ChemComm

Asymmetric Brønsted acid assisted Lewis base catalysis for the synthesis of trifluoromethylated heterocycles by exploiting the negative hyperconjugation of the CF3-group

Journal:	*ChemComm*
Manuscript ID:	CC-COM-04-2014-003229.R1
Article Type:	Communication
Date Submitted by the Author:	14-May-2014
Complete List of Authors:	Rueping, Magnus; RWTH Aachen, Institute of Organic Chemistry Volla, Chandra; RWTH Aachen, Institute of Organic Chemistry Das, Arindam; RWTH Aachen, Institute of Organic Chemistry Atodiresei, Iuliana; RWTH Aachen, Institute of Organic Chemistry

Journal Name

RSCPublishing

COMMUNICATION

Fluorine Effects in Organocatalysis - Asymmetric Brønsted acid assisted Lewis base catalysis for the synthesis of trifluoromethylated heterocycles exploiting the negative hyperconjugation of the CF_3-group

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

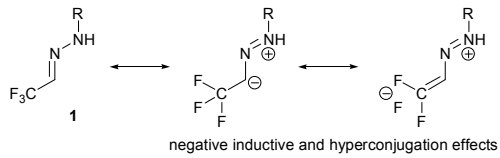
Chandra M. R. Volla, Arindam Das, Iuliana Atodiresei and Magnus Rueping*

An efficient Brønsted acid assisted Lewis base catalysis protocol for the synthesis of enantiomerically pure trifluoromethylated dihydropyridazines starting from readily available hydrazones and α,β-unsaturated aldehydes has been developed. The reaction exhibits high tolerance towards many functional groups and is applicable to various aliphatic, aromatic and hetero-aromatic α,β-unsaturated aldehydes, and provides the products in good yields and with excellent enantioselectivities.

The synthesis of molecules containing a trifluoromethyl group has gained increased attention in recent years as more and more of these derivatives found application in pharmaceutical and agrochemical industries.[1] The substitution of a methyl group by a trifluoromethyl group makes a significant change in their physical properties and hence leads to improved metabolic stability, bioavailability and cell permeability. Indeed, some great contributions emerged in this area in the last few years to prepare trifluoromethylated compounds employing both transition-metal and organocatalysis.[2] In this context, heterocyclic compounds with a trifluoromethyl group are becoming attractive targets in medicinal chemistry.[3] Fluorinated heterocycles exhibit a wide range of pharmacological properties. For example trifluridine was used as an antiviral drug for treating eye infections and mefloquine is an anti-malarial drug. Recently, there are reports on the asymmetric synthesis of fluorinated heterocycles. Shibata and co-workers reported an asymmetric hydroxylamine/enone cascade reaction catalyzed by ammonium salts of *Cinchona* alkaloids for the synthesis of trifluoromethyl substituted 2-isoxazolines.[4] They further expanded the potential of these phase-transfer catalysts in the asymmetric synthesis of trifluoromethylated pyrroline derivatives.[5]

The pyridazine ring system is receiving increased attention as it exists in a wide range of biologically active natural compounds and medicinally important derivatives.[6] Vicario and co-workers recently reported the synthesis of 2,3-dihydropyridazines using an elegant cascade aza-Michael/aldol condensation applying asymmetric iminium catalysis.[7] In addition, they also reported an aza-ene reaction of donor-acceptor substituted hydrazones with α,β-unsaturated aldehydes to give γ-hydrazono aldehydes, which can be transferred to the corresponding acids or dihydropyridazines.[8] Concurrently, a general chiral bis-urea catalyzed aza-ene reaction of formaldehyde derived monoalkyl hydrazones to carbonyl derivatives was developed by Lassaletta and Fernandez and co-workers.[9] Ye and co-workers reported an achiral Brønsted acid/chiral diamine catalytic system for the asymmetric synthesis of 1,4-dihydropyridazines.[10] Prior to these reports, Baldwin and co-workers described the use of monoalkyl-hydrazones in thermal ene reactions[11] when deprotonated with strong bases as acyl anion reagents.[12]

We now envision that monosubstituted trifluoromethylated hydrazones can act as carbon-centered nucleophiles[13] in the presence of acids and so can be reacted with α,β-unsaturated aldehydes to allow for the preparation of fluorinated heterocyles.[14] Because of the high electronegativity of the fluorine atom, CF_3 group exerts a strong negative inductive effect which stabilizes the negative charge on the carbon atom of hydrazone. Also fluorine atom shows negative hyperconjugation which further stabilizes the negative charge and hence exhibits umpolung characteristics (Scheme 1).

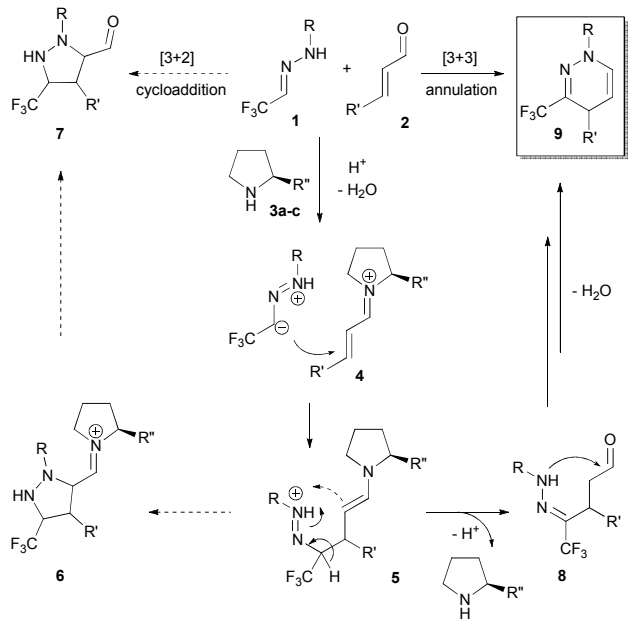


Scheme 1. Negative inductive and hyperconjugation effects of trifluoromethylated azomethine imines.

In this perspective, it is of particular interest to use trifluoromethylacetaldehyde hydrazones **1**, which can be synthesized very easily from the corresponding hydrazines and trifluoromethyl acetaldehyde as substrates in asymmetric iminium catalysis. They will be useful building blocks for the preparation of fluorinated heterocycles. We report here a simple and efficient method for the asymmetric synthesis of pyridazines by the reaction of trifluoroacetaldehyde

arylhydrazones and α,β-unsaturated aldehydes catalyzed by readily available TMS-protected prolinol ethers.[15]

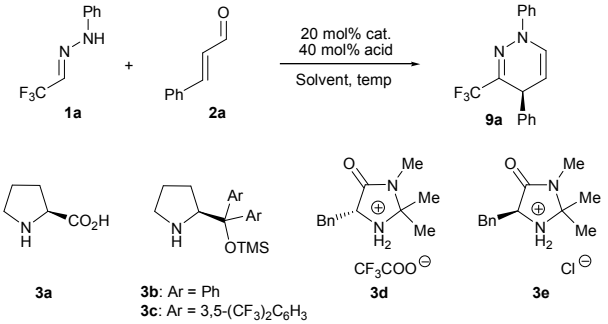
Our hypothesis is based on the fact that after the initial attack of trifluoromethylacetaldehyde hydrazone **1** onto α,β-unsaturated iminium ion **4**, the enamine **5** can either intramolecularly react with the N-N double bond to give trifluoromethylated pyrazolidines **7** similar to 1,3-dipolar cycloaddition[16] or alternatively undergoes hydrolysis to form aldehyde **8** which will cyclize to generate trifluoromethylated pyridazines **9** (Scheme 2).



Scheme 2. Secondary amine catalyzed addition of CF_3-hydrazones to α,β-unsaturated aldehydes.

Preliminary experiments to see the proof of principle were performed using (*E*)-1-phenyl-2-(2,2,2,-trifluoromethylidene)-hydrazine (**1a**) and (*E*)-cinnamaldehyde (**2a**). Various chiral secondary amine catalysts **3a-e**[17] were evaluated in DCM as solvent using acetic acid as acid additive. We were delighted to see that the reaction selectively gave trifluoromethylated pyridazine **9a** in good yields at room temperature. Using 20 mol% of proline (**3a**), the reaction finished after 36 h giving the product in 74% yield with 18% enantiomeric excess (Table 1, entry 1). Diphenyl prolinol ether **3b** as catalyst gave the product in a similar yield with an increased ee of 42% (Table 1, entry 2). In the presence of sterically hindered bis(trifluoromethyl)-phenyl substituted prolinol ether **3c**, the hydrazone reacted slowly in DCM as solvent to afford the product in 83% yield and 70% ee (Table 1, entry 3). Although imidazolidinone salts **3d** and **3e** showed higher reaction rate, the maximum selectivity using these catalysts was 61% at 0 °C (Table 1, entries 4, 5, 7). Performing the reaction in toluene using imidazolidinone-TFA salt **3d** at 0 °C led to the product with 32% enantioselectivity (Table 1, entry 6). We were pleased to see that using 20 mol% of catalyst **3c** and lowering the temperature to 0 °C afforded the product in good yield and with excellent enantioselectivity (Table 1, entry 8). In this case addition of 40 mol% of TFA was required at the end of the reaction for final dehydration (see Scheme 4). Although temperatures either above or below 0 °C showed similar selectivities, the yield was found to be optimum at 0 °C (Table 1, entries 9, 10). Faster reaction rate was observed using TFA as acid additive but the enantioselectivity dropped to 75% at −10 °C (Table 1, entry 11). This may be due to an uncatalyzed reaction going along with the iminium catalysis at this temperature. In the absence of acid catalyst no reaction was observed even after 48 h at room temperature (Table 1, entry 12). This shows clearly that the acid is essential for the reaction (Scheme 1).

Table 1. Optimization of reaction conditions for the addition of hydrazone to cinnamaldehyde.



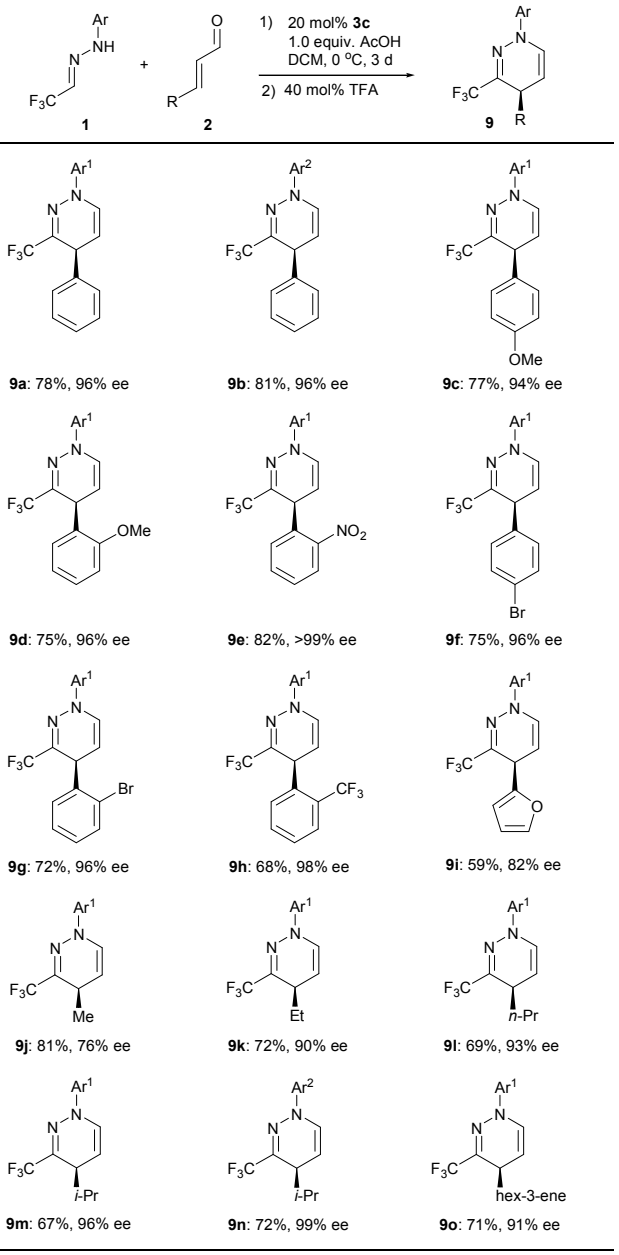
Entry	Cat.	Acid	Solvent	Temp	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**3a**	AcOH	DCM	RT	36	74	18
2	**3b**	AcOH	DCM	RT	36	77	42
3	**3c**	AcOH	DCM	RT	48	83	70
4	**3d**	-	DCM	RT	12	69	42[c]
5	**3d**	-	DCM	0	24	72	61[c]
6	**3d**	-	Toluene	0	72	58	32[c]
7	**3e**	-	DCM	0	12	69	11
8	**3c**[d],[e]	AcOH	DCM	0	72	78	95
9	**3c**[d],[e]	AcOH	DCM	–10	90	72	96
10	**3c**[e]	AcOH	DCM	10	72	71	91
11	**3c**	TFA	DCM	–10	48	82	75
12	**3c**	-	DCM	RT	48	-	-

[a] Yield after column chromatography. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Opposite enantiomer. [d] 1.0 equiv. of acetic acid was used instead of 40 mol%. [e] 40 mol% of TFA was added after the mentioned time.

After having established the optimal conditions for the synthesis of 3-trifluoromethyl-1,2-dihydropyridazines, the scope of the reaction was explored with differently substituted α,β-unsaturated aldehydes **2**. As it can be seen from Table 2, both aliphatic and aromatic substituted α,β-unsaturated aldehydes undergo the diarylprolinol ether catalyzed cyclization. When aliphatic aldehydes were employed, the selectivity gradually increases with the steric bulk as crotonaldehyde, 2-pentenal, 2-hexenal and 4-methyl-2-pentenal provided the corresponding products **9j-m** with 76, 90, 93 and 96% ee respectively. The yield of the reaction is only moderately affected by the difference in chain length. This kind of pattern was previously observed for the addition of 1,3-diketones onto α,β-unsaturated aldehydes.[18-20] We also focused on using differently substituted cinnamaldehydes as the electrophile and these aldehydes exhibited higher selectivities as compared to aliphatic aldehydes. Both electron rich and electron-poor substituents were well tolerated under the reaction conditions. Differently functionalized pyridazines were obtained in good yields and excellent enantioslectivities. Of particular importance are brominated pyridazines as these compounds can be further functionalized using transition metal

catalysis. Electron-withdrawing groups like nitro and trifluoromethyl in the *ortho*-position of the aldehyde showed very high selectivities of >99% and 98% respectively. The reaction can also be performed with hetero-aromatic derived aldehydes as furan derivative **9i** was isolated in 59% yield with 82% ee. As expected, a faster reaction was observed when more electron-rich *p*-methoxyphenyl derived hydrazones were used in reaction with cinnamaldehyde and 4-methyl-2-pentenal. The more electron donating nature of the *p*-methoxy group facilitated the faster cyclization leading to the corresponding pyridazines **9b** and **9n** with 96% and 99% enantioselectivity respectively. Also addition of TFA was not required in these cases for the final dehydration.

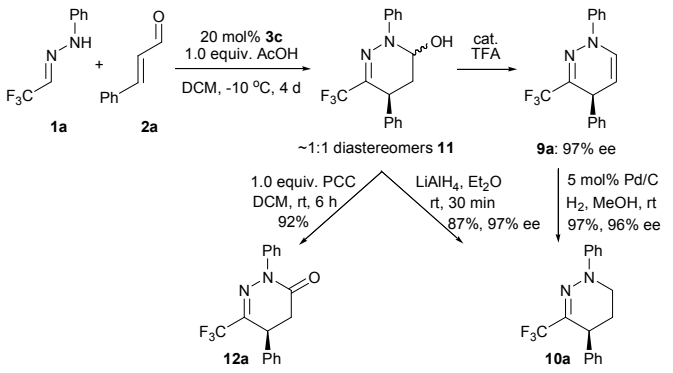
Table 2. Scope of the reaction of addition of hydrazone to α,β-unsaturated aldehydes.



Ar^1 = Ph. For Ar^2 = 4-MeO-C_6H_4 the reaction time is 2 days; no TFA was required in these cases.

The absolute configuration of product **9n** has been determined as (*R*) by X-ray crystal structure analysis.[21]

Subsequently, 1,4-diphenyl-3-(trifluoromethyl)-1,4-dihydropyridazine **9a** was selectively reduced using 5 mol% of palladium on charcoal to tetrahydropyridazine **10a** in quantitative yield with no loss in enantioselectivity (Scheme 3). In order to probe details about the mechanism of this new asymmetric Brønsted acid assisted Lewis base catalysis[22] procedure the reaction between trifluoroacetaldehyde phenyl hydrazone **1a** and cinnamaldehyde (**2a**) was performed using 1.0 equiv. of acetic acid at –10 °C instead of 0 °C (Scheme 3). After the complete consumption of hydrazone, we isolated a 1:1 mixture of hemiaminals **11** by column chromatography on silica gel. The mixture of hemiaminals was converted into the desired pyridazine **1a** by exposure to a catalytic amount of TFA. This clearly demonstrates that after the attack of nucleophile onto iminium ion, the enamine undergoes hydrolysis to form an aldehyde (Scheme 2). Tautomerization of the double bond followed by the intramolecular attack of *N*-atom onto aldehyde provides the hemiaminal which will eliminate one molecule of water to give the desired pyridazines. Isolation of the intermediate hemiaminal **11** was found to be useful as it can be transformed directly into the corresponding tetrahydropyridazine using $LiAlH_4$ in ether. The hemiaminal can also be oxidized by using PCC to 4,5-dihydropyridazinone derivative **12a** in 92% yield (Scheme 3).



Scheme 3. Isolation and derivatization of the intermediate hemiaminal and reduction of pyridazine **9a**.

In summary, we have developed an efficient organocatalytic protocol for the synthesis of valuable enantiomerically pure trifluoromethylated dihydropyridazines.[23] Simple reaction conditions together with operational simplicity allowed for synthesizing differently functionalized pyridazines. The reaction exhibited high tolerance towards many functional groups. Aliphatic, aromatic and hetero-aromatic substituted α,β-unsaturated aldehydes can be employed under the reaction conditions. Furthermore, at lower temperature, the intermediate hemiaminal can be isolated and converted directly into further useful derivatives.

Financial support for this project was provided by the ERC. C.M.R.V. and A.D. gratefully acknowledges the Alexander von Humboldt Foundation (AvH) for a postdoctoral fellowship.

Notes and references

[a] *RWTH Aachen University, Institute of Organic Chemistry, Landoltweg 1, D-52074 Aachen, Germany.*
E-mail: magnus.rueping@rwth-aachen.de; Fax: +49 241 8092665

Electronic Supplementary Information (ESI) available: [Full characterization of the products, spectra and HPLC chromatograms are available as ESI]. See DOI: 10.1039/c000000x/

1 (a) B. E. Smart, *Chem. Rev.*, 1996, **96**, 1555-1556; (b) R. Filler, Y. Kobayashi and L. M. Yagupolskii, *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications (Elsevier, Amsterdam)*, **1993**; (c) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470-477; (d) K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881-1886; (e) S. Purser, P. R. Morre, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320-330; (f) W. K. Hagmann, *J. Med. Chem.*, 2008, **51**, 4359-4369; (g) T. Yamazaki, T. Taguchi and I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: Ojima, I.), Wiley-Blackwell, Chichester, **2009**.

2 (a) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475-4521

3 (a) V. A. Petrov, *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*. Wiley, Hoboken, New Jersey, **2009**; (b) *Fluorinated Heterocycles.* ACS Symposium Series, Ed. A. A. Gakh and K. L. Kirk, **2009**, 1003.

4 K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed.*, 2010, **49**, 5762-5766.

5 (a) H. Kawai, S. Okusu, E. Tokunaga, H. Sato, M. Shiro and N. Shibata, *Angew. Chem. Int. Ed.*, 2012, **51**, 4959-4962; (b) H. Kawai, Y. Sugita, E. Tokunaga, H. Sato, M. Shiro and N. Shibata, *Chem. Commun.*, 2012, **48**, 3632-3634; (c) H. Kawai, T. Kitayama, E. Tokunaga, T. Matsumoto, H. Sato, M. Shiro and N. Shibata, *Chem. Commun.,* 2012, **48**, 4067-4069.

6 P. Kolar and M. Tiler, *Advances in Heterocyclic Chemistry,* Vol. 75; Katritzky, A. R., Ed.; Academic Press: San Diego, **2000**, 167.

7 M. Fernández, J. L. Vicario, E. Reyes, L. Carrillo and D. Badía, *Chem. Commun.,* 2012, **48**, 2092-2094.

8 M. Fernández, U. Uria, J. L. Vicario, E. Reyes and L. Carrillo, *J. Am. Chem. Soc.*, 2012, **134**, 11872-11875.

9 A. Crespo-Peña, D. Monge, E. Martín-Zamora, E. Álvarez, R. Fernández and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2012, **134**, 12912-12915.

10 W. Wu, X. Yuan, J. Hu, X. Wu, Y. Wei, Z. Liu, J. Lu and J. Ye, *Org. Lett.*, 2013, **15**, 4524-4527.

11 J. E. Baldwin, R. M. Adlington, A. U. Jain, J. N. Kolhe and M. W. D. Perry, *Tetrahedron*, 1986, **42**, 4247-4252.

12 J. E. Baldwin, R. M. Adlington, J. C. Bottaro, J. N. Kolhe, M. W. D. Perry and A. U. Jain, *Tetrahedron*, 1986, **42**, 4223-4234.

13 For the reactivity of hydrazones see: (a) D. Perdicchia and K. A. Jørgensen, *J. Org. Chem.*, 2007, **72**, 3565-3568; (b) M. Rueping, E. Sugiono, T. Theissmann, A. Kuenkel, A. Köckritz, A. Pews-Davtyan, N. Nemati, and M. Beller, *Org. Lett.* 2007, **9**, 1065-1068; For important overviews regarding the use of hydrazones, see: (c) R. Brehme, D. Enders, R. Fernández and J. M. Lassaletta, *Eur. J. Org. Chem*. 2007, 5629-5660; (d) R. Fernández and J. M. Lassaletta, *Synlett*, 2000, 1228-1240; (e) D. Enders, M. Bolkenius, J. Vázquez, J. M. Lassaletta and R. Fernández, *J. Prakt. Chem*., 1998, **340**, 281-285.

14 For acid catalyzed synthesis of trifluoromethylated 1,4-dihydropyridazines, see: a) H. Xie, J. Zhu, Z. Chen, S. Li and Y. Wu, *Synlett*, 2012, **23**, 935-937; b) A. Das, C. M. R. Volla, I. Atodiresei, W. Bettray and M. Rueping, *Angew. Chem Int. Ed.*, 2013, **52**, 8008-8011.

15 Reviews on prolinol TMS-ether catalysis: (a) C. Palomo and A. Mielgo, *Angew. Chem. Int. Ed.*, 2006, **45**, 7876-7880; (b) A. Mielgo and C. Palomo, *Chem.-Asian J.*, 2008, **3**, 922-948; (c) K. L. Jensen, G. Dickmeiss, H. Jiang, L. Albrecht and K. A. Jørgensen, *Acc. Chem. Res*., 2011, **38**, 248-264.

16 (a) W. Chen, X.-H. Yuan, R. Li, W. Du, Y. Wu, L.-S. Ding and Y.-C. Chen, *Adv. Synth. Catal.*, 2006, **348**, 1818-1822; (b) W. Chen, W. Du, Y.-Z. Duan, Y. Wu, S.-Y. Yang and Y.-C. Chen, *Angew. Chem. Int. Ed.*, 2007, **46**, 7667-7670; (c) T. Hashimoto, M. Omote and K. Maruoka, *Angew. Chem. Int. Ed.*, 2011, **50**, 3489-3492.

17 For structural and spectroscopic studies on the iminium ion formation: (a) D. Seebach, U. Grošelj, D. M. Badine, W. B. Schweizer and A. K. Beck, *Helv. Chim. Acta*, 2008, **91**, 1999-2034; (b) U. Grošelj, D. Seebach, D. M. Badine, W. B. Schweizer, A. K. Beck, I. Krossing, P. Klose, Y. Hayashi and T. Uchimaru, *Helv. Chim. Acta*, 2009, **92**, 1225-1259; (c) U Grošelj, W. B. Schweizer, M.-O. Ebert and D. Seebach, *Helv. Chim. Acta*, 2009, **92**, 1-13; (d) D. Seebach, R. Gilmour, U. Grošelj, G. Deniau, C. Sparr, M.-O. Ebert, A. K. Beck, L. B. McCusker, D. Šišak and T. Uchimaru, *Helv. Chim. Acta*, 2010, **93**, 603-634; (e) (h) For an excellent article on fluorine conformational effects in catalyst design, see: L. E. Zimmer, C. Sparr and R. Gilmour, *Angew. Chem*. 2011, **123**, 12062

18 M. Rueping, C. M. R. Volla, M. Bolte and G. Raabe, *Adv. Synth. Catal.,* 2011, **353**, 2853-2859.

19 Examples on Lewis Base catalysis from our group: (a) M. Rueping, J. Dufour, and L. Bui, *ACS Catal.*, 2014, **4**, 1021-1025; (b) M. Rueping, R. Rasappan, and S. Raja, *Helv. Chim. Acta*, 2012, **95**, 2296-2303; (c) M. Rueping, C. M. R. Volla, and I. Atodiresei, *Org. Lett.*, 2012, **14**, 4642-4645; (d) M. Rueping, E. Merino, and M. Bolte, *Org. Biomol. Chem*., 2012, 6201-6210; (e) M. Rueping, E. Merino, and E. Sugiono, *ChemCatChem*, 2012, **4**, 987-992; (f) M. Rueping, H. Sundén, and E. Sugiono, *Chem. Eur. J.*, 2012, **18**, 3649-3653; (g) Rueping, J. Dufour, and M. S. Maji, *Chem. Commun.*, 2012, **48**, 3406-3408; (h) M. Rueping, H. Sundén, L. Hubener, and E. Sugiono, *Chem. Commun*., 2012, **48**, 2201-2203; (i) M. Rueping, K. Haack, W. Ieawsuwan, H. Sundén, M. Blanco, and F. R. Schoepke, *Chem. Commun,* **2011**, 3828-3830; (j) M. Rueping, E. Sugiono, and E. Merino, *Angew. Chem. Int. Ed.*, 2008, **47**, 3046 3049.

20 Review: C. M. R. Volla, I. Atodiresei, and M. Rueping *Chem. Rev*., 2014, **114**, 2390-2461.

21 See supporting information.

22 Examples of Brønsted acid assisted Brønsted acid catalysis, see: (a) M. Rueping, and C. Azap, *Angew. Chem. Int. Ed.*, 2006, **45**, 7832-7835; (b) M. Rueping, E. Sugiono, and F. R. Schoepke, *Synlett*, 2007*,* 1441-1446; (c) M. Rueping, and T. Theissmann, *Chem. Sci.*, 2010, **1**, 473-476; (d) M. Rueping, and B. J. Nachtsheim, *Synlett*, 2010, 119-122.

23 Reviews for the applications of organocatalysis in the synthesis of natural products and pharmaceuticals: (*a*) E. Marqués-López, R. P. Herrera and M. Christmann, *Nat. Prod. Rep.*, 2010, **27**, 1138-1167; (*b*) R. M. de Figueiredo and M. Christmann, *Eur. J. Org. Chem.*, 2007, 2575-2600.

