Brønsted Acid Catalysis

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Ortho-Quinone Methides as Reactive Intermediates in Asymmetric Brønsted Acid Catalyzed Cycloadditions with Unactivated Alkenes by Exclusive Activation of the Electrophile**

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Abstract: *An efficient method for the highly enantioselective synthesis of chiral chromanes bearing multiple stereogenic centers was developed. A chiral BINOL-based N-triflylphosphoramide proved to be an effective catalyst for the in situ generation of ortho-quinone methides (o-QMs) and their subsequent cycloaddition reaction with unactivated alkenes provided chromanes with excellent diastereo- and enantioselectivity.*

Within the field of Brønsted acid catalysis, BINOL-based phosphoric acids have been established as one of the most effective classes of metal-free chiral catalysts.[1] BINOL-based *N*-triflylphosphoramides (NTPAs) are more acidic[2] than the corresponding phosphoric acids and have been found to be powerful catalysts for the activation of otherwise unreactive substrates. Since their first introduction by Yamamoto and coworkers,[3] NTPAs have been successfully applied in new asymmetric reactions.[4] NTPAs usually act as bifunctional catalysts in enantioselective reactions, whereby the carbonyl or imine derivatives are activated in the transition state by H-bonding and the nucleophiles are coordinated through the Lewis basic phosphoryl oxygen atom (Figure 1, left). By contrast, transformations based on open transition states with activation of the electrophiles only are rare.

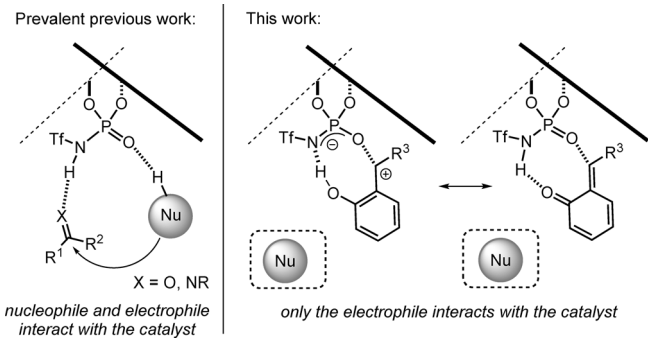

Figure 1. Comparison between a common transition state and the transition state in the present work.

ortho-Quinone methides (*o*-QMs) are highly reactive, transient intermediates that are used in the synthesis of natural products and bioactive compounds.[5,6] Although *o*-QMs constitute a class of useful intermediates that has attracted the attention of organic chemists, the transient nature of *o*-QMs leads to difficulties in asymmetric synthesis applications. Nevertheless, with the recent development of organocatalysis, highly reactive *o*-QMs have successfully been applied in metal-free enantioselective reactions.[7,8] However, the asymmetric catalysis of cycloaddition reactions between *o*-QMs and unactivated alkene dienophiles has not been described.[9] The reason for this lies not only in the poor interaction between the highly unstable *o*-QMs and the chiral catalysts but also in the various side reactions that typically occur. The application of *o*-QMs in enantioselective [4+2] hetero-Diels–Alder reactions is thus a challenging topic in organic chemistry. These reactions are, however, especially useful for synthetic chemistry because they allow direct access to chromane or chromene frameworks.[10]

Chromanes are privileged structural motifs, which are present in a large number of natural products and bioactive agents with a wide range of biological activities, including antioxidant, antifungal, antiviral, cytotoxic, and anti-inflammatory activities.[11] However, efficient ways to access chromanes in an straightforward and enantioselective fashion are still rare.[11]

Given the difficulties associated with *o*-QMs and the lack of efficient asymmetric reactions to access optically active polysubstituted chromanes, we decided to develop a general and highly enantioselective Brønsted acid catalyzed cycloaddition between *o*-QMs and various alkenes to produce valuable optically active 2,4-di- and 2,3,4-trisubstituted chromanes.

From the outset, we were aware that several challenges needed to be addressed. Styrene polymerization in the presence of highly acidic acids is well known and needed to be circumvented. Furthermore, the high acidity of Brønsted acids could also lead to several side reactions of the in-situ generated *ortho*-quinone methides. However, the use of computational and experimental studies suggested that *o*-QMs may be tamed through H-bonding as well as the interaction of O or N lone pairs with the methylene carbon atom.[12,13] With these considerations in mind, we hypothesized that chiral phosphoric acids or NTPAs could serve as bifunctional catalysts to activate the carbonyl group of the *o*-QMs through H-bonding and also stabilize the methylene group through the lone pair of the phosphoryl oxygen atom

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(Figure 1, right). This activation mode has never been demonstrated although it provides strong coordination, which could govern the enantioselection and would allow cycloaddition between *o*-QMs and unactivated alkenes.

To test our hypothesis, we started with the reaction between *o*-hydroxybenzyl alcohol derivatives and various styrenes. Hydroxybenzylic alcohols **1** can be easily accessed in one step from readily available salicylaldehydes through the addition of Grignard reagents. The initial investigations were performed with benzylic alcohol **1a**, styrene (**2a**), and NPTA **4a** since the corresponding phosphoric acids did not give acceptable results.

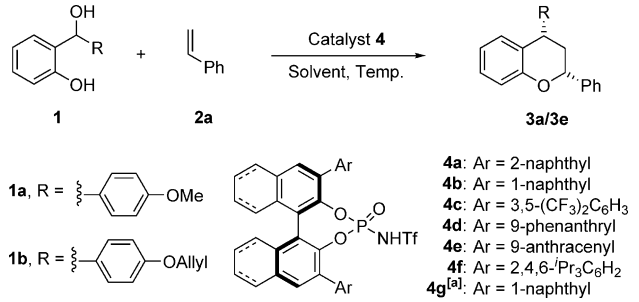
To our delight, cycloadduct **3a** was isolated in 37% yield with 17% *ee* (Table 1, entry 1). Further evaluation of the catalyst structure (entries 2–7) revealed 3,3′-bis-1-naphthyl-substituted [H_8]-NTPA **4g** as the best catalyst for this demanding transformation (entry 7). Performing the reaction in toluene afforded the product in 57% yield and 65% *ee* (entry 8). The use of molecular sieves and a lower concentration increased not only the yield but also the enantioselectivity (entry 10). Lowering the temperature to −60 °C provided the product with higher enantioselectivity (84% *ee* vs. 72% *ee*) but with considerably lower yield (45% versus 77%; entries 11 and 10). Upon increasing the catalyst loading, the product **3a** was isolated in 89% yield, d.r. 20:1, and with comparable enantioselectivity (83% *ee*; entry 12). Upon changing the model substrate from **1a** to **1b**, which has an allyl ether group, the reactivity improved and the product **3e** was isolated in 86% yield with d.r. 49:1 and 85% *ee*. Additional evaluation of various reaction parameters is documented in the Supporting Information.

Subsequently, various styrenes **2** were applied in the *N*-triflylphosphoramide catalyzed [4+2] hetero-Diels–Alder reaction with *o*-QMs (Scheme 1). The reaction is tolerant of various styrenes with diverse substitution patterns and different electronic properties.

In general the cycloadducts **3a–r** were obtained in high yields and with excellent diastereomeric ratios and enantioselectivity. *p*- and *m*-Methylstyrene furnished the corresponding cycloadducts **3d** and **3c** in 91% and 84% yield, respectively, and 90% *ee*. Notably, *o*-methylstyrene afforded cycloadduct **3b** in 82% yield and with excellent enantioselectivity of 99% *ee*. Furthermore, electron-withdrawing groups, including *p*-fluoro *p*-chloro- and *p*-bromostyrene, could be applied and the cycloadducts **3g**, **3h, 3j** were obtained with excellent enantioselectivity. 2-Vinylnaphthalene, a more sterically hindered alkene, provided cycloadduct **3i** in high yield and with high enantioselectivity (87%, 90% *ee*). We continued to explore the scope of the *o*-QM with 1,3-dioxole-substituted hydroxybenzyl alcohol **1c**, which also reacted well with electron-donating and electron-withdrawing styrenes to give **3j** and **3k** with high yield and selectivity. We then focused on applying a variety of substituted *o*-QMs in this newly developed methodology. First, a methoxy substituent was installed on the phenol residue of the *o*-QM precursors. Under the applied conditions, the methoxy-substituted substrate worked very smoothly in reaction with various styrenes to give the desired products **3l–p** in good yields (71–93%) and with excellent enantioselectivity (90–95% *ee*). The methyl-substituted *o*-QM also performed well in the reaction, affording the products **3q** and **3r** in high yields and with excellent diastereoselectivity and high enantioselectivity. Interestingly, with indene as a dienophile, the corresponding cycloadduct **3s** with three stereogenic centers was obtained in excellent yield, with good enantioselectivity, and as a single diastereomer (Figure 2). Finally, we extended the scope of the alkenes to *β*-methyl-*p*-fluorostyrene, which worked very smoothly with *o*-QM and provided the corresponding cycloadduct **3t** in excellent yield and enantioselectivity as a single diastereomer. Other substrates, including cyclopentadiene and α-methylstyrene, can also be successfully applied. The products are obtained in good yields but with lower diasterio- and/or enantioselectivity.[14]

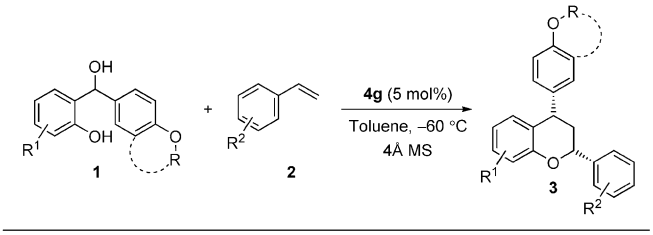
Our proposed mechanism for this new Brønsted acid catalyzed asymmetric reaction is depicted in Scheme 2. In a first step, protonation of the benzylic OH group by the Brønsted acid results in the corresponding *o*-QM. Coordination to the catalyst by means of H-bonding and stabilization of the methylene group by the lone pair of the phosphoryl oxygen atom results in the formation of complex **A**, in which one face of the heterodiene is shielded by the catalyst. The formation of complex **A** is supported by NMR experiments.[14,15] Subsequently, styrene approaches complex **A** in

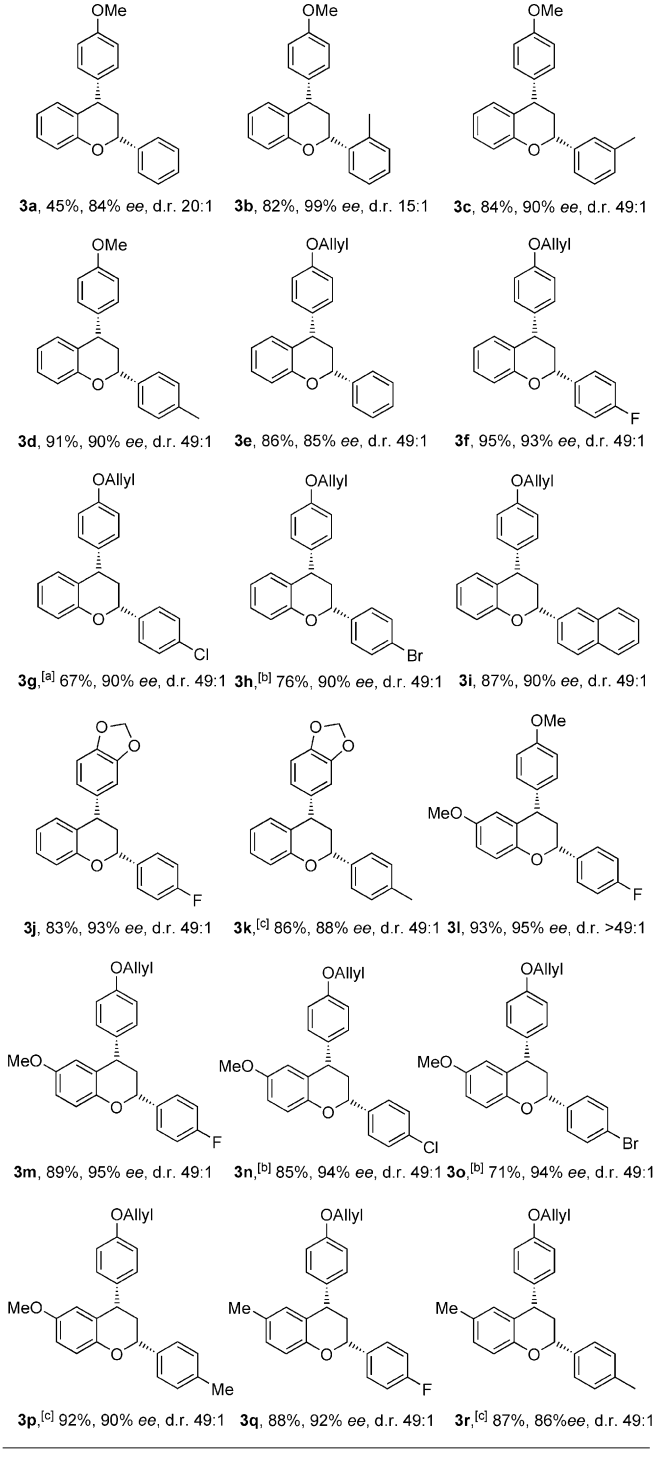
Table 1: Optimization of the Brønsted acid catalyzed [4+2] *hetero*-Diels–Alder reaction with in situ generated *o*-QMs.



Entry[b]	Solvent	1	Temp. [°C]	4	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	CH_2Cl_2	**1a**	−30	**4a**	37	2.4:1	17
2	CH_2Cl_2	**1a**	−30	**4b**	60	5.7:1	29
3	CH_2Cl_2	**1a**	−30	**4c**	45	2:1	18
4	CH_2Cl_2	**1a**	−30	**4d**	62	4:1	28
5	CH_2Cl_2	**1a**	−30	**4e**	56	4.5:1	23
6	CH_2Cl_2	**1a**	−30	**4f**	62	5.7:1	21
7	CH_2Cl_2	**1a**	−30	**4g**	65	4.5:1	35
8	toluene	**1a**	−30	**4g**	57	17:1	65
9[f]	toluene	**1a**	−30	**4g**	69	19:1	70
10[f,g]	toluene	**1a**	−30	**4g**	77	19:1	72
11[f,g]	toluene	**1a**	−60	**4g**	45	20:1	84
12[f,g,h]	toluene	**1a**	−60	**4g**	89	20:1	83
13[f,g]	toluene	**1b**	−60	**4g**	86	49:1	85

[a] With a partially hydrogenated BINOL backbone. [b] Reactions were performed with alcohol **1a** at 0.1 M concentration, styrene **2a** (10 equiv) and 5 mol% **4**. The solution was stirred for 18 h at −30 °C and 72 h at −60 °C. [c] Yield of isolated product after column chromatography. [d] Diastereomeric ratio was determined by ^{1}H NMR. [e] Enantiomeric excess was determined by HPLC on a chiral stationary phase. [f] Addition of 4 Å MS. [g] Reaction was performed with alcohol **1** at 0.025 M concentration. [h] Reaction was performed with 10 mol% **4g**.





Scheme 1. Substrate scope of the organocatalytic enantioselective [4+2] hetero-Diels–Alder reaction. Reactions were performed with alcohol **1** (0.1 M), styrene **2** (10 equiv), and **4g** (5 mol%) in toluene at −60 °C. [a] Reaction performed at −40 °C. [b] Reaction performed at −50 °C. [c] Reaction performed at −70 °C.

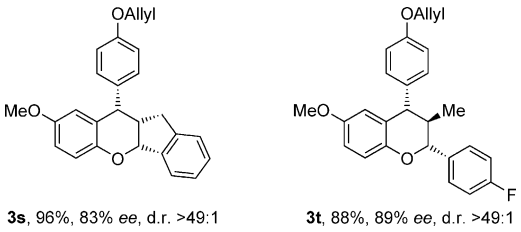
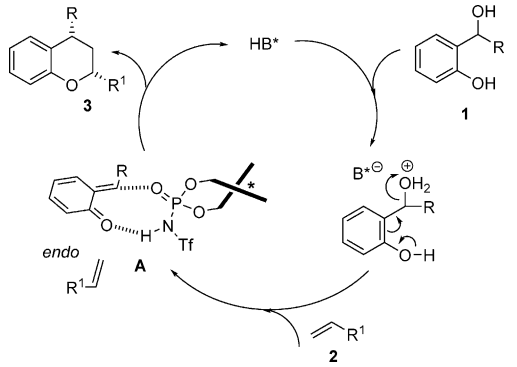


Figure 2. Synthesis of 2,3,4-trisubstituted chromanes.



Scheme 2. Proposed mechanism for the chiral Brønsted acid catalyzed *hetero*-Diels–Alder reaction with *o*-QMs and alkenes.

an *endo* fashion to give the corresponding product and the catalyst starts a new cycle. It is noteworthy that all cycloadducts **3** in Scheme 1 were furnished with excellent diastereoselectivity and were assigned as *syn* adducts by ^{1}H NMR analysis. The absolute configuration of the product **3o** was determined by X-ray crystal structure analysis to be (2*R*, 4*S*) (see the Supporting Information).

In summary, we have developed the first asymmetric [4+2] hetero-Diels–Alder reaction between *o*-QMs and unactivated alkenes. The reaction is catalyzed by a chiral Brønsted acid and affords a variety of valuable chiral chromanes. Various *o*-QMs and a broad range of alkenes led to cycloadducts in high yields (up to 95%) and with excellent enantioselectivity (up to 99%) and very good diastereomeric ratios (up to 49:1). NTPAs proved to be effective catalysts for the in situ generation of *o*-QMs and subsequent cycloaddition reaction with unactivated alkenes, which gave products with two or three stereocenters. More importantly and in contrast to most Brønsted acid catalyzed transformations, the exclusive activation of the electrophile in a bifunctional fashion and further reaction via an open transition state was achieved. Efforts to delineate the detailed mechanism of this new activation mode and the application of this procedure to the synthesis of natural products and biologically active molecules[16] are underway in our laboratory.

Keywords: chromanes · cycloaddition · homogeneous catalysis · *n*-triflylphosphoramide · *ortho*-quinone methide

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[14] For futher information, see Supporting Information.

[15] For this, we synthesized and isolated an *o*-quinone methide which is the proposed intermediate after water elimination. The catalyst was added and the resulting mixture was shaken for 5 seconds. The solution turned deep red and NMR experiments were carried out. Noticeable shifts of the important protons including the methylene proton, the two uncoupled quinoidal protons, and methylenedioxy group protons were observed, thus indicating an interaction between *o*-QMs and catalyst.

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