Brønsted Acid Catalysis

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Modulating the Acidity: Highly Acidic Brønsted Acids in Asymmetric Catalysis

Magnus Rueping, Boris J. Nachtsheim,* Winai Ieawsuwan, and Iuliana Atodiresei*

asymmetric catalysis · Brønsted acids · organocatalysis · superacidic systems

Dedicated to Professor Dieter Enders on the occasion of his 65th birthday

***R**ecently, chiral highly acidic Brønsted acids have emerged as powerful catalysts for enantioselective C–C and C–X bond-forming reactions. Their strong acidity renders them valuable tools for the activation of imines, carbonyl compounds, and other weakly basic substrates. As a result, new perspectives are opened and highly stereoselective transformations based on the concept of chiral contact-ion-pair catalysis can be realized. This Minireview gives an overview of the design and application of these new organocatalysts and presents recent results in this rapidly growing field.*

1. Introduction

Brønsted acids derived from BINOL (1,1'-bi-2-naphthol) have found widespread application as metal-free catalysts.[1] Among them, BINOL phosphoric acids (BPAs), described independently by the research groups of Akiyama and Terada in 2004,[2,3] have broadened and accelerated the development of acid-catalyzed asymmetric reactions and have since been applied in a variety of valuable enantioselective C–C and C–X bond formations.[4] Owing to their acidity they are mainly used to activate basic substrates bearing nitrogen-containing electrophiles, including aldimines, ketimines, and aziridines. The activation of less basic substrates has essentially remained the domain of Lewis acids. However, over the last few years, achiral, "superacidic", organic Brønsted acids have been described with reactivities comparable or even higher than those of either Lewis acids or inorganic Brønsted acids (Figure 1).[5]

Subsequently, strong chiral organic Brønsted acids were developed by Yamamoto and co-workers through the introduction of strong electron-withdrawing triflylamide groups into the BINOL phosphate (BP) framework.[6] The resulting *N*-triflylphosphoramides (NTPAs) proved to be reactive enough for the activation of more challenging substrates.

This Minireview aims to give a comprehensive overview of the design, structural features, and applications of these highly valuable chiral Brønsted acids, and summarizes the work published in this area since their development in 2006.

2. The Origin of BINOL-Derived N-Triflylphosphoramides

2.1. How to Increase the Acidity of an Organic Brønsted Acid

The major approach to the development of highly acidic Brønsted acids is the introduction of strong electron-withdrawing groups into existing acidic scaffolds. Two notable examples are depicted in Scheme 1.[7,8] Benzoic acid (**9**) has a pK_a of 20.7 in acetonitrile. The corresponding triflylamide **10** has a pK_a of 11.1 which implies that it is 9 orders of magnitude more acidic than benzoic acid itself. The double-triflated

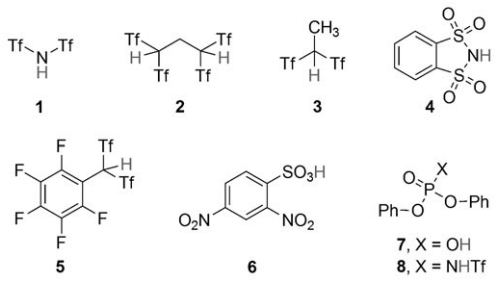
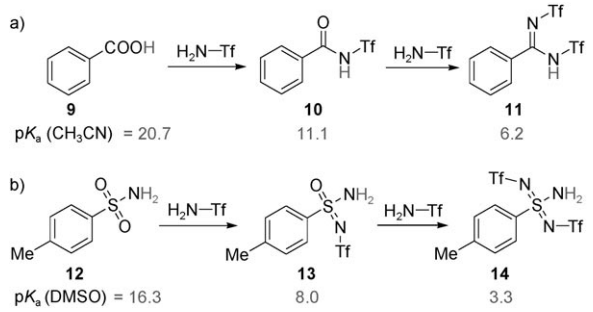


Figure 1. Examples of highly acidic organic Brønsted acids. Tf = trifluoromethanesulfonate.

[*] Prof. Dr. M. Rueping, Dr. W. Ieawsuwan, Dr. I. Atodiresei
Institut für Organische Chemie
RWTH Aachen
Landoltweg 1, 52074 Aachen (Germany)
Fax: (+94) 241-80-92665
E-mail: magnus.rueping@rwth-aachen.de
Prof. Dr. B. J. Nachtsheim
Institut für Organische Chemie
Eberhard Karls Universität Tübingen
Auf der Morgenstelle 18, 72076 Tübingen (Germany)
E-mail: boris.nachtsheim@uni.tuebingen.de



Scheme 1. Influence of electron-withdrawing groups on the pK_a of Brønsted acids.

species **11** reaches a pK_a of 6.2, indicating that it is 14 orders of magnitude stronger in acidity than benzoic acid (Scheme 1 a). A similar pattern can be described for *p*-toluenesulfonamide (**12**). Here the pK_a decreases by 8 orders of magntitude for the monotriflated compound **13** ($pK_a = 8.0$) and by 13 orders of magnitude for the bistriflated species **14** ($pK_a = 3.3$; Scheme 1 b).

The idea of lowering the pK_a of an existing Brønsted acid by introducing strong electron-withdrawing groups was also applied successfully to increase the acidity of BINOL-derived phosphoric acid derivatives **15** (Figure 2).

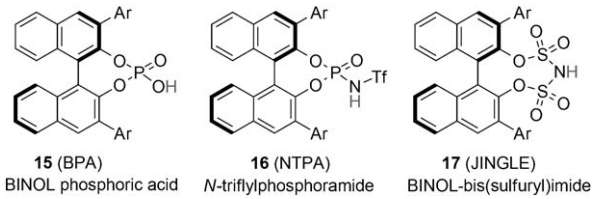


Figure 2. Structural comparison of BINOL-derived Brønsted acids.

BINOL phosphoric acids (BPAs), first described by Terada and Akiyama in their seminal articles on the organocatalytic activation of aldimines in 2004, have estimated pK_a values between 1 and 2 (13–14 in acetonitrile).[2,3,9] Due to their pK_a values, their substrate scope is generally limited to rather basic electrophiles, such as imines. To make this successful BP framework suitable for application to weakly basic and unreactive electrophiles such as carbonyl compounds, the related BINOL-derived *N*-triflylphosphoramides, (NTPAs) with estimated pK_a values between 6 and 7 in acetonitrile, were designed.[9] More recently, considerable efforts have been devoted to the development of new classes of chiral organic Brønsted acids with even higher acidity. In this context, BINOL-derived bis(sulfuryl)imides (JINGLEs) with estimated pK_a values around 5 in acetonitrile[9] have been recently described (Figure 2, right).[10] Hence, further exciting developments in this research area can be expected. Figure 3 summarizes all the BPAs and NTPAs and their derivatives that will be discussed in this Minireview.

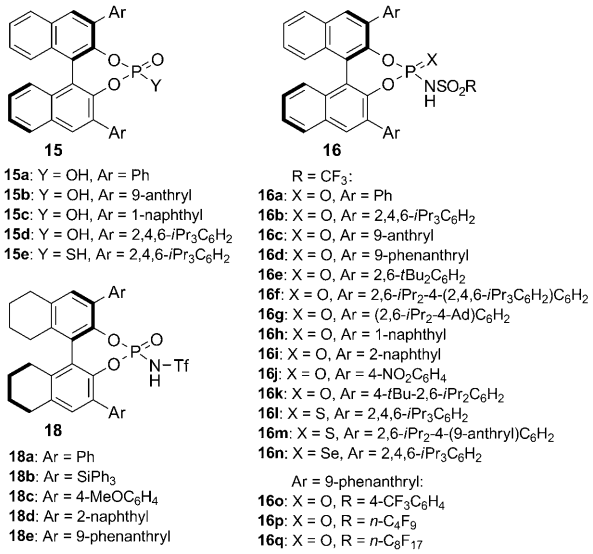


Figure 3. BINOL phosphoric acids (BPAs), *N*-triflylphosphoramides (NTPAs), and derivatives thereof. Ad = adamantyl.

2.2. Metal Ligands or Brønsted Acids

The structure of the core of NTPAs is similar to that of acetylacetonates, which are known to have a high affinity to various transition metals (Figure 4). In addition, BPAs have

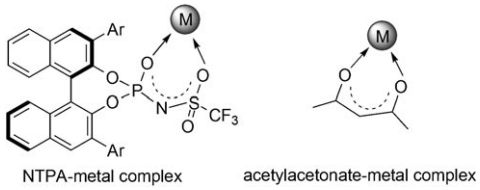


Figure 4. Structural similarities between the coordinating functional groups of NTPAs and acetylacetonate.

been used as chiral counterions and ligands in metal-catalyzed transformations and as "non-innocent" ligands in Brønsted acid assisted metal catalysis.[11] Thus, for accurate and reliable Brønsted acid catalysis, particularly for NTPA-catalyzed reactions, it is crucial to prove the absence of potential metal impurities within a catalyst sample. This aspect was investigated by our research group.[12]

Initially, crystallization experiments were performed in order to determine the structure of the catalyst. However, analysis of the crystal structure revealed the calcium(II) salt (Figure 5 a) and not the free Brønsted acid **18c**.[12] Since neither the synthetic steps nor the workup procedure involved calcium salts, it is probable that the free acid H_8-NTPA **18c** trapped calcium ions during chromatographic purification. However, after the final silica gel column the salt can be washed with 5 N HCl to yield the calcium-free H_8-NTPA **18c** (Figure 5 b).

In addition, total X-ray reflection fluorescence (TXRF) and energy-dispersive X-ray spectroscopy (EDX) analyses were performed with the purified NTPAs. Both methods are

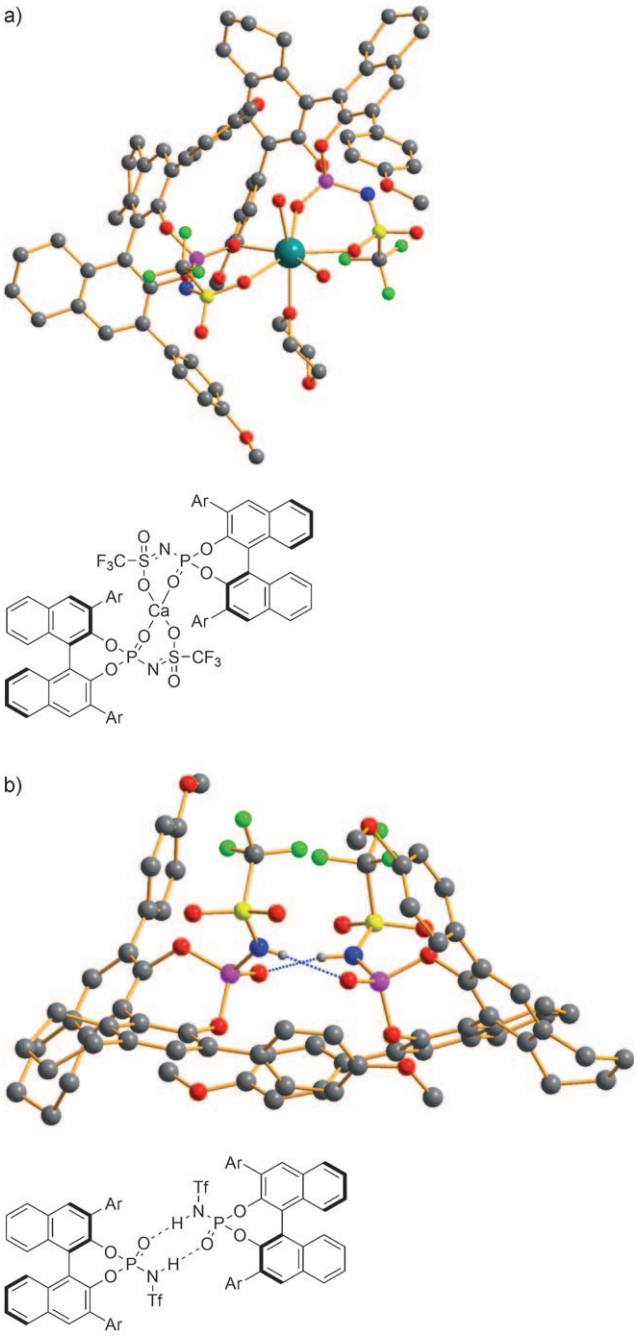


Figure 5. a) Crystal structure of the calcium salt of H_8-NTPA **18c**; Ar = 4-MeOC_6H_4. b) Crystal structure of the free acid H_8-NTPA **18c** (hydrogen atoms have been omitted for clarity); Ar = 4-MeOC_6H_4. Dark gray C, light gray H, turquoise Ca, green F, blue N, red O, pink P, yellow S.

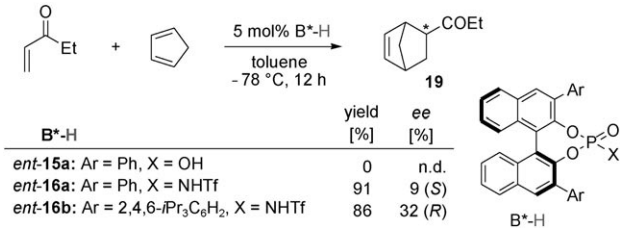
highly sensitive analytical X-ray techniques that allow insight into the elemental composition of the catalyst samples. Neither with EDX nor with TXRF, which is a more sensitive method, could calcium or any other transition-metal impurities be detected in the final sample.[12,13] The chiral calcium salts can also be employed in asymmetric catalysis.

3. NTPA-Catalyzed Cycloadditions

3.1. The First Application of Chiral NTPAs in a Diels–Alder Reaction

Asymmetric Diels–Alder reactions with α,β-unsaturated ketones present a challenge for asymmetric synthesis since the two oxygen lone pairs present on the ketone moiety have similar steric and electronic environments, making their differentiation through an activating Lewis acid inefficient. Hence, examples in which the chiral Lewis acids were used to activate simple enone dienophiles are scarce.[14] Successful Lewis acid catalyzed procedures have been developed with quinone and chelating ketones as dienophiles.[15] The recent progress in the field of chiral Brønsted acid catalyzed asymmetric reactions stimulated the development of alternative metal-free methods for enantioselective Diels–Alder reactions.

The first example of a Brønsted acid catalyzed enantioselective Diels–Alder reaction employing unsaturated diketones as the dienophiles and chiral amidinium ions catalysts was described by Göbel and co-workers, and products were obtained with good selectivity.[16] A more effective protocol was later established by Yamamoto and co-workers, who investigated the reaction of ethyl vinyl ketone with various dienes.[6] The first attempts were conducted with catalytic amounts of the well-known, BPA *ent*-**15a**. Unfortunately, the desired Diels–Alder adduct **19** was not detected (Scheme 2).

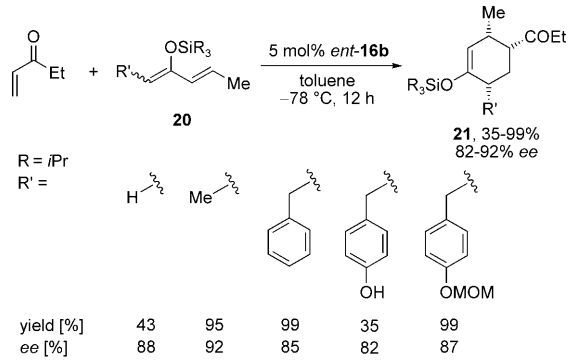


B*-H	yield [%]	ee [%]
ent-**15a**: Ar = Ph, X = OH	0	n.d.
ent-**16a**: Ar = Ph, X = NHTf	91	9 (*S*)
ent-**16b**: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$, X = NHTf	86	32 (*R*)

Scheme 2. First application of NTPAs in a Diels–Alder reaction. n.d. = not detected.

Nevertheless, **19** was obtained in excellent yield (91%), albeit with low enantioselectivity (9% *ee*), when catalyst *ent*-**16a** bearing a strong electron-withdrawing *N*-triflyl functional group was employed in the reaction. The selectivity could be improved slightly (32% *ee*) with an NTPA catalyst bearing bulkier groups in the 3,3′-positions of the BINOL scaffold.

Subsequently, the Diels–Alder reaction between ethyl vinyl ketone and siloxy diene **20** (R' = Me, SiR_3 = triisopropylsilyl, TIPS) was investigated (Scheme 3). Whereas the 3,3′-phenylated NTPA *ent*-**16a** gave only poor yield (< 10%), use of 5 mol% of the bulky 3,3′-2,4,6-*i*Pr$_3$C$_6$H$_2$-substituted NTPA *ent*-**16b** afforded the product in 95% yield and 92% *ee*. The low yield observed in the reaction with *ent*-**16a** as the catalyst is most likely due to catalyst deactivation through N-silylation.[17] In contrast, the steric bulk of the 3,3′-aryl substituents possibly prevents the catalyst *ent*-**16b** from being silylated by the siloxy diene.



Scheme 3. Scope of the NTPA-catalyzed Diels–Alder reaction. MOM = methoxymethyl.

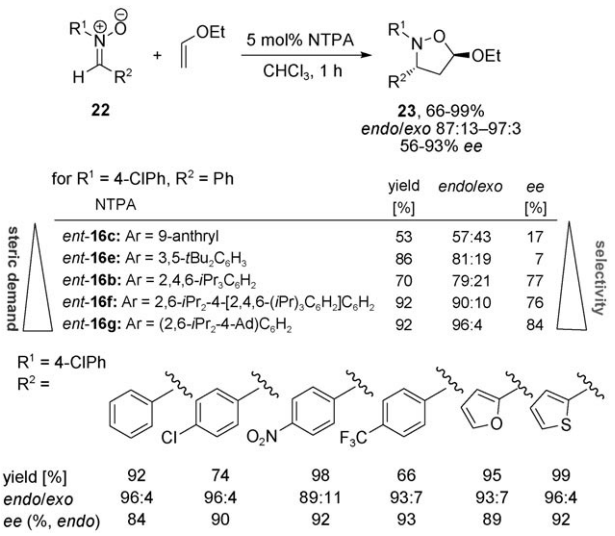
Under the optimized conditions, alkyl- and benzyl-substituted triisopropyl silyloxydienes **20** could be applied efficiently in the reaction. In addition, the presence of acid-sensitive groups is well tolerated in this chiral Brønsted acid catalyzed reaction. Whereas the selectivity was essentially not affected, the yield was considerably influenced by the substrate stability. Accordingly, use of more reactive *tert*-butyldimethylsilyl (TBS) enol ether **20b** (SiR_3 = TBS, R' = Me) or unsubstituted silyloxydiene **20c** (SiR_3 = TIPS, R' = H) led to a decrease in yield, caused by substrate protonation and catalyst deactivation. In contrast to this observation, the same authors recently demonstrated that some N-silylated triflylamides such as squaramides preserve reactivity even in their silylated form and can act as Brønsted acid catalysts in Mukaiyama aldol reactions.[18]

3.2. 1,3-Dipolar Cycloaddition of Nitrones and Ethyl Vinyl Ether

The performance of NTPAs as catalysts was subsequently examined in the 1,3-dipolar cycloaddition reaction between nitrones and ethyl vinyl ether.[19] Catalysts bearing larger groups at the 3,3′-positions proved to be superior in terms of yield and selectivity. Accordingly, the product **23a** (R^1 = 4-ClPh, R^2 = Ph) was obtained in high yield with high *endo* selectivity and good enantioselectivity, when the catalyst was bearing an adamantyl group in the *para* position of the aromatic rings present in the 3,3′-positions (Scheme 4, 92%, 96:4 *endo*/*exo*, 84% *ee*).

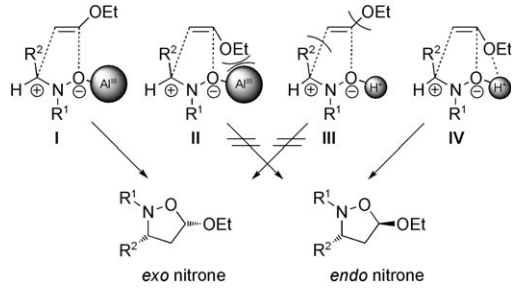
The scope of the reaction was evaluated under the optimized conditions. Products were obtained in good to high yields with high *endo* selectivity and high enantioselectivity (85–92% *ee*) when the nitrones were bearing electron-withdrawing groups on R^2. Nitrone **22** bearing unsubstituted phenyl rings ($R^1 = R^2$ = Ph) afforded products with lower enantioselectivity albeit high *endo* selectivity in reactions with both ethyl vinyl ether and *tert*-butyl vinyl ether (70 and 56% *ee*, respectively).

The method is complementary to the chiral Al–BINOL complex catalyzed dipolar cycloaddition procedure which provides products with high *exo* selectivity.[20] Different transition states have been proposed in order to rationalize the difference in diastereoselectivity between Lewis and



Scheme 4. Acid-catalyzed 1,3-dipolar cycloaddition between nitrones and ethyl vinyl ether. Reaction scope and effect of the catalyst on selectivity.

Brønsted acid catalysis. For the Lewis acid catalyzed cycloaddition reaction, the *endo* TS (**II**) is disfavored because of the high steric hindrance between the ethoxy group of the ethyl vinyl ether and the bulky Lewis acid Al^{III}. The Brønsted acid catalyzed TS (**IV**) does not have this steric hindrance (Scheme 5), and, moreover, hydrogen bonding between catalyst and substrate may stabilize the transition state leading to the *endo* product.

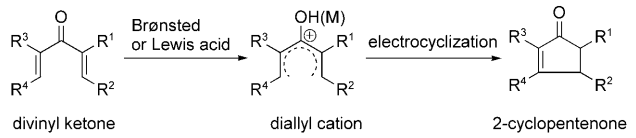


Scheme 5. Transition states for the Lewis and Brønsted acid catalyzed [3+2] cycloaddition of nitrones.

3.3. Nazarov Cyclization of Divinyl Ketones to Highly Substituted Cyclopentenones

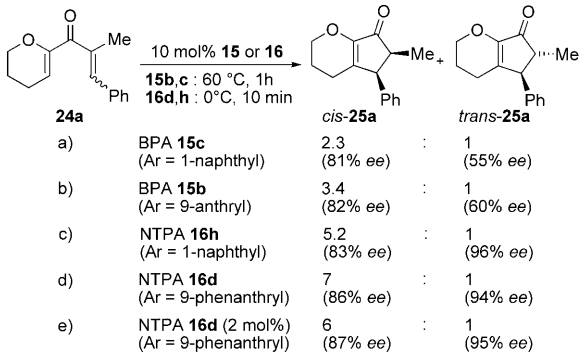
The Nazarov cyclization is defined as a 4π-electrocyclization of vinyl allyl ketones or divinyl ketones to 2-cyclopentenones and it is one of the most versatile methods for the synthesis of five-membered rings (Scheme 6).[21]

Inspired by the putative appearance of a carbocation as the reactive intermediate, we investigated an asymmetric version of this valuable transformation employing chiral Brønsted acids.[22] With 10 mol% of the chiral BPA **15b** the Nazarov cyclization of divinyl ketone **24a** afforded at 60 °C a 3.4:1 mixture of *cis* and *trans* cyclopentenones **25a** and **25b** with good enantioselectivities of 82 and 60% *ee*, respectively.



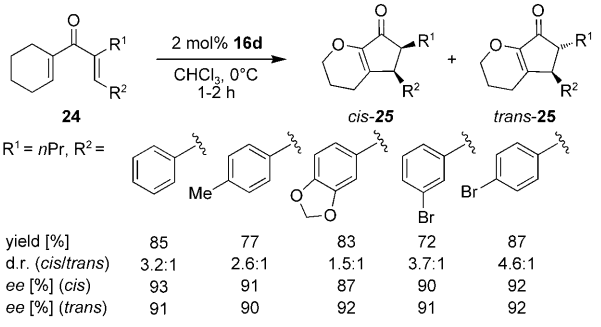
Scheme 6. Principle mechanism of the Lewis and Brønsted acid catalyzed Nazarov cyclization.

However, in order to lower the reaction temperature, a more reactive and thus stronger Brønsted acid was necessary. Different 3,3′-aryl-substituted NTPAs were evaluated and the 3,3′-phenanthryl-substituted catalyst **16d** was found to efficiently catalyze the same electrocyclization at 0 °C. The reaction was completed within 10 min and the diastereomeric ratio was improved to 7:1. Whereas the enantioselectivity of reaction leading to the *cis* cyclopentenone *cis*-**25a** was comparable to that observed with the BPA, the enantiomeric excess of the *trans* isomer *trans*-**25b** increased significantly (Scheme 7 entries (c) and (d) versus (a) and (b)). Furthermore, the catalyst loading could be decreased to 2 mol% without affecting the selectivity (6:1 *de*, 87% and 95% *ee*, Scheme 7e).



Scheme 7. Comparison of BPAs and NTPAs in the asymmetric Nazarov cyclization.

Under optimized conditions, several divinyl ketones were evaluated and products obtained with moderate to good diastereoselectivities and high enantioselectivities (Scheme 8). The methodology tolerates both electron-donating and electron-withdrawing functionalities on the aryl group

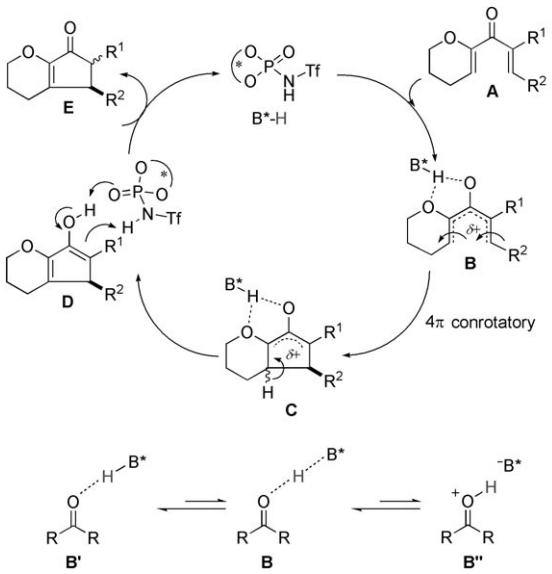


Scheme 8. Scope of the Brønsted acid catalyzed Nazarov cyclization.

R^2. In addition, dialkyl-substituted dienones are tolerated as well (R^1, R^2 = alkyl).

Moreover, the *cis* isomer was converted into the thermodynamically favored *trans* isomer without any loss of enantioselectivity by simply stirring *cis*-**25a** with basic alumina. In contrast to the known Lewis acid catalyzed methodologies which give the *trans* isomer as the main diastereoisomer,[23,24] with NTPAs both diastereoisomers are accessible with high enantioselectivities.

The postulated mechanism of the acid-catalyzed Nazarov cyclization is shown in Scheme 9. Firstly, activation of the



Scheme 9. Mechanism of the asymmetric Brønsted acid catalyzed Nazarov cyclization.

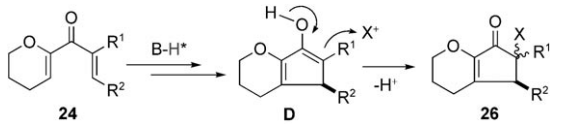
divinyl ketone **A** by the NTPA (B*-H) results in the formation of divinyl cation **B** which is stabilized by the chiral counterion B*; secondly, conrotatory 4π electrocyclization gives the oxyallyl cation **C** which upon deprotonation leads to enolate **D**. Finally, protonation of **D** furnishes the desired cyclopentenone **E** and liberates the chiral Brønsted acid catalyst B*-H (Scheme 9). Two enantiodiscriminating steps are possible within this catalytic cycle: electrocyclization leading to oxyallyl cation **C** and protonation of enolate **D**. While the chiral Brønsted acid must be the enantiodiscriminating force in the first step, it is not clear whether the second chiral center is exclusively induced by the first, or whether it is also generated by the chiral Brønsted acid.

3.4. Nazarov Cyclization/Bromination Cascade

According to the mechanism proposed in Scheme 9, the in situ generated enolate **D** may be trapped with electrophiles other than H^+. Thus a variety of Nazarov cyclization/electrophilic trapping cascades may follow this procedure. In particular, the subsequent halogenation of **D** would be of great interest since enantioenriched α-halogenated ketones

are versatile structural motifs for the synthesis of natural products and pharmaceuticals.

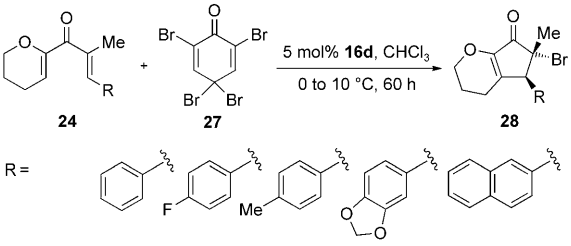
In this context, a Nazarov cyclization/bromination cascade reaction has been developed in our group (Scheme 10).[25] For this purpose several halogenating agents



Scheme 10. Principle idea of the Nazarov cyclization/halogenation cascade.

such as Selectflor, *N*-fluorobenzenesulfonimide, *N*-chlorosuccinimide, and *N*-bromosuccinimide were investigated. While the two fluorinating agents did not show satisfactory reactivity, modest amounts of the desired halogenated cyclopentenone (15%) could be observed with both halogenated succinimides in high enantioselectivities (up to 92% *ee*).

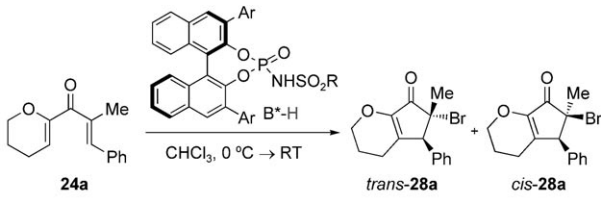
With 2,4,4,6-tetrabromocyclohexa-2,5-dienone **27** as the brominating reagent, various 3-substituted divinylketones **24** could be used as substrates for this cyclization/bromination cascade. With 5 mol% of the 3,3′-phenanthryl-substituted NTPA **16d**, the desired bromocyclopentenones **28** were isolated in good yields of up to 66% and high enantioselectivities of up to 94% *ee* (Scheme 11). In agreement with the previously described Nazarov cyclization, electron-donating as well as electron-withdrawing substituents are tolerated for R.



yield [%] (*trans*)	66	50	61	43	63
d.r. (*trans*/*cis*)	2:1	20:1	1.7:1	8:1	4.8:1
ee [%] (*trans*)	89	94	92	92	94

Scheme 11. Scope of the asymmetric NTPA-catalyzed Nazarov cyclization/bromination cascade.

In addition, the influence of the fluorinated residue of the NTPA on both the reactivity and the selectivity of the reaction was investigated (Scheme 12). When CF_3-substituted NTPA **16d** was replaced with the perfluorinated derivatives **16p** and **16q**, the yields and enantioselectivities were essentially unaffected. In contrast, the 4-$CF_3C_6H_4$-substituted derivative **16o** gave only a poor yield while the enantioselectivity decreased slightly from 90% *ee* to 88% *ee*. In conclusion, the R group of the catalyst has a significant influence on the yield but not on the enantioselectivity.



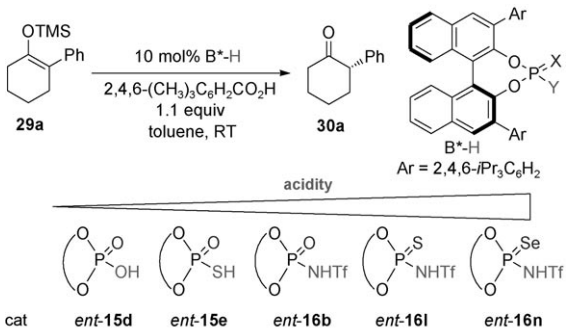
B*-H	Ar	R	*trans*/*cis*	yield [%] *trans*	*ee* [%] *trans*
16o	9-phenanthryl	R = 4-$CF_3C_6H_4$	4:1	5	88
16p	9-phenanthryl	R = *n*-C_4F_9	3:1	37	94
16q	9-phenanthryl	R = *n*-C_8F_{17}	2.8:1	40	93
16d	9-phenanthryl	R = CF_3	2.3:1	44	90

Scheme 12. Influence of the substituent R on the sulfonyl group on the asymmetric Nazarov cyclization/bromination cascade.

4. Asymmeric Protonation of Enol Derivatives

4.1. Enantioselective Protonation of Silyl Enol Ethers

The enantioselective protonation of prochiral enols is an attractive approach to chiral, α-substituted carbonyl compounds.[26] Over the past 20 years various methodologies have been investigated involving enzymes, catalytic antibodies, and chiral proton sources. In a further approach, the combination of a chiral Brønsted acid such as BINOL with achiral Lewis acids such as $TiCl_4$ or $SnCl_4$ (LBA: Lewis acid assisted Brønsted acid catalysis) leads to a pK_a decrease of the acid and successfully drives the protonation of prochiral silyl enol ethers to the corresponding α-alkylated ketones.[27] A chiral Brønsted acid that is strong enough to protonate a silyl enol ether without the aid of a Lewis acid would be desirable. Recently, the first Brønsted acid catalyzed enantioselective protonation of silyl enol ethers was described by Yamamoto and co-workers.[28] The authors investigated the protonation of the trimethylsilyl(TMS)-protected silyl enol ether **29a** in the presence of stoichiometric amounts of an achiral proton source to give enantiomerically enriched 2-phenylcyclohexanone **30a** (Scheme 13). Whereas BPA *ent*-**15d** and its thioderivative *ent*-**15e** did not show any catalytic activity, the corresponding NTPA *ent*-**16b** efficiently catalyzed this

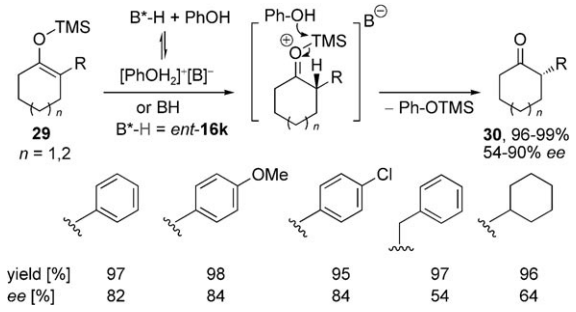


cat	*ent*-**15d**	*ent*-**15e**	*ent*-**16b**	*ent*-**16l**	*ent*-**16n**
t [h]	96	96	4.5	3.5	3.5
yield [%]	0	traces	98	97	97
ee [%]	-	-	54	78	72

Scheme 13. Enantioselective protonations of silyl enol ethers catalyzed by various BP derivatives.

valuable transformation with a short reaction time, excellent yield, and promising enantioselectivity (4.5 h, 98%, 54% *ee*). To increase the acidity of NTPA *ent*-**16b**, the authors introduced higher homologues of oxygen, for example, sulfur and selenium into the phosphoramidate scaffold. It is well known that the replacement of oxygen with sulfur or selenium can increase the acidity as a result of the increased stabilization of the conjugate anion. For example, the pK_a values of PhOH, PhSH, and PhSeH in DMSO are 18.0, 10.3, and 7.1, respectively. With *N*-triflyl thio- and selenophosphoramides *ent*-**16l** and *ent*-**16n**, the desired 2-phenylcyclohexanone (**30a**) could be obtained in quantitative yields and good enantioselectivities of 78 and 72% *ee*, respectively (Scheme 13).

A further improvement in enantioselectivity was obtained when the bulky 3,3′-4-*t*Bu-2,6-*i*$Pr_2C_6H_2$-substituted NTPA *ent*-**16k** catalyst was used in the reaction (Scheme 14). For



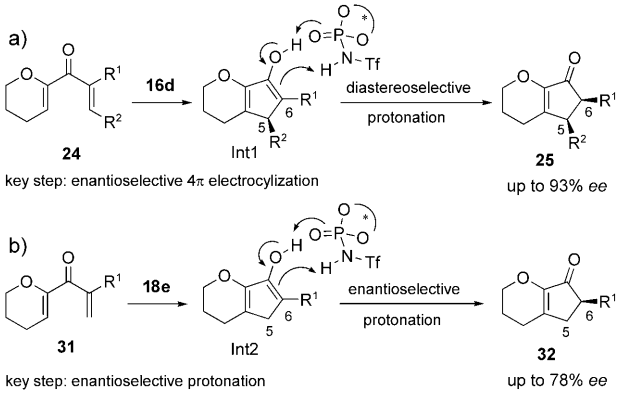
Scheme 14. Scope of the enantioselective protonation of silyl enol ethers with phenol as a stoichiometric Brønsted acid additive.

elucidating the substrate scope, phenol was used as a stoichiometric proton source instead of benzoic acid derivatives. It was assumed that phenol is able to trap the arising TMS cation more efficiently, thus preventing catalyst poisoning. Even though 5 mol% of NTPA was used for this transformation, the reaction could be performed with lower catalyst loadings, for example, 0.05 mol% NTPA *ent*-**16k**, without a significant loss in enantioselectivity and only a small decrease in yield (yield dropped from 99% to 80% for $n = 2$, R = Ph).

Various electron-rich and electron-deficient aromatic substituents are tolerated in the reaction. Additionally, benzyl- and cyclohexyl-substituted derivatives can be protonated although with slightly decreased enantioselectivities (54 and 64% *ee*, respectively). The present chiral protonation of silyl enol ethers confirms the power of the highly acidic chiral NTPAs in promoting enantioselective catalytic reactions.

4.2. Asymmetric Nazarov Cyclization/Protonation Reaction

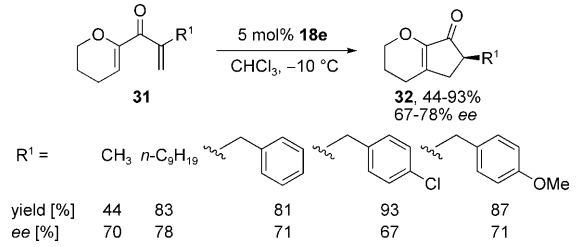
In the proposed reaction mechanism of the asymmetric Brønsted acid catalyzed Nazarov cyclization (Scheme 9), the last step of the catalytic cycle includes protonation of a prochiral enol derivative. For the Nazarov reaction of disubstituted divinylketones **24** the key step is the acid-catalyzed enantioselective 4π electrocyclization. The resulting intermediate Int_1 subsequently undergoes a diastereoselective kinetic protonation to yield the desired *cis* cyclopentenone **25** (Scheme 15a). Along these lines, if one



Scheme 15. Comparison between the Nazarov cyclization of a) disubstituted divinyl ketones **24** and b) substituted divinyl ketones **31**.

considers substituted divinylketones **31**, the 4π electrocyclization yields the intermediate Int_2, this time without a diastereodiscriminating group R^2. Hence, if the 6-substituted cyclopentenone **32** can be synthesized in an enantioselective manner, the enantiodiscriminating step is the Brønsted acid catalyzed protonation of Int_2 (Scheme 15b).[29]

To prove this assumption, a variety of substituted divinylketones **31** were synthesized and evaluated in the Nazarov reaction. Notably, the reaction could be performed with only 5 mol% of the 9-phenanthryl-substituted H_8-NTPA **18e**. Alkyl chains as well as different benzyl groups are tolerated and the desired cyclopentenones **32** are obtained in up to 93% yield and 78% *ee* (Scheme 16).

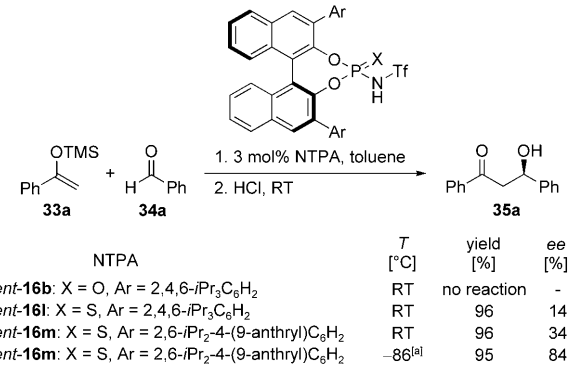


Scheme 16. Scope of the asymmetric Nazarov cyclization/protonation sequence.

5. Brønsted Acid Catalyzed Mukaiyama Aldol Reactions of Silyl Enol Ethers

The Mukaiyama aldol reaction is a convenient method for the synthesis of enantioenriched β-hydroxy ketones and was, until recently, an exclusive domain of Lewis acid activation.[30] Even though Brønsted acids and hydrogen-bond donors have been described for this transformation, in general highly activated substrates such as silyl ketene acetals had been

utilized. More stable, but on the other hand much less reactive silyl enol ethers had not been used as nucleophiles for Brønsted acid catalyzed Mukayiama aldol reactions. Recently, Yamamoto and co-workers were able to develop a highly enantioselective synthesis of β-hydroxy ketones starting from silyl enol ethers and aromatic aldehydes.[31] While NTPAs were not active enough to promote this transformation, the more acidic thio derivative *ent*-**16l** (Ar = 2,4,6-iPr$_3$C$_6$H$_2$) was able to catalyze the reaction of **33a** and benzaldehyde (**34a**) and β-hydroxy ketone **35a** was obtained in good yield and promising enantioselectivity (96%, 14% *ee*). Bulky 2,6-iPr$_2$-4-(9-anthryl)-C$_6$H$_2$ groups in the 3,3′-positions of the catalyst and a lower reaction temperature were both essential to improve further the enantioselectivity to 84% *ee* (Scheme 17).



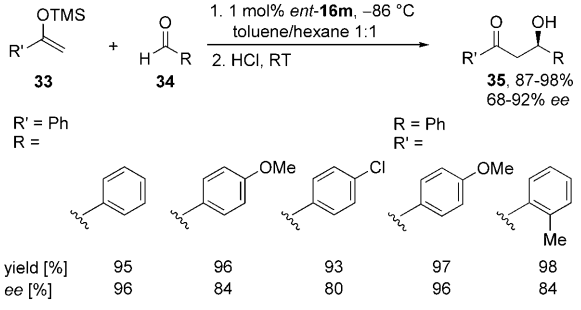
NTPA	*T* [°C]	yield [%]	*ee* [%]
ent-**16b**: X = O, Ar = 2,4,6-iPr$_3$C$_6$H$_2$	RT	no reaction	-
ent-**16l**: X = S, Ar = 2,4,6-iPr$_3$C$_6$H$_2$	RT	96	14
ent-**16m**: X = S, Ar = 2,6-iPr$_2$-4-(9-anthryl)C$_6$H$_2$	RT	96	34
ent-**16m**: X = S, Ar = 2,6-iPr$_2$-4-(9-anthryl)C$_6$H$_2$	−86[a]	95	84

[a] 1 mol% *ent*-**16m**, toluene/hexane 1:1

Scheme 17. Brønsted acid catalyzed Mukaiyama aldol reaction.

Beside benzaldehyde, a broad range of electron-rich and electron-deficient aromatic aldehydes as well as heteroaromatic aldehydes such as 2-thienyl aldehyde are tolerated in this reaction. Furthermore, various silyl enol ethers react under these conditions (Scheme 18).

In a similar procedure, List and co-workers used a chiral disulfonimide as a potential highly acidic catalyst. In this case, a Lewis acid generated in situ through silylation of the bisulfonimide turned out to be the actual catalytically active species.[32] In order to establish whether the Brønsted acid is involved as the catalytic active species, Yamamoto and co-workers performed experiments in the presence of 2,6-di(*tert*-butyl)pyridine (DTBP), a proton scavenger known to strongly inhibit Brønsted acid catalysis. Surprisingly, DTBP inhibited the Mukaiyama aldol reaction between **33a** and benzaldehyde (**34a**) at −86 °C but not at room temperature; this result strongly implies a temperature-dependent mode of activation with a dominant Brønsted acid catalyzed pathway at low temperature.



Scheme 18. Scope of the Brønsted acid catalyzed Mukaiyama aldol reaction.

6. Enantioselective Acid-Catalyzed Friedel–Crafts Alkylations

6.1. 1,4-Addition of Indoles to α,β-Unsaturated Carbonyl Compounds

The potential of Brønsted acids to activate carbonyl compounds such as enones toward various C-nucleophiles was investigated by Rueping et al.[33,34] Owing to the abundance of indole as a core structure in many natural products and biologically active substances, indole derivatives were preferred as nucleophiles in these studies. Chalcones and β,γ-unsaturated α-ketoesters were selected as versatile electrophilic substrates. Since BPAs proved to be not reactive enough, NTPAs were again used as highly acidic Brønsted acids for this purpose.

Although the two substrates (α-ketoesters and chalcones) appear to be similar, for enantioselective transformations the second carbonyl compound of the α-ketoester is essential (Figure 6). This second coordinating group fixes the system in

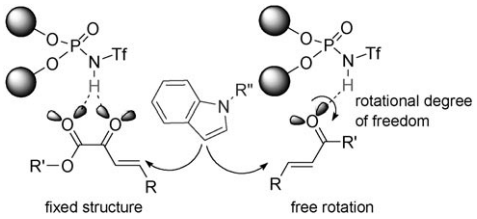
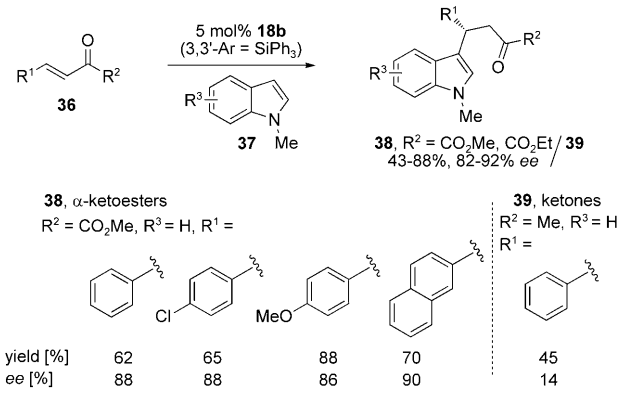


Figure 6. Comparison of the acid-catalyzed activation of α-ketoesters and chalcones.

a rigid conformation, whereas chalcones have an additional rotational degree of freedom around the protonation site. Efforts to activate both α-ketoesters and chalcones toward addition were made; however, while γ-arylated α-ketoesters **38** were isolated with excellent enantioselectivities (up to 92% *ee*), the β-arylated ketone **39** (R^1 = Ph, R^2 = Me, R^3 = H) was isolated in only moderate yield (45%) with moderate selectivity (14% *ee*, Scheme 19).

Detailed studies showed that the shape of the catalyst is highly important for the desired 1,4-addition. The 3,3′-silylated H$_8$-NTPA **18b** was the only catalyst that gave the desired 1,4-addition products **38** in satisfactory yields. All other utilized catalysts including the 3,3′-phenanthryl-substituted NTPA **16d** yielded the atropisomeric bisindole **40** as the major product (Figure 7). This result can be rationalized with a steric model of both catalysts. Firstly, the 3,3′-Si–C bonds in **18b** are longer than the corresponding C–C bonds in **16d** and secondly the 3,3′ substituents in H$_8$-NTPA **18b** have a



Scheme 19. Substrate scope of the NTPA-catalyzed 1,4-addition between *N*-methylindole and β,γ-unsaturated α-ketoesters and chalcones.

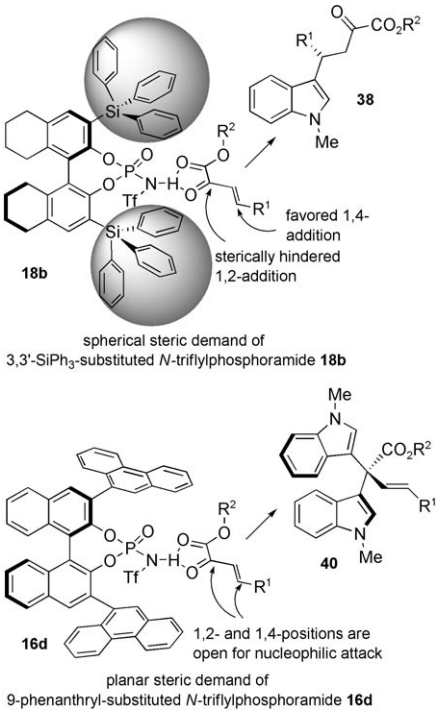
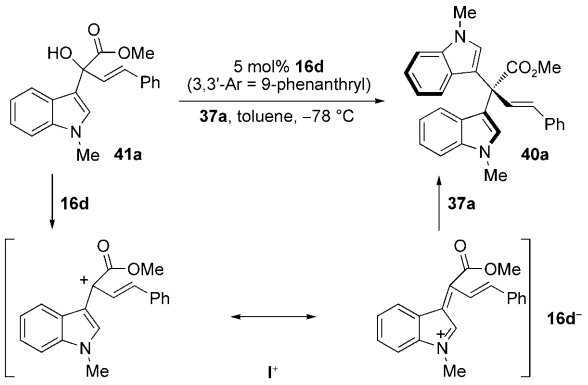


Figure 7. Steric reasons for the favored 1,4-addition with 3,3′-silylated NTPA **18b**.

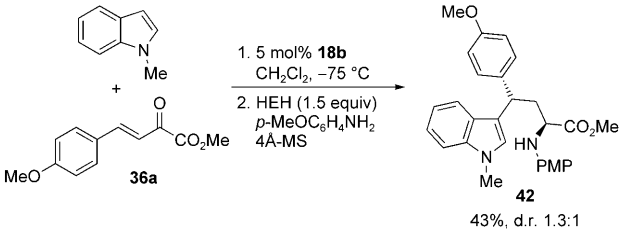
spherical shape, while the 3,3′-aryl groups in **16d** are planar. Therefore, in the case of catalyst **18b**, the carbonyl group, which must be attacked by the *N*-methylindole for bisindole formation, is blocked by the bulky silylated substituents, while in the case of the 9-phenanthryl-substituted catalyst **16d** this 1,2-attack is sterically favored.

To understand the mechanism of the bisindole formation, racemic **41a** was synthesized and subjected to the established reaction conditions (5 mol% **16d**, indole **37a**, toluene, −78 °C, Scheme 20). Bisindole **40a** was obtained with an enantiomeric ratio of 78:22. This result confirms that **41a** undergoes acid-catalyzed nucleophilic substitution to give bisindole **40a** via the corresponding chiral ion pair $\mathbf{I}^{+}\mathbf{16d}^{-}$.



Scheme 20. Brønsted acid catalyzed formation of a bisindole.

In addition, a one-pot two-step procedure for the synthesis of protected α-amino acids through a Brønsted acid catalyzed Friedel–Crafts alkylation with subsequent reductive amination was also described (Scheme 21).

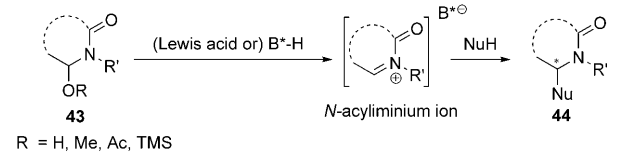


Scheme 21. Sequential Friedel–Crafts alkylation/reductive amination reaction. HEH = Hantzsch ester.

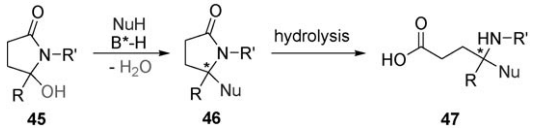
6.2. The Acid-Catalyzed Generation of N-Acyliminium Ions

The generation of *N*-acyliminium ions and their subsequent reaction with nucleophiles is an interesting method for the enantioselective synthesis of amines and amides bearing a chiral center in the α position. A variety of Lewis and Brønsted acid catalyzed procedures are known, in which the corresponding protected N,O-acetals are utilized as precursors for the in situ generation of reactive *N*-acyliminium intermediates (Scheme 22).[35]

It was envisaged that strong organic Brønsted acids such as NTPAs may also be able to generate *N*-acyliminium ions from N,O-acetals. In particular, γ-hydroxylactams **45** are of interest since subsequent hydrolysis of the enantioenriched γ-lactams **46** would lead to γ,γ′-substituted γ-amino acids of type **47**, a frequently used structural motif in drugs with neuroleptic activity such as pregabalin (Scheme 23).

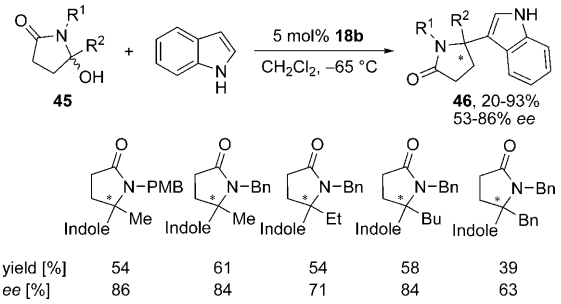


Scheme 22. Acid-catalyzed formation of *N*-acyliminium ions. Nu = nucleophile.



Scheme 23. Substitution and hydrolysis of γ-hydroxylactams.

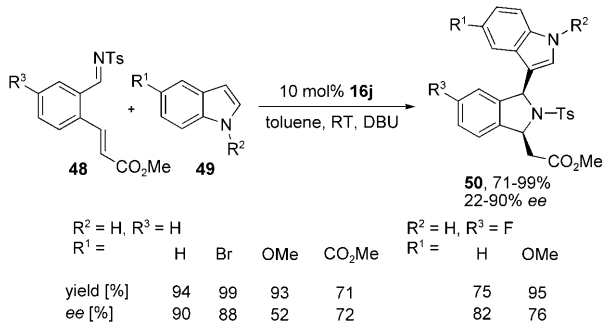
With indoles as nucleophiles it was found that 5 mol% of the 3,3′-silylated NTPA **18b** catalyzes the substitution of γ-hydroxylactams efficiently.[36] The desired indole-substituted γ-lactams **46** were isolated with good enantioselectivities of up to 86% *ee*. Since most of the yields are around 50%, selective recognition of one of the enantiomers of racemic **45** by the chiral Brønsted acid can be assumed. In substrate **45** the protecting group on the nitrogen atom (R^1) and the substituent at C5 of the γ-lactam could be varied. Here, different alkyl chains and benzyl groups are tolerated (Scheme 24). Secondary alcohols reacted with significantly lower yields and selectivities ($R^2 = H$, $R^1 = Bn$ 39%, 25% *ee*).



Scheme 24. Scope of the NTPA-catalyzed substitution of γ-hydroxylactams **45**. Bn = benzyl, (3)-Ind = (3)-indolyl, PMB = *para*-methoxybenzyl.

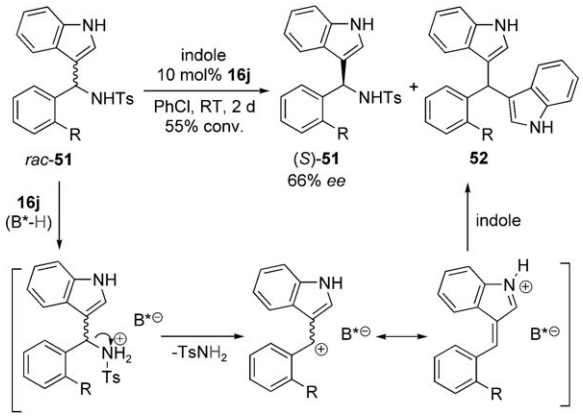
6.3. Asymmetric Isoindoline Synthesis by Stereoablative Kinetic Resolution

Enders and co-workers developed an acid-catalyzed domino aza-Friedel–Crafts/aza-Michael reaction in which enantioenriched isoindolines could be synthesized in one step starting from ε-iminoenoates.[37] Although BPAs are known to catalyze the Friedel–Crafts reaction of indoles with various imines, in this particular case no catalytic activity could be detected. However, the reaction could be promoted by the more acidic NTPAs. The reaction proved to be regioselective as no Friedel–Craft-type 1,4-addition of indole to the α,β-unsaturated carboxylic ester was observed. Apparently the imine is far more reactive than the enoate functionality. The electronic effects and the substitution pattern of the 3,3′ substituents of the catalyst seemed to have a big impact on selectivity. The bulky 3,3′-$SiPh_3$- and 4-biphenyl-substituted NTPAs showed significantly lower selectivities than the 4-$NO_2C_6H_4$-substituted NTPA **16j**. For the subsequent 1,4-addition, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was necessary. Accordingly, the desired isoindolines were isolated in good to excellent yields and up to 90% *ee* (Scheme 25).



Scheme 25. Scope of the NTPA-catalyzed isoindoline synthesis. Ts = toluene-4-sulfonyl.

As previously described in Section 6.1,[34] bisindole **52** (Scheme 26) was the major side product, which arises from the acid-catalyzed nucleophilic substitution of the tosylamine



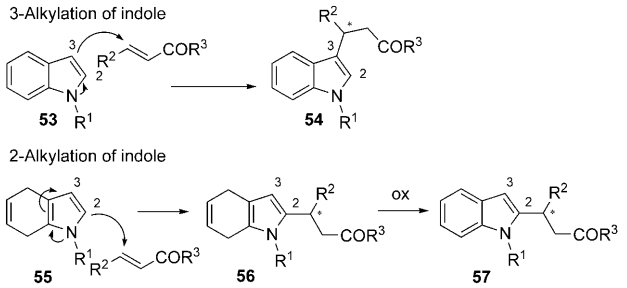
Scheme 26. Chiral Brønsted acid induced kinetic resolution of *rac*-**51**.

formed in situ. Interestingly, with increasing reaction time, the formation of the undesired bisindole **52** increased and the yield of isoindoline **50** decreased, while the enantioselectivity increased. This indicates a stereoablative kinetic resolution during the acid-catalyzed step. To test this presumption, *rac*-**51** was synthesized and reacted with indole in the presence of catalyst **16j**. When the reaction was interrupted prior to completion, enantioenriched (*S*)-**51** was reisolated with 66% *ee* and bisindole **52** could be observed (Scheme 26). Furthermore, the reaction stops at 55% conversion. This strongly indicates enantioselective recognition of **51** by the chiral NTPA and subsequent reaction of only one of the enantiomers with a second equivalent of indole.

6.4. 1,4-Addition of Dihydroindoles to α,β-Unsaturated Carbonyl Compounds

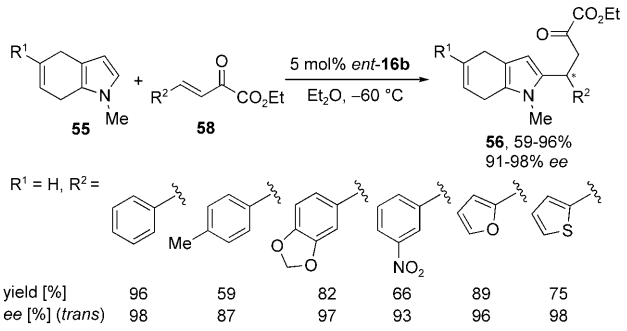
Whenever indole derivatives **53** are utilized as nucleophiles in Friedel–Craft-type transformations or in Michael-type additions, C3 of the indole scaffold is alkylated with nearly perfect regioselectivity yielding 3-alkylated indoles **54**.[38] In contrast, alkylation of C2 is a much more challenging

task. 4,7-Dihydroindoles **55** in general are preferentially alkylated at the C2 position yielding 2-alkylated 4,7-dihydroindoles **56** as major regioisomer. A subsequent oxidation step gives the desired 2-substituted indoles **57** (Scheme 27).



Scheme 27. Different approaches to 2- and 3-alkylated indoles **57** and **54**, respectively.

Based on this knowledge, You and co-workers developed an elegant NTPA-catalyzed synthesis of C2-alkylated indoles utilizing 4,7-dihydroindoles **55** as indole precursors.[39] Using only 5 mol% of 2,4,6-iPr$_3$C$_6$H$_2$-substituted NTPA *ent*-**16b** they could isolate the desired 2-alkylated dihydroindoles **56** in good yields and excellent enantioselectivities of up to 98% *ee* (Scheme 28). When the product of the Friedel–Craft reaction

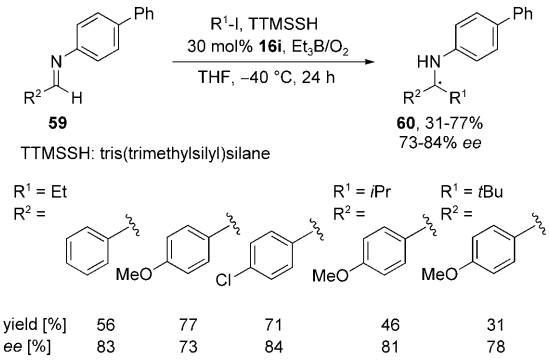


Scheme 28. Scope of the NTPA-catalyzed alkylation of 4,7-dihydroindole.

was oxidized with *p*-benzoquinone, the corresponding indole **57** was obtained in 59% yield (yield over two steps) without loss of enantioselectivity. This was the first organocatalytic approach to 2-substituted indoles. Until then only Lewis acid catalyzed procedures utilizing Zr^{IV} and Sc^{III} had been known for this valuable transformation.

7. NTPA-Catalyzed Activation of Aldimines

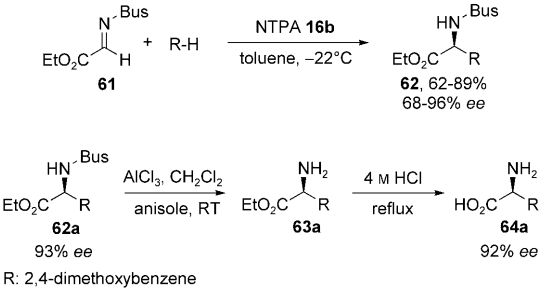
As described in Section 2.1, NTPAs were initially designed as strong Brønsted acids for the activation of weakly basic electrophiles such as carbonyl compounds. However, there are an increasing number of examples in which NTPAs activate strongly basic aldimine substrates more efficiently than the corresponding BPAs. Kim and Lee developed a radical addition reaction of alkyl iodides to *N*-aryl imines (Scheme 29).[40] The 2-naphthyl-substituted NTPA **16i** outperformed its phosphoric acid counterpart in terms of both reactivity and enantioselectivity. Although a high catalyst



Scheme 29. NTPA-catalyzed radical addition of alkyl iodides to imines.

loading of 30 mol% was necessary for sufficient reactivity, a variety of aryl aldimines **59** could be alkylated and gave the desired secondary amines **60** in enantioselectivities of up to 84% *ee* and moderate yields. In particular, the yields of *i*Pr- and *t*Bu-substituted amines were low because of the undesired ethylation reaction with the radical starter Et_3B.

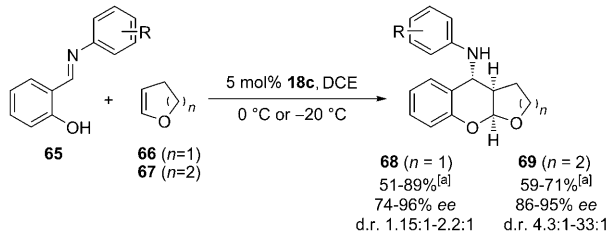
An NTPA-catalyzed Friedel–Crafts reaction of arenes with glyoxylate imines **61** was described by Enders and coworkers.[41] With only 1 mol% of NTPA **16b**, highly valuable arylglycines **62** were isolated in high yields and excellent enantioselectivities of up to 96% *ee* (Scheme 30). Electron-



Scheme 30. Enantioselective synthesis of arylglycines through an acid-catalyzed Friedel–Crafts alkylation of glyoxylate imines. Bus = *tert*-butylsulfonyl.

rich arenes such as anisole, 1,3-dimethoxybenzene, 1-methoxynaphthalene, and *S*-methyl thiophenols were tolerated. The arylglycine **62a** was converted into the free amino acid derivative **64a** by $AlCl_3$-mediated deprotection of the amine and subsequent hydrolysis of the ester without a significant loss in enantiomeric excess.

An asymmetric domino Mannich/ketalization reaction between *ortho*-hydroxybenzaldimines **65** and 2,3-dihydro-2*H*-furan (**66**, $n=1$) or 3,4-dihydro-2*H*-pyran (**67**, $n=2$) was described by Rueping et al. (Scheme 31).[42] The desired furanobenzopyranes **68** were isolated with excellent enantioselectivities of up to 96% *ee*, albeit with low diastereoselectivities. Improved diastereomeric ratios were observed in the



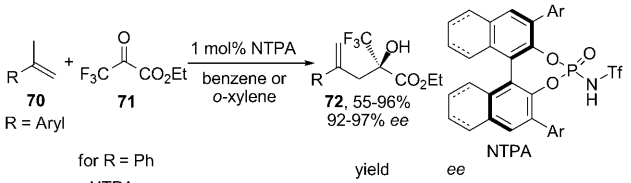
[a] Yields refer to the mixture of the two diastereomers.

Scheme 31. Asymmetric Mannich ketalization reaction for the synthesis of aminobenzopyranes. DCE = 1,2-dichloroethane.

case of pyranobenzopyrans **69**. This protocol complements the Brønsted acid catalyzed inverse-electron-demand aza-Diels–Alder reaction between *N*-(2-hydroxyphenyl)aldimines and dihydropyrans which gives access to tetrahydroquinolines as described by Akiyama and co-workers.[43] In the latter case the reaction is proposed to occur through a transition state in which the BINOL phosphoric acid acts as hydrogen-bond donor and hydrogen-bond acceptor simultaneously.

8. Organocatalytic Carbonyl-Ene Reaction

The asymmetric ene reaction with carbonyl enophiles is an attractive method for the preparation of valuable homoallylic alcohols.[44] Given that Brønsted acids have been successfully employed to activate α-ketoesters, the activation of highly reactive trifluoromethylpyruvate as the electrophilic component in the carbonyl-ene reaction was explored.[45] The first enantioselective carbonyl-ene reaction was developed with α-methylstyrene as the nucleophile (Scheme 32). Only

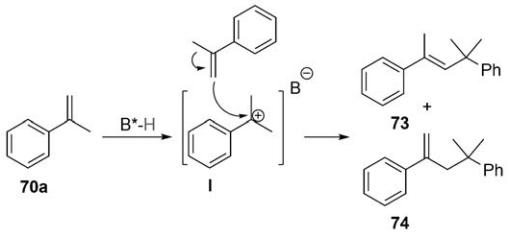


for R = Ph NTPA	yield [%]	ee [%]
18b: Ar = $SiPh_3$, [H_8]	15	7
16d: Ar = 9-phenanthryl	52	28
16c: Ar = 9-anthryl	24	26
16i: Ar = 2-naphtyl	63	81
16j: Ar = 4-$NO_2C_6H_4$	70	86
18c: Ar = 4-$MeOC_6H_4$, [H_8]	86	94

Scheme 32. The Brønsted acid catalyzed carbonyl-ene reaction.

1 mol% of the 3,3′-4-$MeOC_6H_4$-substituted H_8-NTPA **18c** sufficed to provide access to useful homoallylic alcohols **72** in up to 96% yield and 97% *ee*. The reaction is of interest not only because important fluorinated α-hydroxyesters are obtained, but also because of the observed catalyst–reactivity and catalyst–selectivity relationships. While the bulky 3,3′-$SiPh_3$-substituted H_8-NTPA **18b** and the 9-phenanthryl-substituted NTPA **16d** gave only low yields and selectivities (7 and 28% *ee*, respectively), the 3,3′-4-$NO_2C_6H_4$-substituted NTPA **16j** and the 3,3′-4-$MeOC_6H_4$-substituted H_8-NTPA **18c** gave high yields and excellent enantioselectivities. The two substituents have one similarity—strong π-conjugation along the aromatic systems arising from the electon-donating character of OMe and the electron-withdrawing propensity of NO_2. However, the reason for their similar catalytic behavior was not explained.

Kinetic studies indicate that the catalyst concentration does not influence the reaction kinetics, which implies a specific acid-catalyzed reaction. Apart from the designed ene reaction, the concurrent side reaction observed in halogenated solvents is also of interest. With α-methyl styrene, **73** and **74** were observed as side products when the reaction was performed in chlorinated solvents (Scheme 33). These side

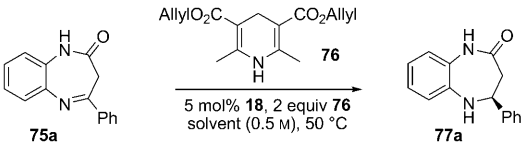


Scheme 33. Major side product of the NTPA-catalyzed carbonyl-ene reaction.

products, which result from the dimerization of methyl styrene, confirm the extremely high acidity of NTPAs and their ability to generate carbocationic intermediates of type **I** from simple alkenes such as styrenes. This result is important for the development of novel Brønsted acid catalyzed C–C bond-forming reactions.

9. Reduction of Imines

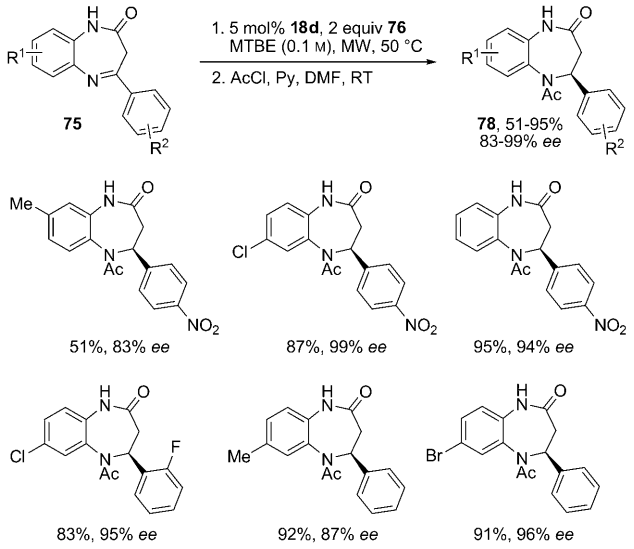
Benzodiazepines constitute a class of privileged structures in medicinal chemistry and are widely used in the treatment of anxiety neurosis and insomnia. So far, chiral compounds with a [1,5]benzodiazepine-2-one framework have been obtained through racemic resolution with D-(+)-3-bromocamphor-8-sulfonic acid. The first enantioselective catalyzed reaction leading to 4-substituted 4,5-dihydro-1*H*-[1,5]benzodiazepine-2(3*H*)-ones was recently reported by Rueping and co-workers.[46] In contrast to BPAs, which showed only low catalytic activity in the reduction of cyclic imines, promising results were obtained with H_8-NTPAs (Scheme 34). At 50 °C in THF, comparable selectivities were achieved with the H_8-NTPAs bearing 2-naphthyl, phenyl, or 4-$MeOC_6H_5$ groups in the 3,3′-positions. The selectivity improved further when the reaction was conducted in methyl *tert*-butyl ether (MTBE) solvent under microwave irradiation. Under these optimized conditions a broad range of cyclic imines were reduced and subsequently acetylated to give the corresponding products **78** in moderate to high yields and high to excellent selectivities (Scheme 35).



NTPA	Solvent	*ee* [%]
18d: Ar = 2-naphthyl [H_8]	THF	68
18a: Ar = Ph [H_8]	THF	63
18c: Ar = 4-MeOC$_6$H$_4$ [H_8]	THF	64
18d: Ar = 2-naphthyl [H_8]	MTBE	87
18d: Ar = 2-naphthyl [H_8]	MTBE[a]	90

[a] 0.1 M, MW irradiation

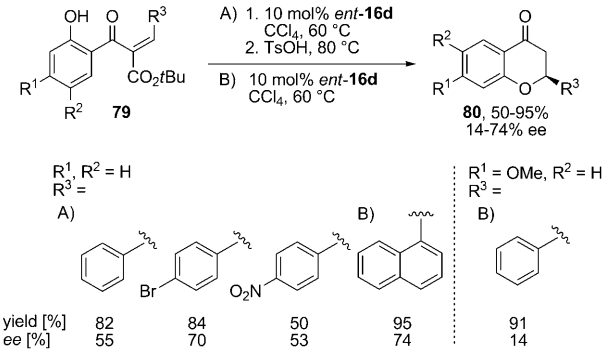
Scheme 34. NTPAs in the enantioselective reduction of 1,5-benzodiazepin-2-ones. MW = microwave.



Scheme 35. Scope of the NTPA-catalyzed enantioselective reduction of cyclic imines. Py = pyridine.

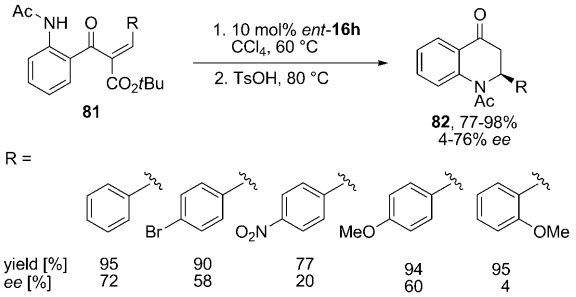
10. 1,4-Additions

NTPAs were recently reported to catalyze the asymmetric intramolecular oxa- and aza-Michael addition to activated α,β-unsaturated ketones.[47,48] In the addition of O-nucleophiles, nonpolar solvents and a bulky *tert*-butyl ester group on the substrate proved to be beneficial for asymmetric induction. Under optimized conditions, substrates **79** bearing various aryl groups could be cyclized and decarboxylated to give flavanones **80** in moderate to high yields and up to 74% *ee* (Scheme 36).[47]



Scheme 36. NTPA-catalyzed intramolecular oxa-Michael addition.

2-Aryl-2,3-dihydroquinolin-4-ones **82** were obtained in a similar manner through an asymmetric aza-Michael addition starting from **81** (Scheme 37).[48] The yields ranged from good to excellent, whereas the selectivity varied with the electronic properties of the aryl substituent.

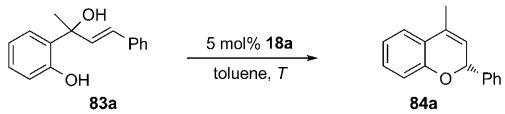


Scheme 37. NTPA-catalyzed intramolecular aza-Michael addition.

11. Asymmetric Allylic Alkylation

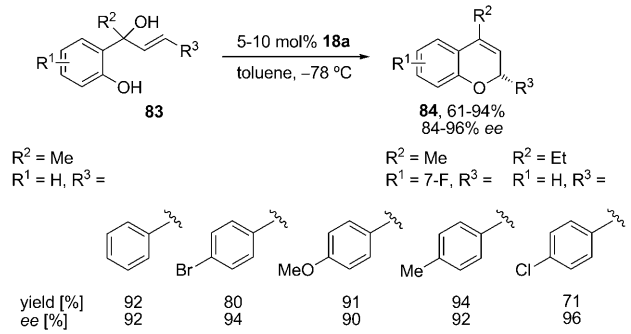
Asymmetric allylic alkylation is a well-established method for the construction of C–C and C–X bonds, and is frequently applied in the synthesis of complex organic molecules.[49] In contrast to metal-catalyzed processes, which have been extensively studied, metal-free asymmetric versions have remained less developed.[50] An asymmetric allylic alkylation promoted by NTPAs was recently described.[51] The evaluation of different BPAs and NTPAs revealed the latter as promising catalysts for the enantioselective synthesis of 2*H*-chromene **84a** starting from phenol **83a** (Scheme 38). H_8-NTPA **18a** bearing phenyl groups at the 3,3′-positions gave the best results in terms of yield and selectivity. Further improvements were achieved by lowering the temperature and increasing the catalyst loading.

Under optimized conditions a large variety of phenol derivatives **83** underwent alkylation to give the corresponding chromenes **84** in good to very high yields and up to 96% *ee* (Scheme 39). The reaction tolerates different alkyl substitu-



NTPA	*T* [°C]	yield [%]	*ee* [%]
18a: Ar = Ph [H_8]	0	77	56
18a: Ar = Ph [H_8]	–48	80	73
18a: Ar = Ph [H_8]	–78	76	88
18a: Ar = Ph [H_8] (10 mol%)	–78	92	92

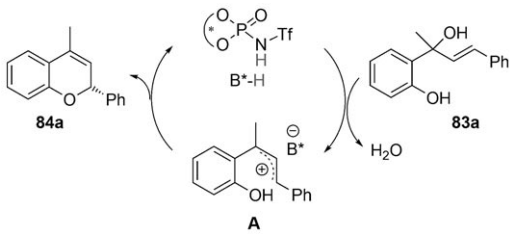
Scheme 38. Effect of temperature and catalyst loading on the selectivity of the allylic alkylation reaction.



Scheme 39. Scope of the NTPA-catalyzed asymmetric allylic alkylation.

ents R^2 and various residues on the phenol and phenyl rings (R^1 and R^3).

It is assumed that the first step involves protonation of the allylic alcohol. Dehydration yields a carbocation which forms a chiral contact ion pair **A** with the NTPA anion B*. Deprotonation of the phenolic hydroxy group by the catalyst and subsequent intramolecular attack of the O-nucleophile yields the product and regenerates the catalyst (Scheme 40).



Scheme 40. Proposed mechanism for the enantioselective allylic alkylation.

12. Summary and Outlook

This Minireview describes the development and various applications of NTPAs as highly acidic Brønsted acid catalysts. The introduction of a triflylamide into well-known BPs leads to a significant decrease in pK_a and thus to a wider range of substrates from protonated imines to carbonyl compounds and more recently to simple alkenes through the generation of carbocations (Figure 8).

Owing to the structure of the catalyst, its steric and electronic properties can be fine-tuned so that the best catalyst structure for a given transformation can be gained. Chiral NTPAs have been crucial in various protocols for the enantioselective construction of C–C and C–X bonds. NTPAs have been applied in asymmetric cycloadditions, Nazarov cyclizations, 1,4-additions, nucleophilic substitutions, asymmetric protonations, reductions, and ene reactions. Further developments in this exciting area can be expected in the near future. However, further elaboration of the NTPAs is necessary in order to increase acidity, improve selectivities, decrease the catalyst loadings, and perform the reactions under milder conditions.

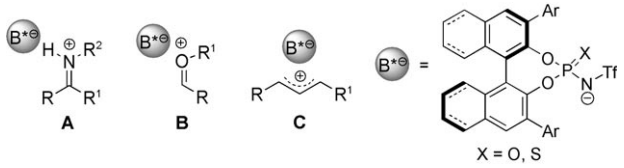


Figure 8. Activation modes for the NTPA-catalyzed enantioselective reactions.

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