Multiple Hydrogen Bond Activation in Asymmetric Brønsted Acid Catalysis

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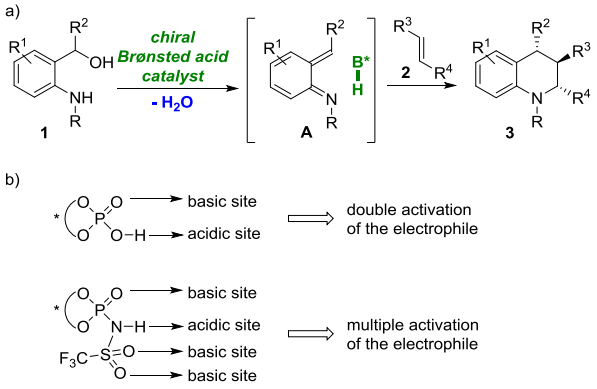
Abstract: An efficient protocol for the asymmetric synthesis of chiral tetrahydroquinolines bearing multiple stereogenic centers by means of asymmetric Brønsted acid catalysis has been developed. A chiral SPINOL-based *N*-triflylphosphoramide proved to be an effective Brønsted acid catalyst for the *in situ* generation of *aza*-*ortho*-quinone methides (*aza*-*o*-QMs) and their subsequent cycloaddition reaction with unactivated alkenes to provide the products with excellent diastereo- and enantioselectivities. In addition, DFT calculations provided an insight into the activation mode and nature of the interactions between the *N*-triflyl phosphoramide catalyst and generated *aza*-*o*-QMs.

Introduction

Aza-*ortho*-quinone methides (*aza*-*o*-QMs) are valuable intermediates[1] utilized essentially for the assembly of natural products with complex frameworks as well as for the design of unnatural molecules for biological and pharmaceutical applications. Historically, the generation of *aza*-*o*-QMs has been reported under various conditions including thermal extrusions of SO_2 or CO_2 from benzosultams or benzoxazinones,[2] photochemical fragmentation,[3] strong Lewis and Brønsted acid-mediated or pyrolytic elimination of *o*-hydroxymethyl-aniline,[4] and base induced elimination of chloromethylanilines or ammonium salts.[5] Compared with their analogues, *ortho*-quinone methides (*o*-QMs),[6] *aza*-*o*-QMs have been much less investigated in asymmetric transformations. To date, only few organocatalyzed asymmetric reactions employing reactive *aza*-*o*-QMs as intermediates have been reported.[5g,h,7-9] However, most of the described reactions are based on the ability of *aza*-*o*-QMs to undergo conjugate addition reactions. The use of *aza*-*o*-QMs as intermediates in metal-free enantioselective cycloaddition reactions, affording nitrogen-containing heterocycles with multiple chiral centers remains challenging.[9] This is due to unfavorable reaction conditions for the *aza*-*o*-QM intermediate formation as well as compatibility with sensitive reaction partners. In addition, the high reactivity of the *aza*-*o*-QM intermediate can lead to various side reactions.[10] Therefore, we decided to examine an asymmetric Brønsted acid catalyzed method,[11] which allows the *in situ* formation of *aza*-*o*-QM intermediates under mild reaction conditions and their usage in enantioselective inverse-electron-demand [4+2] cycloaddition reaction (Scheme 1a). This reaction is particularly interesting as it provides valuable tetrahydroquinolines (THQs). THQs are privileged structural motifs with a broad spectrum of biological activities and widespread natural occurrence.[12] Hence considerable efforts have been made for the development of improved and simplified syntheses to rapidly access the important THQ core structure.[13]

Recently, we reported the *in situ* generation of *aza*-*o*-QMs with the aid of chiral BINOL phosphoric acids and their use in enantioselective conjugate addition reactions.[8c,d] In these protocols the chiral phosphoric acids catalyzed the water elimination from *ortho*-amino benzyl alcohols and provided *aza*-*o*-QMs complexes of type **A** in a mild and targeted fashion. However, chiral phosphoric acids proved less effective for our desired cycloaddition reaction of *aza*-*o*-QMs with unactivated alkenes. Hence, chiral *N*-triflyl phosphoramide derivatives[14] were considered as potential catalysts for this reaction. Whereas in the case of phosphoric acids a double activation of the substrate through the acidic and basic sites is possible, in the case of *N*-triflyl phosphoramide derivatives activation through multiple interactions with the substrate is feasible (Scheme 1b). This activation mode provides strong coordination which can govern the enantioselection, allowing the cycloaddition between *aza*-*o*-QMs and unactivated alkenes via an open transition state (*vide infra*).



Scheme 1. Proposed Brønsted acid catalysis with *in situ* formed *aza*-*o*-QMs

Results and Discussion

We started our investigation with *ortho*-aminobenzyl alcohol **1a** and styrene **2a**. Catalyst **4a** provided the desired product *ent*-**3a** with 33% yield and 9% enantioselectivity (Table 1, entry 1). Changing the substituent on the BINOL-scaffold from phenyl to sterically more bulky 1-naphthyl (**4b**), 2-naphthyl (**4c**) and 9-

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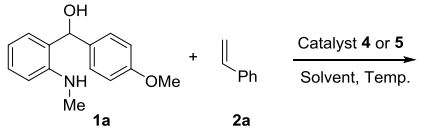
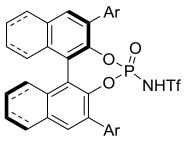
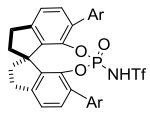
phenanthryl (**4d**) gave similar results (entries 2-4). A better enantioselectivity was achieved with 3,3'-bis-2,4,6-(^{i}Pr)$_3$C$_6$H$_2$ substituted BINOL-derived NTPA **4e** (entry 5). With $CHCl_3$ as the solvent, a slightly improved yield and higher enantioselectivity (76% *ee*) were observed (entry 6).[15] Further modifications were made to adjust the temperature; however, no satisfactory results were obtained (entries 8-9). To our delight, when the SPINOL-derived NTPA **5a** was employed as a catalyst, the product **3a** was obtained with an excellent enantioselectivity of 96% along with 65% yield (entry 10). With 4Å MS as additive, an excellent yield and enantioselectivity (96%, 96% *ee*) were observed (entry 11).

Table 1. Optimization of the Brønsted acid catalyzed *aza*-Diels-Alder reaction with *in situ* generated *aza-o*-QM and styrene.[a]





4a: Ar = phenyl
4b: Ar = 1-naphthyl
4c: Ar = 2-naphthhyl
4d: Ar = 9-phenanthryl
4e: Ar = 2,4,6-(*i*Pr)$_3$-C$_6$H$_2$
4f: Ar = [H$_8$]-2,4,6-(*i*Pr)$_3$-C$_6$H$_2$



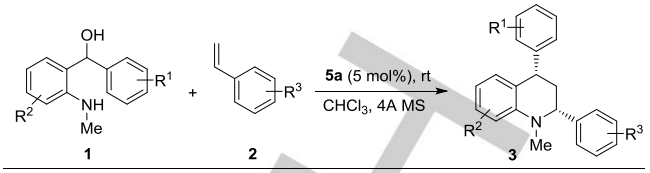
5a: Ar = 2,4,6-(*i*Pr)$_3$-C$_6$H$_2$

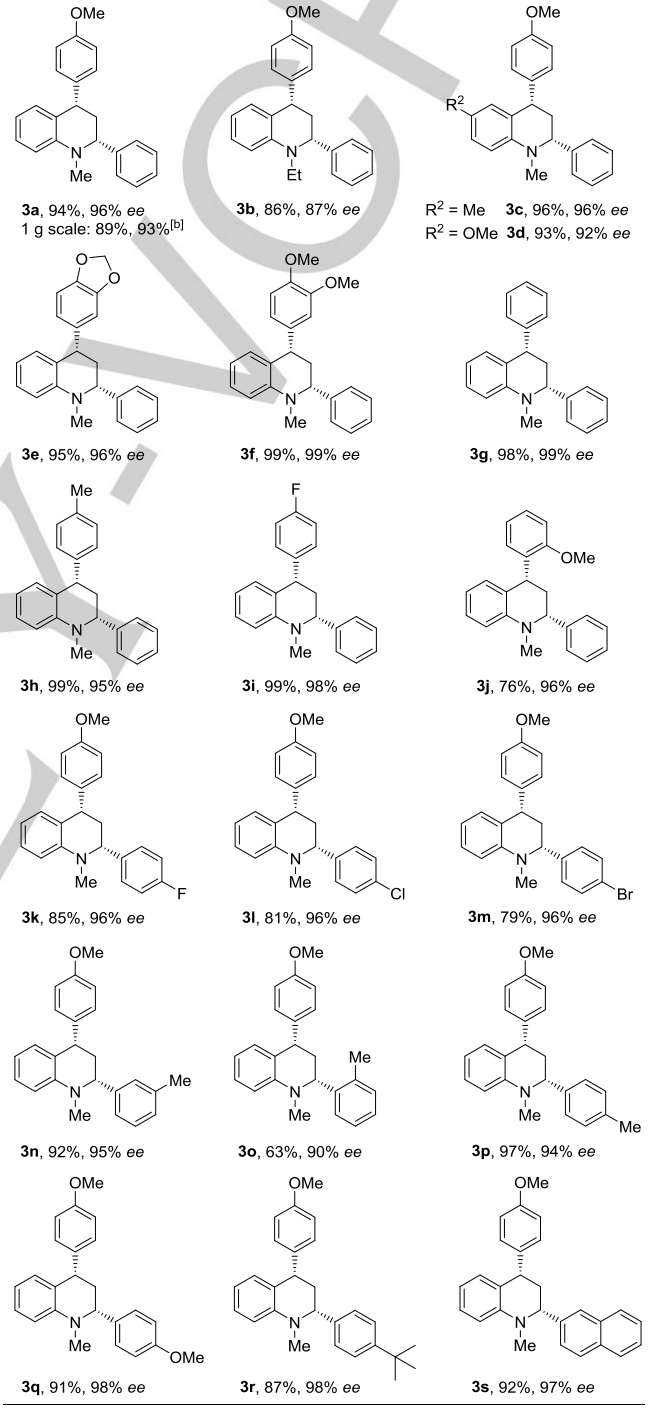
Entry	Solvent	Temp.(°C)	4	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	rt	**4a**	33	9[d]
2	CH_2Cl_2	rt	**4b**	31	10[d]
3	CH_2Cl_2	rt	**4c**	36	5[d]
4	CH_2Cl_2	rt	**4d**	35	20[d]
5	CH_2Cl_2	rt	**4e**	39	60[d]
6	$CHCl_3$	rt	**4e**	52	76[d]
7	$CHCl_3$	rt	**4f**	54	50[d]
8	$CHCl_3$	10	**4e**	9	69[d]
9	$CHCl_3$	40	**4e**	64	60[d]
10	$CHCl_3$	rt	**5a**	65	96
11[e]	$CHCl_3$	rt	**5a**	92	96

[a] Reactions were performed with alcohol **1a** at 0.05 M concentration, styrene **2a** (5 equiv.) and 5 mol% **4** or **5**. The solution was stirred for 18 h at the corresponding temperature. [b] Yield of the isolated product after column chromatography. Diastereomeric ratio was >99:1. [c] Enantiomeric excess was determined by HPLC on a chiral stationary phase. [d] *ent*-**3a** is the product. [e] Addition of 4Å MS.

With the optimal conditions for the synthesis of optically enriched THQs in hand, we continued to explore the scope and generality of the Brønsted acid catalyzed reaction between *aza-o*-QMs and various styrenes. In general, all cycloadducts **3a-s** were obtained in high yields and with excellent enantiomeric excesses along with a single *syn* diastereomer regardless of the electronic properties of the substrates (Table 2). Furthermore, various aminobenzyl alcohols bearing aromatic groups with different steric and electronic properties were tolerated and the products isolated in good to excellent yields and with good to excellent enantioselectivities (87-99% *ee*).

Table 2. Substrate scope of the organocatalytic enantioselective [4+2] aza-Diels-Alder reaction between *in situ* generated *aza-o*-QMs and styrenes.[a]





[a] Reactions were performed with alcohol **1** (0.0777 mmol) at 0.05 M concentration, styrene **2** (5 equiv.), 5 mol% **5a** and 4Å MS. The solution was stirred for 18 h at room temperature. Yield of isolated products **3a-s** after column chromatography. Diastereomeric ratio was in all cases >99:1. Enantiomeric excess was determined by HPLC on a chiral stationary phase. [b] The reaction was performed with 2 mol% catalyst loading.

We then focused on applying various styrenes **2** in this newly developed methodology. The results obtained showed high tolerance toward various styrenes with diverse substitution patterns and different electronic properties. Particularly noteworthy are the good yields (79-85%) and excellent enantiomeric excesses (96% *ee*) for THQs **3k-m** observed for reactions with styrenes **2b-d** bearing electron-withdrawing substituents. Styrenes bearing electron-donating substituents also furnished the corresponding cycloadducts **3n-q** with pleasing results (63-97% yield, 90-98% *ee*). Switching to more sterically hindered styrenes appears to have no influence either on the yield or on the enantioselectivity (**3r**: 87%, 97% *ee*, **3s**: 92%, 98% *ee*). In addition, to show the synthetic applicability of this newly developed process, a reaction on a one gram scale was carried out and the corresponding product **3a** was obtained in 89% yield and 93% *ee* with only 2 mol% catalyst loading. Particularly noteworthy is that all cycloadducts were obtained as single diastereomers, which were indicated as *syn* products by ^{1}H-NMR analysis. The absolute configuration of the products has been determined as (2*R*, 4*S*) by X-ray single crystal structure analysis of product **3m** (Figure 1).

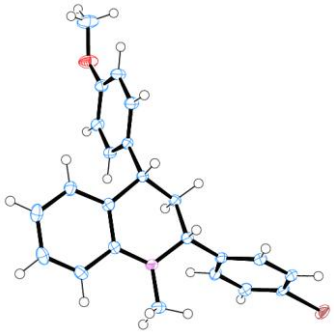
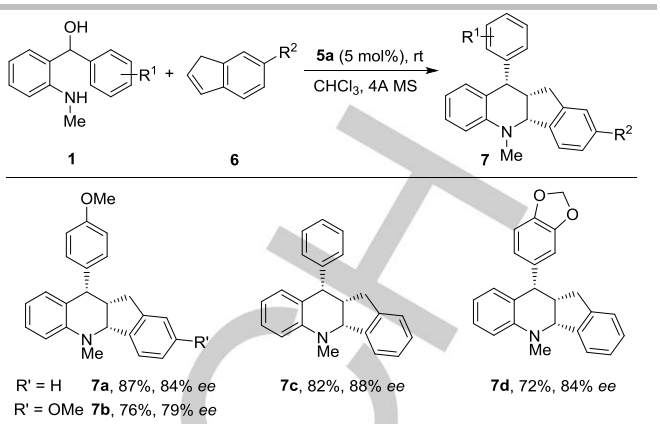


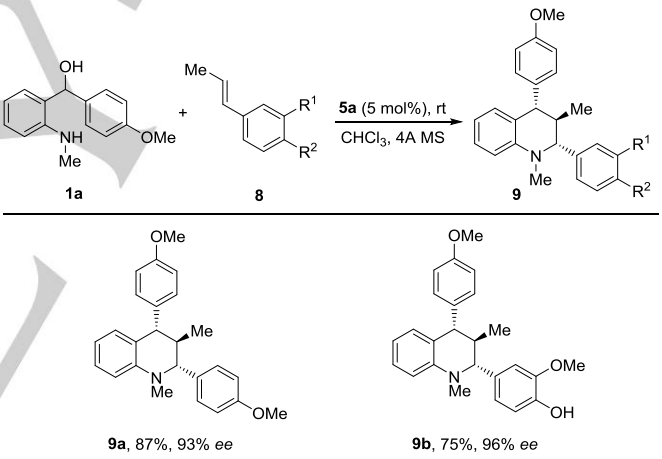
Figure 1. X-ray crystal structure of product **3m**. Thermal ellipsoids set at 50% probability.

After examining the wide scope of 2,4-disubstituted THQs, we turned our attention to explore more challenging THQs with three stereogenic centers. Thus, we examined the use of indenes as dienophiles to afford valuable 2,3,4-trisubstituted THQs (Scheme 2). Under the same optimized conditions, various polycyclic compounds **7a-d** were obtained as a single diastereomer with satisfactory yields and good to high enantioselectivities (72-87%, 79-88% *ee*).



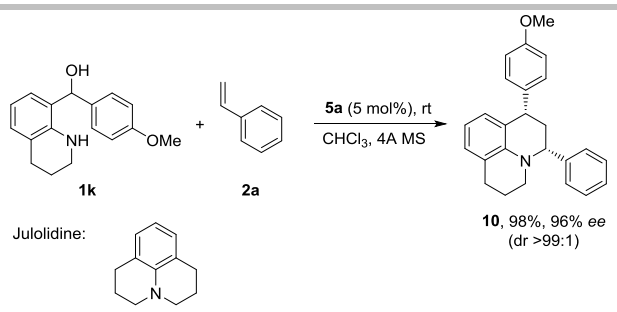
Scheme 2. Substrate scope of the organocatalytic enantioselective cyclo-addition reaction between *in situ* generated *aza-o*-QMs and indenes (dr >99:1).

Furthermore, we extended the scope of the reaction to *β*-methyl-styrenes bearing different substituents on the aromatic group (Scheme 3). Pleasingly, also *β*-methyl-styrenes gave excellent results and derivatives **9a** and **9b** were obtained as single diastereomers with 87% and 75% yield and 93% and 96% *ee* respectively.



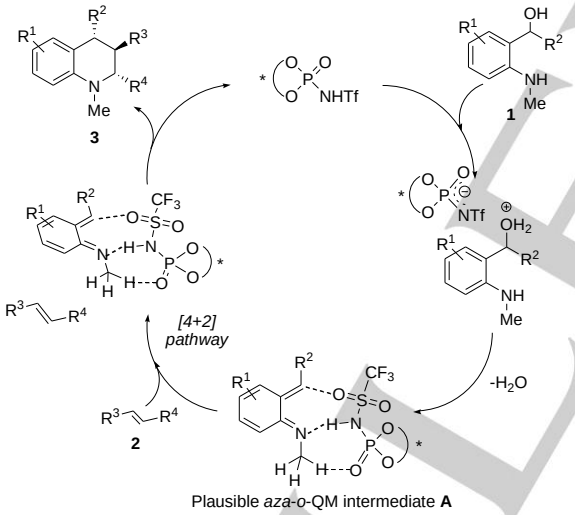
Scheme 3. Substrate scope of the organocatalytic enantioselective [4+2] *aza*-Diels-Alder reaction between *in situ* generated *aza-o*-QM and *β*-methyl-styrenes (dr >99:1).

Julolidine and derivatives are known not only for their potential use in anti-depressants and tranquilizers, but also for their practical function in optical materials.[16] Hence, we attempted to synthesize such derivatives in an optically active form. To our delight, under our newly developed methodology, Julolidine analog **10** was obtained as single diastereomer with excellent yield and enantioselectivity (98%, 96% *ee*) (Scheme 4).



Scheme 4. Synthesis of enantioenriched Julolidine analogue **10.**

Based on our observations and previous studies we propose the following mechanism for this newly developed and effective Brønsted acid catalyzed reaction of *in situ* generated *aza-o*-QM: the first step of the catalytic cycle consists of the protonation of *ortho*-aminobenzyl alcohol by the Brønsted acid, followed by dehydration to obtain the corresponding *aza-o*-QM *in situ*. Activation of the *aza-o*-QM by H-bonding coordination to the imine group and stabilization of the methylene carbon by the catalyst results in the more stable complex **A**. Subsequent *endo*-approach of the styrene via an open transition state furnishes the enantioenriched THQ **3** and regenerates the chiral Brønsted acid catalyst (Scheme 5).[17]



Scheme 5. Proposed mechanism for Brønsted acid catalyzed cycloaddition involving the *in-situ* generation of *aza-ortho* quinone methides.

DFT calculations provided an insight into the activation mode and nature of the interactions between the *N*-triflyl phosphoramide catalyst and generated *aza-o*-QM.[18] The geometry optimization and frequency calculations of the possible catalyst-substrate complexes were performed using Gaussian09 program package[19-21] at the B3LYP/6-31G* level.[22,23] The thermal corrections were calculated at 298 K. Solvent effects were taken into account at the PCM/B3LYP/6-31G*//B3LYP/6-31G* level.[24] The corrections for dispersion interactions were estimated with the DFT-D3 program developed by Grimme.[25] Several possible complexes between the catalyst and the *aza-o*-QM have been examined and the two most stable are depicted in Figure 2. Our DFT calculations revealed that multiple interactions are accounting for the stability of the complex between the *N*-triflyl phosphoramide catalyst and *aza-o*-QM. In the most stable structure (Figure 2 left), the *aza-o*-QM is fixed through H-bonding and additional interaction between the methylene group and the lone pair of one of the oxygen atoms of the triflyl group as well as interaction between the NMe group and phosphoryl oxygen. In the structure depicted in Figure 2 right (1.427 kcal/mol higher in energy), in which the phenyl rest on the *aza-o*-QM has a different orientation, an additional weak (S)O···HC hydrogen bond interaction between the second oxygen atom of the triflyl group and an aromatic CH is present. Both assessed structures explain the absolute configuration of the products obtained through an *endo*-approach of the styrene from the less hindered face of the *aza-o*-QM.

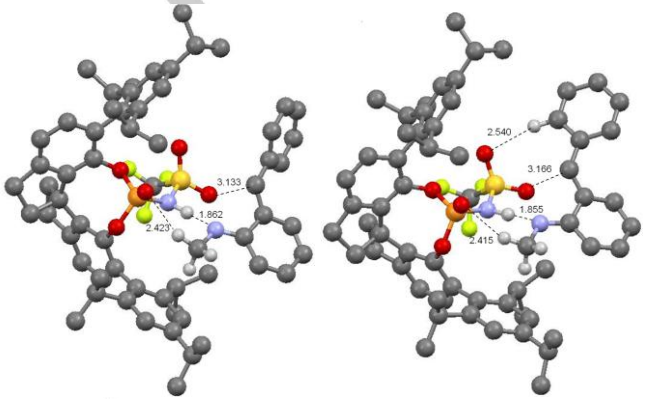


Figure 2. The two most stable catalyst-substrate complexes according to DFT-calculations (not relevant hydrogen atoms are omitted for clarity).

Conclusions

In summary, the work herein describes an efficient enantioselective cycloaddition reaction for the synthesis of various multi-substituted optically enriched THQs by means of asymmetric Brønsted acid catalysis. A chiral SPINOL-derived NTPA was able to generate *aza-o*-QMs *in situ* and promote their subsequent asymmetric cycloaddition with unactivated alkenes, affording valuable THQ derivatives bearing two or three stereogenic centers with excellent yields as well as enantioselectivities. Particularly noteworthy is the high tolerance toward a broad range of *aza-o*-QMs and alkenes and the fact that all cycloadducts were obtained as a single diastereomer. Furthermore, valuable optically enriched Julolidine analogs can also be obtained using this protocol.[26] Given the wide applicability of *aza-o*-QMs in organic synthesis, and the many possibilities for the extension of this mild asymmetric catalysis protocol to other cycloadditions as well as nucleophilic additions we believe that this work is a good basis to stimulate further work and applications of this developed catalysis methodology.

Experimental Section

General procedure for the Diels Alder reaction.

Styrene (5.0 equiv.) was added to a solution of hydroxybenzyl aminoalcohol **1** (1.0 equiv, 0.0777 mmol) and 40 mg 4Å molecular sieves in dry $CHCl_3$ (2.0 mL) and the mixture was stirred at room temperature. Catalyst **5a** (5 mol%, 3.3 mg) was added at room temperature to the reaction mixture and stirring was continued at the same temperature until alcohol **1** was completely consumed. The reaction was quenched by adding a few drops of NEt_3. The crude reaction mixture was directly loaded on a silica column. The column was eluted by using ethylacetate /hexane solvent mixture to obtain the enantiopure [4+2] cycloaddition products.

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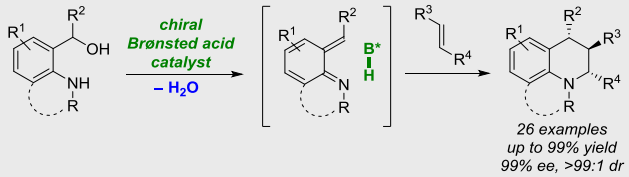
Layout 2:

FULL PAPER



An efficient protocol for the asymmetric synthesis of chiral tetrahydroquinolines bearing multiple stereogenic centers by means of asymmetric Brønsted acid catalysis has been developed. A chiral SPINOL-based *N*-triflylphosphoramide catalyzed the *in situ* generation of *aza*-*o*-QMs and their subsequent cycloaddition reaction with unactivated alkenes, providing the corresponding products with high yields and excellent diastereo- and enantioselectivities.

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