methides.



Scheme 1. Application of aza-*ortho*-quinone methides in asymmetric syntheses.

Hence we wondered whether thiols or alcohols could add to aza-*ortho*-quinone methides in an enantioselective manner, thereby forming C–S and C–O bonds (Scheme 1, bottom). In this context, especially the stereoselective formation of C–S bonds is meaningful, as sulfur-containing, chiral compounds can be used not only as ligands in metal-catalyzed reactions,[13] chiral auxiliaries, and organocatalysts,[14] but also as potent drug candidates. On example is the benzothiazepine CGP37157,[15] a potent inhibitor of the mitochondrial sodium/calcium exchange. Another example is CG34068,[16] which prevents the biosynthesis of squalene and may therefore serve as an anti-arteriosclerosis agent and as a cholesterol-lowering drug.

An enantioselective addition of alcohols would be also of great interest, as optically active diaryl methanols and their ether analogues show high biological activity and are also applicable as important synthetic building blocks; one

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example is lapaquistat,[17] an effective squalene synthase inhibitor.

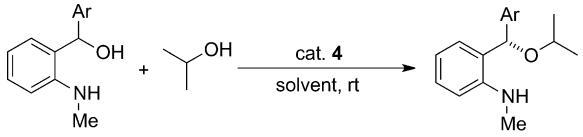
Thus we decided to investigate the enantioselective nucleophilic addition of alcohols and thiols to aza-*ortho*-quinone methides. The challenge in the development of a generally efficient asymmetric synthetic method is to find a suitable catalyst that can distinguish between sterically rather similar aryl substituents of the reactive intermediate and therefore ensures high enantioselectivity. In addition, the catalyst needs to feature an adequately high reactivity to catalyze the dehydration. As alcohols and thiolates are better leaving groups than the products generated by carbon nuclophiles, there is a risk of a direct conversion back to the aza-*ortho*-quinone methide leading to undesired side reactions, if the catalyst is too acidic. At the same time, because of possible deprotonation of the acidic benzylic proton, the catalyst must not be too basic, otherwise the racemic product is obtained. Among the suitable organocatalysts that fulfill the above-mentioned requirements are axially chiral amidium ions,[18] chiral thioureas[19] and their salts,[20] and chiral phosphoric acid diesters.[21,22]

Herein we describe the development of an enantioselective nucleophilic addition of alcohols and thiols to aza-*ortho*-quinone methides in the presence of chiral Brønsted acids.

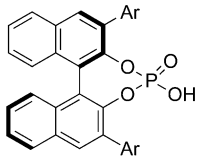
For the stereoselective formation of benzylic ethers, first the benzylic amino alcohol **1a** was reacted with isopropanol **2a** in toluene at room temperature, in the presence of various phosphoric acid diesters **4a**–**4h** (Table 1). In general, the desired adduct **3a** was isolated in good yields, irrespective of the applied acid (entries 1–7). The stereoselectivity, however, fluctuated between almost racemic products (entry 1) and products with moderate *ee* values (entries 2, 3, 5, and 6). Promising results were obtained only when catalysts with the sterically demanding triisopropylphenyl substituent were applied (entries 4, 7), whereby catalyst **4h** with a $[H_8]$-BINOL backbone performed slightly better than the BINOL-based catalyst **4d**. Similar results were obtained when catalyst **4i** was used (entry 8). The application of the corresponding *N*-triflylphosphoramides[8d] resulted in lower enantiomeric excesses.[23]

The utilization of different solvents had a great impact on the reaction outcome with regard to the stereoselectivity; however, no clear trend could be deduced from the results (entries 9–12). Surprisingly, reactions conducted in benzene and xylene provided the addition products with clearly lower *ee* values than in toluene, and also when DCM was used, no improvement was achieved. Only the application of more polar solvents, such as THF, led to a noticeable increase of stereoselectivity (85% *ee*). As expected, lowering the reaction temperature, here to 15°C, improves the enantiomeric excess, though at the expense of reactivity. Indeed, in THF at 15°C, product **3a** was obtained with 99% *ee*, virtually enantiomerically pure, but the yield dropped to 46%—merely half of that of the reaction at room temperature. As a compromise, the reaction could be performed in toluene under analogous conditions. Under these optimized reaction conditions, product **3a** was obtained in 93% yield and with 91% *ee*. It is possible to lower the catalyst loading to 2 mol%; however, this leads to a decreased yield (Table 1, entry 15).[23]

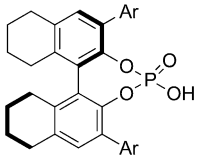
Table 1: Determination of the optimal reaction conditions for the oxa-Michael addition.[a]



1a Ar = PMP **2** **3a**



4a: Ar = 9-phenanthryl
4b: Ar = $SiPh_3$
4c: Ar = 9-anthracenyl
4d: Ar = 2,4,6-(^{i}Pr)$_3$-C_6H_2
4i: Ar = 2,4,6-(Cy)$_3$-C_6H_2



4e: Ar = 9-phenanthryl
4f: Ar = $SiPh_3$
4g: Ar = 9-anthracenyl
4h: Ar = 2,4,6-(^{i}Pr)$_3$-C_6H_2

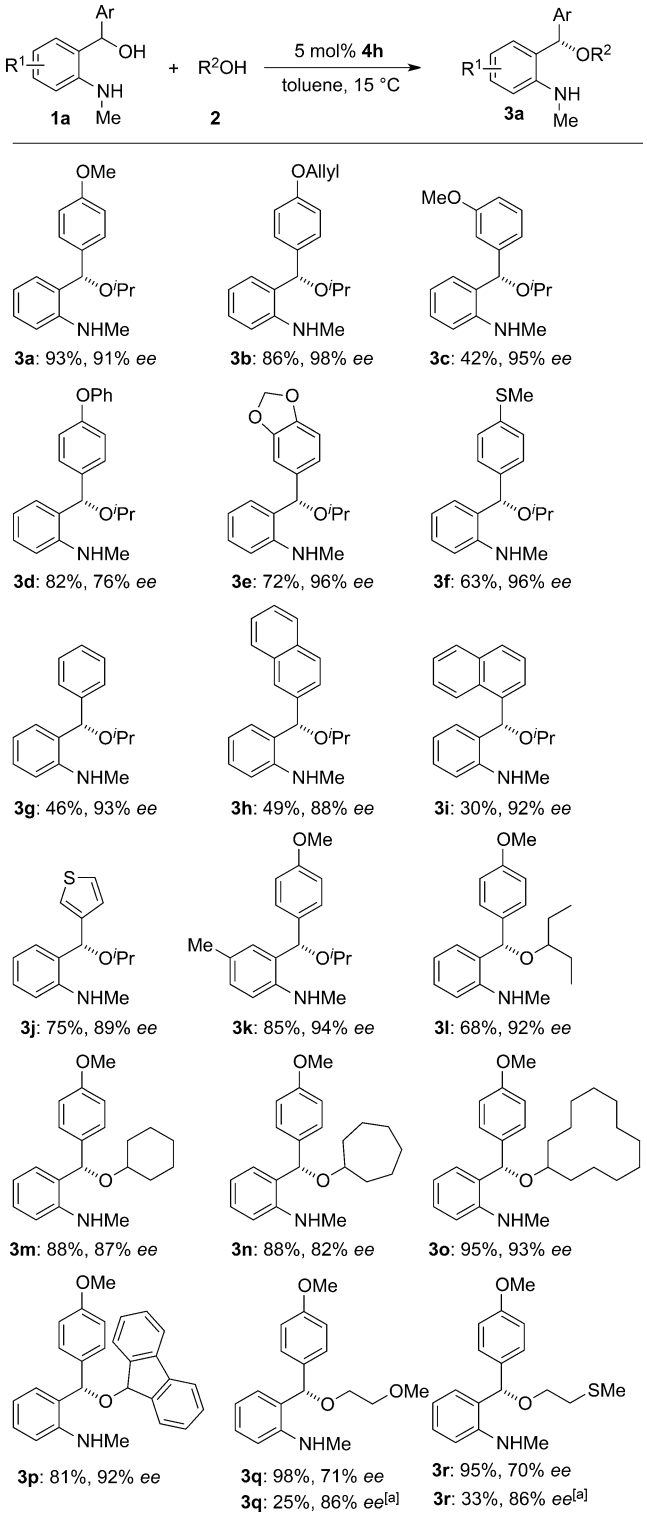
Entry	4	Solvent	Yield [%][b]	*ee* [%][c]
1	**4a**	toluene	88	5
2	**4b**	toluene	97	41
3	**4c**	toluene	93	60
4	**4d**	toluene	98	78
5	**4f**	toluene	99	51
6	**4g**	toluene	88	57
7	**4h**	toluene	99	81
8	**4i**	toluene	96	82
9	**4i**	benzene	92	55
10	**4i**	*o*-xylene	99	58
11	**4i**	DCM	99	58
12	**4i**	THF	91	85
13[d]	**4h**	THF	46	99
14[e]	**4h**	toluene	93	91
15[f]	**4h**	toluene	75	94

[a] Reaction conditions: **1a** (0.067 mmol), **2a** (0.13 mmol), cat. **4** (5 mol%), solvent (1.0 mL), RT, 36 h. [b] Yield of **3a** after purification by flash column chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] At 15°C, in the presence of molecular sieves (4 Å). [e] At 15°C with 1.2 equivalents of **2a**, 48 h. [f] Using 2 mol% of **4h**, 56 h.

With the optimized reaction conditions in hand, amino alcohols and alcohols with various substituents were tested (Scheme 2). Generally it was possible to apply electron-rich ether, thioether, and methyl groups in *para*- or *meta*-position as the distal[24] aromatic substituents (**3a**–**f**). In most cases yields and selectivity comparable to those of **3a** were obtained. Only **3c** (*meta*-OMe) was obtained in modest 42% yield.

Moderate yields were also obtained when electron-neutral aromatic compounds were used, such as phenyl and naphthyl (**3g**–**i**), but in some cases with excellent *ee* values of up to 93%. Above all, even substrates with heteroaromatic substituents were accessible (**3j**), likewise with a good yield of 75% and 89% *ee*.

The aromatic compound that is part of the aza-*ortho*-quinone methide unit could also be substituted and the corresponding product (**3k**) was obtained with excellent results. The utilization of various alcohols was also possible. Generally, excellent results with secondary alcohols were obtained (**3l**–**p**); primary alcohols, however, were only transferred to the corresponding benzyl ethers with moderate

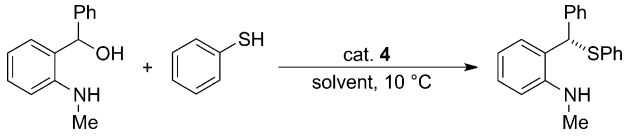


Scheme 2. Substrate scope of the oxa-Michael addition. [a] In THF for 56 h.

selectivities of about 70% *ee* (**3q**,**r**), but always with excellent yields. When THF was used as the solvent, the reaction provided better enantiomeric excesses of up to 86% *ee*; however, the yields were inferior even with longer reaction times.

Following up, we decided to investigate the corresponding organocatalytic addition[25] of thiols to in situ generated aza-*ortho*-quinone methides. In the case of sulfa-Michael additions to aza-*ortho*-quinone methides, initial experiments were conducted to determine the influence of various BINOL- and [H_8]-BINOL-derived phosphoric acids on the conversion of the benzylic amino alcohol **1g** with thiophenol **5a** in toluene at 10 °C (Table 2). In the presence of 5 mol% of the respective Brønsted acid, the desired addition product **6a** was always obtained in good yields, however, with strongly varying enantioselectivities (entries 1–5).

Table 2: Determination of the optimal reaction conditions for the sulfa-Michael addition.[a]



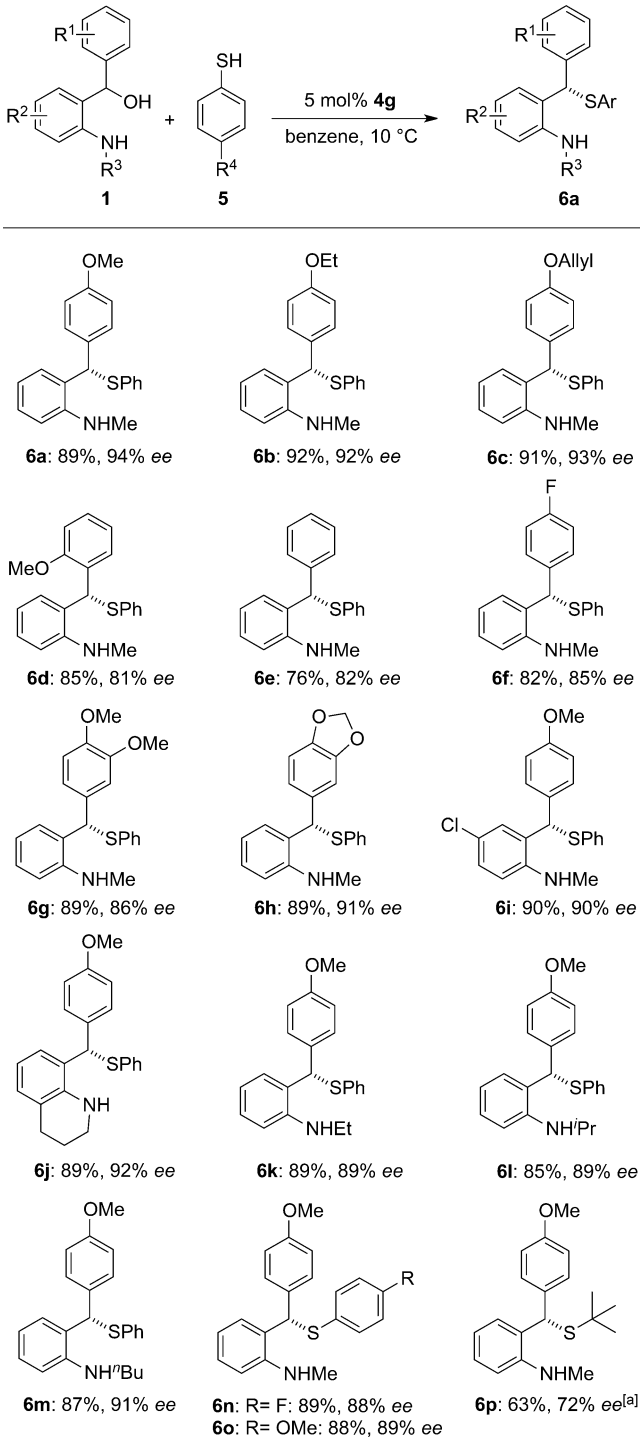
Entry	4	Solvent	Yield [%][b]	*ee* [%][c]
1	**4a**	toluene	82	74
2	**4b**	toluene	84	63
3	**4c**	toluene	84	85
4	**4e**	toluene	89	74
5	**4f**	toluene	89	86
6	**4f**	benzene	91	88
7	**4f**	*o*-xylene	87	81
8	**4f**	chlorobenzene	89	84
9	**4f**	DCM	92	80
10	**4f**	DCE	93	80
11	**4g**	benzene	89	94

[a] Reaction conditions: **1g** (0.08 mmol), **5a** (0.09 mmol), cat. **4** (5 mol%), solvent (1.5 mL), 10 °C, 120 h. [b] Yield of **6a** after purification by flash column chromatography. [c] Determined by HPLC on a chiral stationary phase.

The best result was obtained by using the anthracenyl-substituted catalyst **4c**; yet it turned out that in the presence of the corresponding catalysts with the [H_8]-BINOL backbone, better enantiomeric excesses were achieved (compare entries 1/4 and 2/5).

When we conducted the reaction in various solvents and applying catalyst **4f**, we found that benzene and its derivatives toluene, xylene, and chlorobenzene yield better results (up to 88% *ee* in benzene) than aliphatic, chlorinated solvents such as DCM and DCE. With the optimized reaction conditions in hand, the product **3a** was obtained in 89% yield and 94% *ee* using the [H_8]-BINOL phosphoric acid diester **4g** (entry 11).[21]

Based on this result, we investigated the amenability of the reaction to various substituted diaryl methanols and thiols, to prove the general applicability of the developed methodology (Scheme 3). To our delight, benzylic alcohols with electron-rich substituents in *ortho*- and *para*-position of the distal aromatic substituent (**6a**–**d**, **6g**,**h**), as well as electronically neutral and electron-deficient aromatic compounds (**6e** and **6f**) could be applied. The products of the nucleophilic addition were obtained with yields (76–92%) and selectivities (86–93% *ee*) comparable to that of model substrate **1g**. Beyond that, it was possible to use an electron-



Scheme 3. Substrate scope of the sulfa-Michael addition. [a] Using catalyst **4h**.

poor amino alcohol that possessed a chloro substituent in the *para*-position of the amino group, which is pivotal for the reactivity. In this case the corresponding adduct **6i** was isolated in 90% yield and with 90% *ee*. Similar results were also obtained for substituted amines (R^3 = Et, *i*Pr, *t*Bu; **6k–m**) as well as for the tetrahydroquinoline derivative **6j**. The utilization of various thiophenols led to comparable results, irrespective of their electronic properties (**6n,o**). Besides aromatic thiols, it was possible to use an aliphatic thiol, giving the desired product (**6p**) in good yield and with satisfying enantiomeric excess.

In conclusion, we have developed a novel Brønsted acid catalyzed enantioselective sulfa- and oxa-Michael addition to in situ generated quinone methides. The generation of the intermediate aza-*ortho*-quinone methide proceeds under very mild reaction conditions in the presence of low amounts of chiral phosphoric acids and leads to the corresponding benzylic ethers and thioethers with excellent yields and enantioselectivities. As functionalized diaryl methanol ethers and the corresponding thioethers are difficult to access, the herein presented asymmetric organocatalytic addition reaction should be of great benefit in the synthesis of biologically relevant compounds. Further investigations concerning the substrate scope and the applicability are currently in progress.

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Keywords: Brønsted acids · carbenium ions · Michael addition · *ortho*-quinone methides · substitution

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[23] For further information on the optimization of reaction conditions, see the Supporting Information.

[24] In this context, distal denotes the aromatic compound that is not part of the aza-quinone methide unit.

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