Asymmetric Catalysis

DOI: 10.1002/ange.201301638

Asymmetric Ion Pair Catalysis of 6π Electrocyclizations: Brønsted Acid Catalyzed Enantioselective Synthesis of Optically Active 1,4-Dihydropyridazines**

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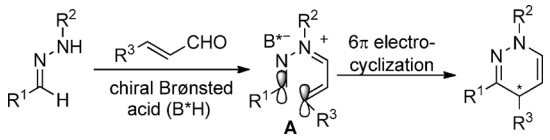
Electrocyclic reactions are reliable, powerful, synthetic tools for the generation of complex molecules in synthetic organic chemistry.[1,2] However, whereas other pericyclic reactions such as sigmatropic rearrangements[3,4] and cycloaddition reactions have generated much interest, electrocyclic reactions have not been fully exploited with regard to control of their absolute stereochemistry. This is mainly because of the high temperatures needed for the initiation of the electrocyclization process. Additionally these high temperatures may also limit the use of highly functionalized substrates in target-oriented synthesis.[2a] In particular, enantioselective 6π-electrocyclization reactions are rare and very difficult to achieve.[2b,c] The first success in the field was reported by Veenstra and Speckamp who applied chiral alcohols as cosolvents in a [1,5]-electrocyclization reaction, thus leading to indolines.[5] In this context, Smith et al. recently described an elegant protocol for the asymmetric synthesis of functionalized indolines by asymmetric 6π electrocyclization using cinchona-alkaloid-derived chiral quaternary ammonium salts as phase-transfer catalysts.[6] Another organocatalytic [1,5]-electrocyclization reaction was developed by List and Müller using chiral Brønsted acid catalysts. In this protocol, α,β-unsaturated aryl hydrazones which are isoelectronic with the pentadienyl anion were applied as substrates in the enantioselective synthesis of 2-pyrazolines.[7] In the case of [1,6]-electrocyclization reactions,[8–11] high levels of enantiocontrol were described by the groups of Toda[8] and Bach[9] in the enantioselective 6π photocyclization of acrylanilides mediated by chiral hosts. Recently Trauner and co-workers reported an interesting carba-6π electrocyclization.[11]

In our continuous research to develop highly enantioselective metal-free procedures for the synthesis of relevant bioactive heterocycles, we became interested in the asymmetric synthesis of dihydropyridazines by using a new chiral Brønsted acid[12–14] catalyzed 6π-electrocyclization reaction. When designing this reaction we assumed that the condensation of a hydrazone with an α,β-unsaturated aldehyde may proceed under chiral Brønsted acid catalysis with the initial formation of the ion pair **A**, consisting of a hydrazonium ion and a chiral acid anion (Scheme 1). The hydrazonium ion



Scheme 1. Brønsted acid catalysis of the 6π electrocyclization.

intermediate represents a 6π-electron system comprising nitrogen heteroatoms in the conjugated unsaturated moiety. We envisioned that the presence of nitrogen atoms in the π system would overcome the problems associated with the high temperatures often required to promote such electrocyclizations,[15] thus opening the possibility of stereochemical control by using a chiral catalyst.

Pyridazine-derived molecules are of great interest, as they possess potent biological activities including antifungal, antimicrobial, anti-inflammatory, and antihypertensive activities.[16] Furthermore, the presence of fluorine in organic molecules considerably influences the chemical, physical, and biological properties of the parent compounds.[17] This prompted us to examine an enantioselective Brønsted acid catalyzed condensation/6π electrocyclization of fluorinated hydrazones and α,β-unsaturated aldehydes.[18] Herein, we report the first synthesis of optically active trifluoromethyl-substituted dihydropyridazines using the chiral ion pair catalysis.

At the outset of our investigation, we examined the reaction of (*E*)-1-phenyl-2-(2,2,2-trifluoroethylidene)hydrazine (**1a**) and (*E*)-cinnamaldehyde (**2a**) in toluene, in the presence of various chiral binol-derived phosphoric acid diesters **3** (Table 1). We were pleased to see that chiral phosphoric acids catalyze the reaction to give 3-trifluoromethyl-1,4-dihydropyridazine **4a** in good yield and with good enantioselectivity at room temperature. The initial reaction was conducted with 5 mol% of the 3,3′-bis-phenyl-substituted binol phosphate **3a**, which provided the trifluoromethylated pyridazine **4a** with 43% enantioselectivity (entry 1). Changing the substituent on the binol phosphate catalyst from phenyl to the sterically more bulky biphenyl (**3b**), 2-naphthyl (**3c**), and 1-naphthyl (**3d**) groups increased the enantioselectivity to 57, 58, and 60%, respectively (entries 2–4). The best

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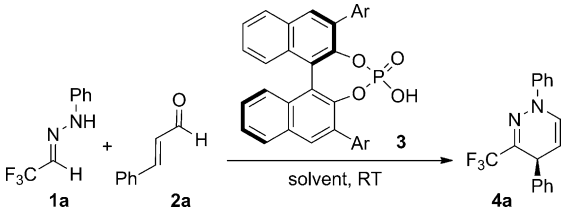
[**] Financial support from the DFG is acknowledged. A.D. and C.M.R.V. thank the Alexander von Humboldt Foundation for a fellowship. The absolute configuration was determined by I.A., and W.B. carried out the MS-measurements.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201301638.

Table 1: Evaluation of various Brønsted acids and solvents.



1a 2a 4a

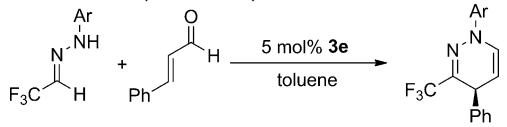
Entry[a]	3 (Ar)	Solvent	t [h][b]	Conv. [%]	*ee* [%][c]
1	**3a** (C_6H_5)	toluene	20	100	43
2	**3b** (biphenyl)	toluene	26	100	57
3	**3c** (2-naphthyl)	toluene	20	100	58
4	**3d** (1-naphthyl)	toluene	20	100	60
5	**3e** (9-phenanthryl)	toluene	16	100	80
6	**3f** [2,4,6-(iPr)$_3$-C_6H_2]	toluene	96	43	33
7	**3e** (9-phenanthryl)	CH_2Cl_2	18	100	77
8	**3e** (9-phenanthryl)	$CHCl_3$	15	100	67
9	**3e** (9-phenanthryl)	benzene	24	100	81

[a] Reaction conditions: **2a** (1.5 equiv) and 5 mol% of catalyst **3** in a 0.1 M solution of hydrazone **1a** using the solvent indicated at room temperature. [b] Refers to the time at which all starting material was consumed. [c] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase.

result in terms of selectivity (80% *ee*) was obtained with the 3,3′-bis-(9-phenanthryl)-substituted binol phosphate **3e** (entry 5). Evaluation of different solvents revealed that aromatic solvents provide better selectivity over chlorinated ones.

Apart from the various binol phosphate catalysts and solvents, we also examined the influence of the temperature and *N*-aryl group of the hydrazone on the enantioselectivity and reactivity of the 6π-electrocyclization reaction (Table 2). Interestingly, the reaction could be performed at lower

Table 2: Effect of temperature and *N*-aryl group on the Brønsted acid catalyzed condensation/6π electrocyclization.



1 2a 4

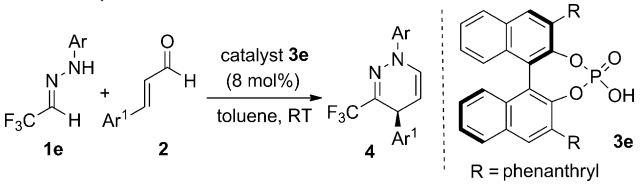
Entry[a]	Ar	4	T [°C]	t [h][b]	Yield [%]	*ee* [%][c]
1	C_6H_5	**4a**	RT	16	85	80
2	C_6H_5	**4a**	0	24	83	86
3	4-MeOC_6H_4	**4b**	0	15	73	78
4	4-MeOC_6H_4	**4b**	−45	60	69	73
5	4-ClC_6H_4	**4c**	0	28	76	80
6	1-naphthyl	**4d**	0	24	–	–
7	1-naphthyl	**4d**	15	48	84	90
8	1-naphthyl	**4d**	5	60	81	82
9[d]	4-bromonaphthyl	**4e**	RT	72	87	90
10	2,4-$(NO_2)_2C_6H_3$	**4f**	RT	48	–	–
11	4-nitrobenzoyl	**4g**	RT	24	–	–

[a] Reaction conditions: **2a** (1.5 equiv) and 5 mol% of catalyst **3e** in a 0.1 M solution of hydrazone **1** in toluene using the temperature as indicated in the table. [b] Refers to the time at which all starting material was consumed. [c] Enantiomeric excess was determined by HPLC analysis using a chiral stationary phase. [d] Reaction was performed using 8 mol% catalyst loading.

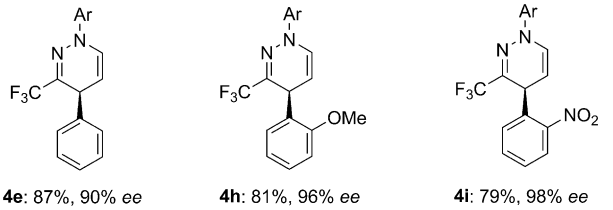
temperature and the reaction at 0°C in toluene with the catalyst **3e** led to an improved enantioselectivity of 86% and 83% yield within 24 hours (entry 2). The *N*-aryl group of the hydrazone has impact on both the yield and enantioselectivity. In general electron-rich *N*-aryl hydrazones react faster whereby larger groups result in better enantioselectivity.

After establishing a reliable practical procedure for the synthesis of optically enriched trifluoromethyl-1,4-dihydropyridazines, we explored the scope and generality of this methodology (Table 3). As shown, various α,β-unsaturated aldehydes with different substitution patterns and including both electron-donating and electron-withdrawing groups provided the desired pyridazines with good yields and excellent enantioselectivities. It is noteworthy that several functional groups including nitro, nitrile, or ester groups on

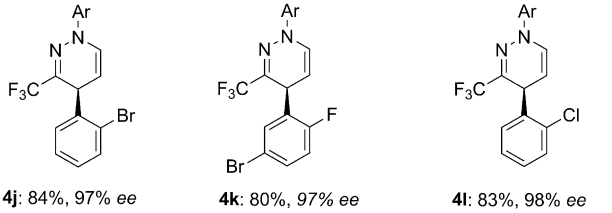
Table 3: Scope of the asymmetric Brønsted acid catalyzed condensation/6π-electrocyclization reaction.[a,b]



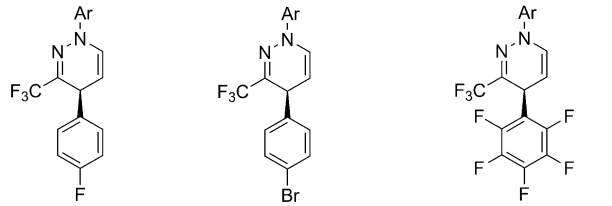
1e 2 4



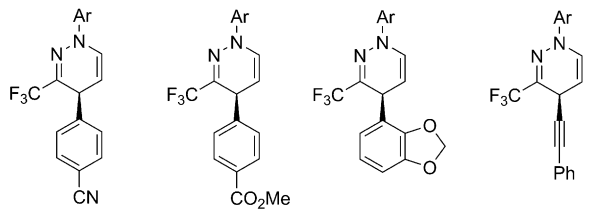
4e: 87%, 90% *ee* **4h**: 81%, 96% *ee* **4i**: 79%, 98% *ee*



4j: 84%, 97% *ee* **4k**: 80%, 97% *ee* **4l**: 83%, 98% *ee*



4m: 85%, 95% *ee* **4n**: 82%, 93% *ee* **4o**: 87%, 93% *ee*



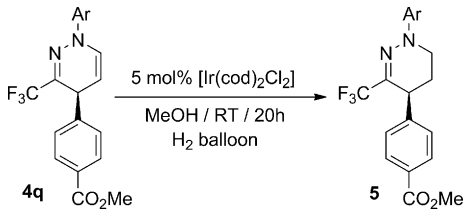
4p: 79%, 94% *ee* **4q**: 81%, 94% *ee* **4r**: 64%, 87% *ee* **4s**: 78%, 69% *ee*

[a] Enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase. [b] Ar = 4-bromonaphthyl.

the aryl residue are tolerated. Interestingly, (*E*)-5-phenylpent-2-en-4-ynal also worked smoothly and gave the corresponding phenyl-acetylene-substituted pyridazine **4s** derivative, albeit with reduced enantioselectivity. However, starting from readily available substrates this new method provides a simple and fast access to valuable optically active 1,4-dihydropyridazines.[19]

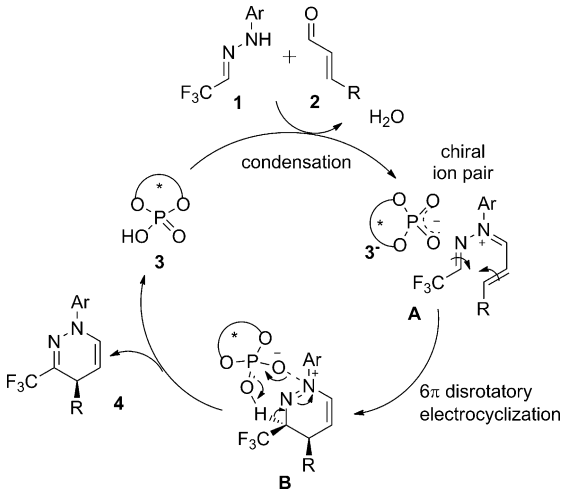
The absolute configuration of the stereogenic center generated in the process of the 6π electrocyclization was determined unambiguously as *S* by CD spectroscopic analysis of the phenyl-substituted pyridazine derivative **4a** (see the Supporting Information).

The products can, for instance, be further converted into the corresponding tetrahydropyridazines using a chemoselective hydrogenation protocol. As an example, **4q** was selectively hydrogenated to the tetrahydropyridazine **5** in 93% yield (Scheme 2).



Scheme 2. Reduction of the 1,4-dihydropyridazine derivative **4q**.

Additional studies were performed to gain information about the mechanism of the Brønsted acid catalyzed reaction. For this purpose the course of the diphenyl phosphate catalyzed reaction between **1e** and **2a** was monitored by NMR spectroscopy and ESI-MS measurements (see the Supporting Information). Based on these experimental observations we suggest the following catalytic cycle for this effective Brønsted acid catalyzed condensation/6π electrocyclization (Scheme 3). The first step of the catalytic cycle consists of the Brønsted acid catalyzed condensation between **1** and **2**, thus resulting in the formation of the chiral ion pair **A**, consisting of the iminium ion and the chiral counter anion $\mathbf{3}^-$. The following 6π disrotatory electrocyclization provides the intermediate **B**. The stereochemical outcome of the 6π electrocyclization originates from the chiral Brønsted acid counter anion $\mathbf{3}^-$, which blocks one π face of the delocalized 6π system, thereby controlling the torquoselectivity.[20] Subsequent proton abstraction results in the regenerated catalyst **3** and the enantioenriched product **4**. An alternative reaction pathway involving the conjugate addition of **1** to **2** followed by subsequent isomerization/hemiaminal formation and dehydration is also plausible. While the presence of the starting materials as well as the product formation can be undoubtedly seen in the NMR spectra, signals corresponding to the intermediate expected from the conjugate addition could not be detected. Additionally, ESI-MS measurements of the reaction mixture were carried out at different reaction times. Both the formation of the iminium ion and product **4** can undoubtedly be assigned and monitored as the reaction progresses. Therefore, we conclude that the asymmetric Brønsted acid catalyzed synthesis of 1,4-dihydropyridazines follows a condensation/6π electrocyclization reaction pathway.



Scheme 3. Proposed catalytic cycle for the asymmetric Brønsted acid catalyzed condensation/6π-electrocyclization reaction.

In summary, the work described herein represents the first report on the catalytic asymmetric 6π electrocyclization reaction for the synthesis of enantiomerically enriched 1,4-dihydropyridazines. The protocol allows the synthesis of various valuable 1,4-dihydropyridazine derivatives with an excellent level of enantioselectivity. Readily available substrates, operational simplicity, as well as high tolerance toward functional groups are features of this newly developed procedure. Given the difficulties associated with the development of asymmetric electrocyclization reactions, this new asymmetric Brønsted acid catalysis procedure provides a good basis and scope for further extensions and explorations.

Received: February 25, 2013
Revised: May 6, 2013
Published online: June 20, 2013

Keywords: Brønsted acid · electrocyclic reactions · heterocycles · reaction mechanisms · synthetic methods

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