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Organocatalysis

A Catalytic Asymmetric 6π Electrocyclization: Enantioselective Synthesis of 2-Pyrazolines**

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Pericyclic reactions are powerful tools for organic synthesis and a long-standing challenge for catalysis. While catalytic asymmetric cycloadditions are well-developed[1] and sigmatropic rearrangements are rapidly advancing,[2] the corresponding electrocyclizations are extremely rare.[3] The first examples were achieved when the groups of Trauner and Aggarwal discovered chiral Lewis acid catalyzed enantioselective Nazarov 4π electrocyclizations.[4,5] In the meantime, Trauner and Bergman have also established the feasibility of catalysis of certain 6π electrocyclizations.[6] In connection with a different project, we speculated on the potential for asymmetric catalysis of the rearrangement of α,β-unsaturated hydrazones into the corresponding potentially biologically active pyrazolines. This powerful acid-mediated reaction was originally discovered by Fischer, and Huisgen later noticed the isoelectronic relationship between this transformation and the 6π electrocyclization of the pentadienyl anion (Scheme 1).[7,8] Although truly catalytic versions of Fischer's

Scheme 1. 6π electrocyclizations.

pyrazoline synthesis are scarce, we reasoned that a chiral Brønsted acid catalysis strategy might be applicable. Herein we show that such catalysis is indeed possible and report what is, to our knowledge, the first catalytic asymmetric 6π electrocyclization.

Possessing manifold potent biological activities, such as antidepressant, anticancer, anti-inflammatory, antibacterial, and antiviral activity, pyrazolines are interesting synthetic targets.[9] In addition to the [2+3]-dipolar cycloaddition of diazoalkanes and α,β-unsaturated carbonyl compounds, discovered by Buchner et al. and von Pechmann,[10] Fischer's pyrazoline synthesis is among the most general approaches.[11] While several elegant catalytic asymmetric versions of the Buchner–von Pechmann type cycloaddition have been reported during the last years,[12] Fischer's reaction has not received much attention in this regard. In 2007 Kanemasa and Yanagita reported an enantioselective conjugate addition cyclocondensation cascade between different aryl hydrazines and 3-phenyl-1-(2-pyridyl)-1-propenone, catalyzed by a chiral nickel complex, affording optically enriched pyrazolines in moderate enantioselectivities.[13–15] In contrast to the mechanism of this reaction, the Fischer pyrazoline synthesis proceeds by condensation between enones and hydrazines to give the corresponding, often isolable hydrazone, which then cyclizes to the pyrazoline.[16] Although this pathway is frequently used for the synthesis of pharmaceutically relevant molecules, no catalytic asymmetric version has been reported to date. Assuming a protonated and as thus positively charged hydrazone as the reactive intermediate, we anticipated the opportunity of directing the stereochemical outcome of the 6π electrocyclization with a chiral counteranion.

At the outset of our studies we investigated the electrocyclization of the benzylideneacetone-derived phenylhydrazone **1a** with various catalysts. To our delight we found that chiral phosphoric acids indeed catalyze the reaction, displaying promising reactivity and enantioselectivity.[17] With these catalysts, the cyclization proceeded smoothly at 50 °C in toluene to give pyrazoline **2a** within a few hours in high yields and enantioselectivities of up to 81:19 e.r. (see the Supporting Information). The 3,3′-bis-(9-anthracenyl) substituted binol phosphate **3** gave the highest enantioselectivity of all catalysts tested. Optimization revealed that using chlorobenzene as solvent and lowering the temperature to 30 °C had a beneficial effect on the enantioselectivity. Furthermore, the catalyst loading could be reduced to 10 mol % without diminishing the enantioselectivity, although the reaction rate decreased slightly. These optimized reaction conditions were then applied to several different substrates (Table 1). The reaction turned out to be well suited for hydrazones bearing electron-withdrawing substituents at the aromatic ring of the enone part. All kinds of halogen atoms (entries 2–4 and 7–9), as well as strongly electron-withdrawing substituents (entries 5, 6, and 10) were tolerated, giving the desired products in enantioselectivities of up to 98:2 e.r. (entry 10). Electron-donating substituents accelerate the reaction and are likewise well-tolerated (entries 12 and 13). The use of a 4-methoxyphenylhydrazone **1k** resulted in a faster reaction but slightly lower enantioselectivity (entry 11).

Finally, 4-fluorophenylhydrazone **1n** also cyclized readily to give pyrazoline **2n** in 88 % yield and an enantiomeric ratio of 88:12 e.r. (Table 1, entry 14). This compound as well as its

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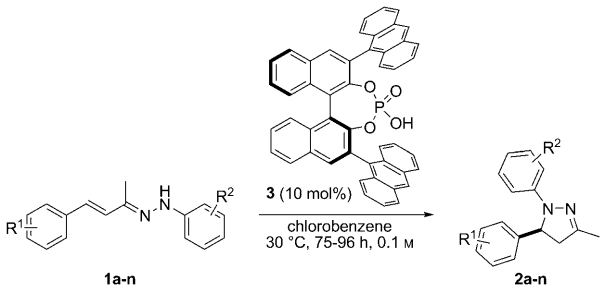
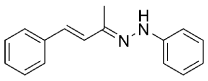
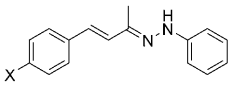
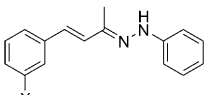
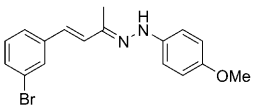
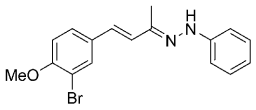
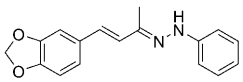
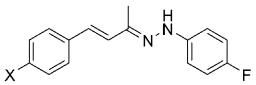
Table 1: Enantioselective 6π electrocyclization of α,β-unsaturated aryl hydrazones **1a–n**.[a]



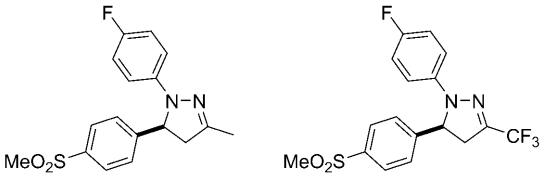
1a-n **2a-n**

Entry	Substrate **1**		Yield [%][b]	e.r.[c]
1		**1a**	92	88:12
2		**1b**: X = F	94	94:6
3		**1c**: X = Cl	96	95:5
4		**1d**: X = Br	95	95:5
5[d]		**1e**: X = NO_2	93	96:4
6[e]		**1f**: X = CF_3	88	96:4
7		**1g**: X = F	91	94:6
8		**1h**: X = Cl	96	96:4
9[f]		**1i**: X = Br	95	96:4
10[d,g]		**1j**: X = NO_2	99	98:2
11[h]		**1k**	91	92:8
12		**1l**	93	95:5
13[i]		**1m**	85	93:7
14[j]		**1n**: X = SO_2Me	88	88:12

[a] Unless otherwise noted, the reactions were run in Ar atmosphere with hydrazones **1a–n** (0.10 mmol) and phosphoric acid **3** (10 mol%) in chlorobenzene (1.0 mL) at 30°C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase (the absolute configuration of **2i** was determined by X-ray structure analysis). [d] Reaction was run at 40°C. [e] 9 d. [f] 109 h. [g] 60 h. [h] 36 h. [i] Reaction was run at 20°C. [j] Reaction was run at 50°C.

3-trifluoromethyl analogue (*S*)-E-6244 are patented COX-2 inhibitors (Figure 1).[18]

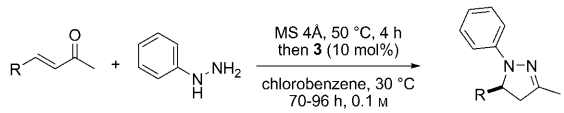
After establishing a reliable protocol for the asymmetric electrocyclization, we started to also investigate a direct method that does not require isolation of the hydrazone intermediate. After initial attempts we found that, although the hydrazone formation is acid-catalyzed, the overall reaction proceeded only slowly when we directly reacted enones **4** and phenylhydrazine (**5**) in the presence of acid **3**. Fortunately, we found that hydrazone formation in chlorobenzene proceeds well in the presence of 4 Å molecular sieves, even in the absence of a catalyst. Addition of acid catalyst **3** after formation of the aromatic enone-derived hydrazone intermediate and filtration furnished the desired products **2** in excellent yields maintaining the high enantioselectivity of the two-step protocol (Table 2, entries 1–4).



2n (*S*)-(−)-E-6244

Figure 1. COX-2 inhibitors **2n** and (*S*)-(−)-E-6244.

Table 2: Enantioselective synthesis of 2-pyrazolines starting from α,β-unsaturated ketones **4** and phenylhydrazine (**5**).[a]



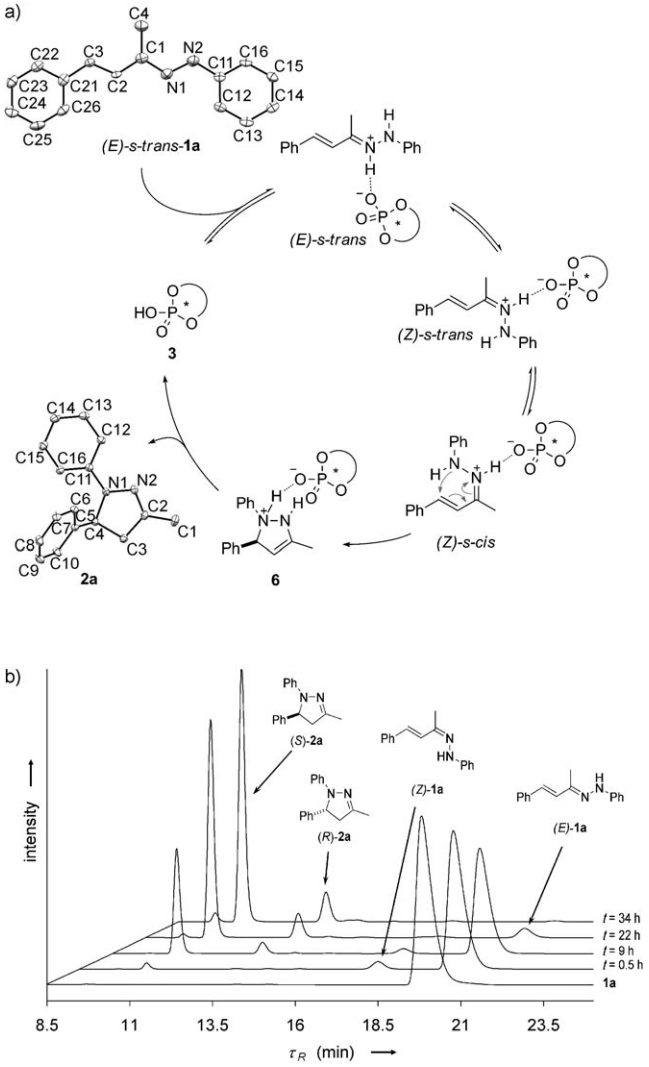
4 **5** **2**

Entry	Product	R	Yield [%][b]	e.r.[c]
1	**2c**	R = 4-Cl-C_6H_4	97	94:6
2	**2i**	R = 3-Br-C_6H_4	90	95:5
3[d]	**2j**	R = 3-NO_2-C_6H_4	99	96:4
4	**2o**	R = 3-I-C_6H_4	89	95:5
5[e]	**2p**	R = *n*-C_5H_{11}	18	35:65
6[f]	**2p**	R = *n*-C_5H_{11}	40	75:25

[a] Unless otherwise noted, the reactions were run in Ar atmosphere with enones **4** (0.105 mmol), phenylhydrazine (0.10 mmol), MS 4 Å, and phosphoric acid **3** (10 mol%) in chlorobenzene (1.0 mL) at 30°C. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction was run at 40°C. [e] Reaction was run for 24 h at 100°C with 0.11 mmol of enone and **3** (20 mol%) as catalyst. [f] Reaction was run for 24 h at 50°C with 0.11 mmol of enone and the *N*-triflyl-phosphoramide of **3** (20 mol%) as catalyst.

When aliphatic enones were subjected to the same reaction conditions, the cyclization proceeded only sluggishly even at elevated temperatures and gave poor yields and enantioselectivities (Table 2, entry 5). Interestingly, these results could be improved by using the more acidic but, in the case of aromatic hydrazones less selective, *N*-triflyl-phosphoramide analogue of **3** (see the Supporting Information) as catalyst. In this case, pyrazoline **2p** was obtained in 40% yield and with an enantiomeric ratio of 75:25 e.r. (entry 6), thus illustrating the potential generality of our method.

To undergo the reaction, linear hydrazone (*E*)-**1a** (see X-ray crystal structure in Scheme 2a) has to adopt the "cyclization-reactive" (*Z*)-*s-cis*-conformation. This requires both C–C single-bond rotation and C–N double-bond isomerization. While the *s-trans* to *s-cis* isomerization should be facile even at room temperature, the *E*/*Z* isomerization of the hydrazone



Scheme 2. a) Crystal structures of **1a** and **2a** (ellipsoids are drawn at 50% probability) and proposed catalytic cycle; b) HPLC traces of the reaction mixture at different times *t* (reaction run at 40 °C).

bond requires acid catalysis. Indeed, in the absence of catalyst we detected only one peak for pure **1a** by HPLC. After adding catalyst **3**, a second peak of identical mass (LC-MS) emerged, which disappeared again during the course of the reaction, thus indicating an intermediate (Scheme 2b). Since the *E*/*Z* isomerization of related α,β-unsaturated hydrazones is known to be catalyzed by phosphoric acid,[19] this peak most likely corresponds to (*Z*)-**1a**. After adopting an *s-cis*-conformation, the protonated intermediate (*Z*)-**1a**, which is the cation of a chiral hydrogen-bond-assisted ion pair, undergoes a 6π electrocyclization, furnishing 3-pyrazoline **6**. Subsequent isomerization and deprotonation then gives the thermodynamically more stable 2-isomer **2a** (see X-ray crystal structure in Scheme 2a).

In summary we have shown that chiral Brønsted acids efficiently catalyze the cycloisomerization of α,β-unsaturated hydrazones to give pyrazolines in high yields and enantioselectivities. This transformation is, to the best of our knowledge, the first example of a catalytic asymmetric 6π electrocyclization.[20] Additional research including a detailed analysis of the transition state and the mechanism of stereoinduction, an expansion of the substrate scope, and the asymmetric catalysis of other electrocyclic reactions is ongoing.

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