Asymmetric Synthesis (2)

DOI: 10.1002/anie.200802139

Highly Enantioselective Organocatalytic Carbonyl-Ene Reaction with Strongly Acidic, Chiral Brønsted Acids as Efficient Catalysts**

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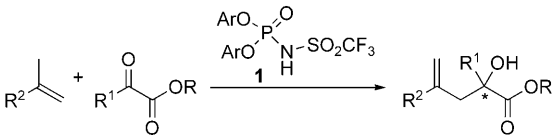
Asymmetric Brønsted acid catalysis has emerged as a powerful tool in organic synthesis.[1] In particular, chiral phosphoric acids have become established as useful organocatalysts for highly enantioselective transformations. The central role performed by the phosphoric acids in such reactions is the activation of the electrophile by catalytic protonation to form an intermediary ion pair composed of the activated (protonated) electrophile and a chiral phosphate counterion. This counterion induces the high enantioselectivities observed. Various enantioselective transformations of aldimines and ketimines have been carried out by applying this strategy.[2–3] We demonstrated that not only imines,[4] but also carbonyl compounds can be activated effectively by chiral phosphoric acids.[5] Our studies also revealed superior catalysts to chiral phosphates: Greatly improved reactivities and selectivities were observed with the more acidic *N*-triflylphosphoramides, which can also be used as catalysts for other transformations of carbonyl groups. It is therefore astonishing that only four enantioselective transformations with these effective acidic catalysts have been developed to date: our Nazarov cyclizations[5] and 1,2- and 1,4-additions,[6] as well as two cycloaddition reactions described by Yamamoto and co-workers.[7]

Herein we report a new application of these highly reactive phosphoramides in the development of the first highly enantioselective organocatalytic carbonyl-ene reaction. The carbonyl-ene reaction is an important carbon–carbon bond-forming reaction for the preparation of synthetically valuable homoallylic alcohols.[8] Substantial progress has been made in the development of enantioselective inter- and intramolecular variants with different metal catalysts, including chiral aluminum, titanium, zinc, copper, palladium, platinum, and chromium complexes.[9,10] However, a highly enantioselective organocatalytic carbonyl-ene reaction has not been described. Recently, Clarke et al. reported the application of the Schreiner catalyst[11] (1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea) in the first organocatalytic ene reaction.[12] However, the further extension of this methodology to an asymmetric variant by using a chiral thiourea derivative proved difficult; only low reactivities and moderate selectivities were observed.[13] Given the importance of the carbonyl-ene reaction and the resulting products, the development of an intermolecular, highly enantioselective organocatalytic ene reaction appeared to us to be of great significance. On the basis of our continuing studies on Brønsted acid catalyzed carbonyl-group activations, we believed that an asymmetric carbonyl-ene reaction should be possible with the strongly acidic *N*-triflylphosphoramides as catalysts [Eq. (1)].



(1)

We started our investigations of the Brønsted acid catalyzed ene reaction by testing various combinations of alkene donors and carbonyl acceptors. Preliminary studies revealed that *N*-triflylphosphoramides catalyze intermolecular carbonyl-ene reactions of various glyoxalate and pyruvate derivatives. The corresponding α-hydroxy esters, valuable pharmaceutical intermediates and chiral building blocks for natural products synthesis, were isolated in good yields. Next, we explored an asymmetric variant of the ene reaction by employing the chiral *N*-triflylphosphoramide catalysts **1a**–**j** and the α,α,α-trifluoropyruvate **3a** as the carbonyl acceptor (Table 1). α-Trifluoromethyl esters, such as the products **4**, are of great significance for the synthesis of pharmaceuticals and agrochemicals owing to their unique electronic structure, which affects both their pharmacodynamic and pharmacokinetic properties.[14,15]

Thus, the reaction of α-methylstyrene **2a** with the trifluoropyruvate **3a** in the presence of a catalytic amount of the chiral *N*-triflylphosphoramides **1a**–**1j** provided the desired α-hydroxyester **4a**. The best result with regard to reactivity, yield, and selectivity was observed with catalyst **1j**, which provided the desired product **4a** with 94% *ee*.

Further optimization of the reaction focused on the temperature and the solvent employed, as both played a crucial role in our earlier studies on Brønsted acid catalyzed reactions. The *N*-triflylphosphoramide-catalyzed ene reaction can be carried out in various apolar, nonprotic solvents at different temperatures. However, the use of aromatic solvents gave the best results: The α-hydroxy ester **4a** was formed in *o*-xylene at 10°C with 96% *ee* (see the Supporting Information).[16]

Interestingly, in chlorinated solvents, the dimerization of methylstyrene occurred, and **5a** and **5b** were isolated as the

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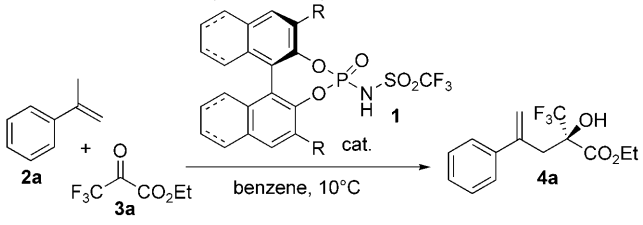
[**] We thank Evonik Degussa and the DFG (Priority Programme Organocatalysis) for financial support, as well as the Fonds der Chemischen Industrie for a scholarship awarded to A.K.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200802139.

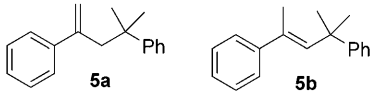
Table 1: Survey of *N*-triflylphosphoramide catalysts for the enantioselective Brønsted acid catalyzed carbonyl-ene reaction.[a]



Entry	**1**	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	phenyl	25	41	53
2	**1b**	2-naphthyl	23	63	81
3	**1c**	3,5-$(CF_3)_2C_6H_3$	26	32	36
4	**1d**	phenanthryl	23	52	28
5	**1e**	anthracenyl	38	24	26
6	**1f**	biphenyl	25	61	77
7	**1g**	*p*-$NO_2C_6H_4$	13	70	86
8	**1h**	$SiPh_2Me$ [H_8]	26	34	56
9	**1i**	$SiPh_3$ [H_8]	38	15	7
10	**1j**	*p*-$MeOC_6H_4$ [H_8]	34	86	94

[a] Reaction conditions: **2a**, **3a** (2.0 equiv), **1** (5 mol%), benzene (2 mL). [b] The yield was determined after column chromatography. [c] The *ee* value was determined by HPLC on a chiral phase.

major products. This result not only demonstrates the high acidity of the *N*-triflylphosphoramide catalysts; more importantly, it opens up many further possibilities for new Brønsted acid catalyzed C–H activation and C–C bond-forming reactions.

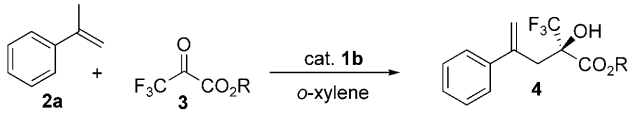


Therefore, we examined the catalytic enantioselective carbonyl-ene reaction in the presence of different amounts of the *N*-triflylphosphoramides **1** (Table 2). With the chiral Brønsted acid catalyst **1g**, we were able to decrease the catalyst loading from 10 to 0.1 mol% without a considerable loss in selectivity (Table 2, entries 1–5). However, the best result with regard to both reactivity and selectivity was observed with 1 mol% of the chiral Brønsted acid **1j** in the reaction of the ethyl ester **3a** with α-methylstyrene (Table 2, entry 7).

We investigated the scope of the Brønsted acid catalyzed enantioselective carbonyl-ene reaction with respect to the styrene substrate under the optimized reaction conditions (Table 3). A broad range of styrene derivatives, **2a–q**, with electron-withdrawing and electron-donating substituents underwent the desired reaction with **3a** to provide the α-hydroxyesters **4a–q** in good yields with excellent enantioselectivities (92–97% *ee*).[17]

With regard to the reaction mechanism and catalyst structure, we were able to obtain suitable crystals of the actual *N*-triflylphosphoramide catalyst **1j**. Previously, only X-ray crystal structures of salts of these strongly acidic Brønsted acids were known, typically with a calcium atom as a chelating

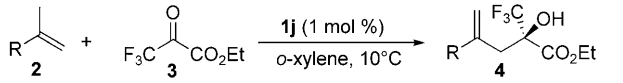
Table 2: Evaluation of the catalyst loading and ester moiety.[a]



Entry	**1** (mol%)	R	Yield [%][b]	*ee* [%][c]
1	**1g** (10)	Me (**3b**)	74	84
2	**1g** (5)	Me (**3b**)	83	84
3	**1g** (2)	Me (**3b**)	66	84
4	**1g** (1)	Me (**3b**)	82	88
5	**1g** (0.1)	Me (**3b**)	46	81
6	**1g** (1)	Et (**3a**)	86	93
7	**1j** (1)	Et (**3a**)	76	96

[a] Reaction conditions: **2** (0.20 mmol), **3** (2.0 equiv), **1**, *o*-xylene (2 mL). [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC on a chiral phase.

Table 3: Scope of the Brønsted acid catalyzed carbonyl-ene reaction.[a]



Entry	R	Yield [%][b]	*ee* [%][c]
1	Ph (**2a**)	76	96
2	*p*-$MeOC_6H_4$ (**2b**)	69	92
3	*p*-MeC_6H_4 (**2c**)	92	96
4	*m*-MeC_6H_4 (**2d**)	91	96
5	*p*-EtC_6H_4 (**2e**)	96	95
6	*p*-FC_6H_4 (**2f**)	88	92
7	2-naphthyl (**2g**)	95	95
8	biphenyl (**2h**)	87	97
9	*p*-*t*BuC_6H_4 (**2i**)	83	94
10	*m*,*p*-$Me_2C_6H_3$ (**2j**)	92	92
11	*p*-BrC_6H_4–C_6H_4 (**2k**)	87	96
12	tetralinyl (**2l**)	96	95
13	indanyl (**2m**)	93	95
14	*p*-ClC_6H_4 (**2n**)	55	93
15	*p*-*i*PrC_6H_4[d] (**2o**)	85	92
16	*p*-IC_6H_4[d] (**2p**)	89	97
17	*p*-BrC_6H_4[d] (**2q**)	71	93

[a] Reaction conditions: **2**, **3a** (2.0 equiv), **1j** (1 mol%), 0.25 M solution in *o*-xylene. [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC or GC on a chiral phase. [d] The reaction was carried out with catalyst **1g** at −20°.

counterion. These less reactive Ca-complexes exhibit a phosphoramide/calcium ratio of 2:1.[18] However, total reflection X-ray fluorescence (TXRF) measurements and the X-ray crystal structure of **1j** (Figure 1) show unambiguously that the acidification of the calcium complex results in the calcium-free, completely protonated, highly reactive *N*-triflylphosphoramide. These results dispel the theory that the corresponding calcium complex may act as the catalyst in such reactions.

In the crystalline state, the Brønsted acid **1j** exists as a dimer in which the nitrogen atom is protonated and forms a hydrogen bond to the Lewis basic oxygen atom of the second phosphoramide group. In contrast, no dimeric structures were observed by diffusion-ordered spectroscopy (DOSY) for **1j** dissolved in toluene. Therefore, we conclude that the actual

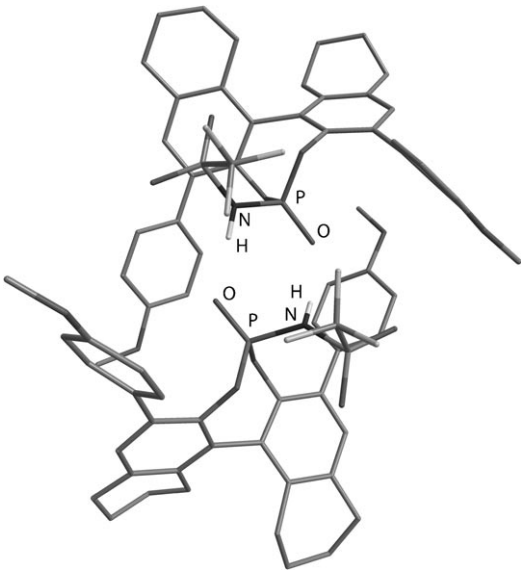


Figure 1. Molecular structure of the *N*-triflylphosphoramide catalyst **1j**.

catalyst in our transformations is the monomer of the protonated chiral *N*-triflylphosphoramide.

In summary, we have developed a highly enantioselective organocatalytic carbonyl-ene reaction, which led to a range of substituted α-hydroxyesters in good yields with excellent enantioselectivities (92–97% *ee*). This efficient reaction proceeds under mild conditions with just 1 mol% of an air-stable, highly reactive Brønsted acid catalyst and provides direct access to optically active compounds with quaternary stereocenters from simple and readily available starting materials. Furthermore, we have described the structure of the chiral Brønsted acids for the first time and demonstrated that the actual catalyst in this very efficient organocatalytic noncovalent carbonyl-group activation is the protonated *N*-triflylphosphoramide. This information is important for future catalyst design and the development of further Brønsted acid catalyzed reactions.

Received: May 7, 2008
Published online: July 24, 2008

Keywords: asymmetric catalysis · Brønsted acids · carbonyl-ene reaction · ion pairs · organocatalysis

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[16] The enantioselective Brønsted acid catalyzed ene reaction with methyl pyruvate or methyl glyoxalate resulted in lower reactivities or selectivities.

[17] See the Supporting Information for detailed procedures and the characterization of all products.

[18] A detailed description of the procedure for the synthesis of the catalysts, the structural investigations by TXRF and DOSY, and the crystal structures of the phosphoramide/calcium complexes and *N*-triflylphosphoramides will be reported in due course.

