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Organocatalytic Asymmetric Reaction Cascade to Substituted Cyclohexylamines

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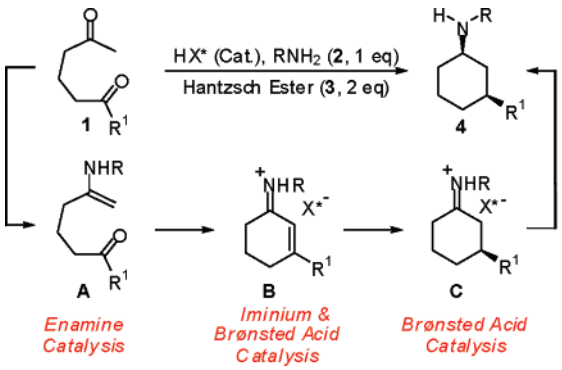
Combining different organocatalytic reactions into cascades has recently become a fruitful concept for complex molecule synthesis.[1] The approach fundamentally relies on the reaction compatibility, often realized in organocatalysis. Especially, amines and their salts trigger such cascade reactions via enamine or iminium ion formation.[2] Several new carbon−carbon bonds and stereogenic centers can be created in a highly controlled fashion from readily available precursors in one-pot operations.[3] These aminocatalytic cascades require chiral secondary amines to facilitate the reaction and to induce asymmetry. Meanwhile, asymmetric Brønsted acid catalysis has been introduced and shown to be compatible with amine substrates and products.[4,5] The combination of asymmetric Brønsted acid catalysis with amine catalysis, however, is largely undeveloped. We now demonstrate the remarkable efficiency of this concept by combining both enamine and iminium catalysis with asymmetric Brønsted acid catalysis. We have developed a highly enantioselective synthesis of pharmaceutically relevant 3-substituted cyclohexylamines from 2,6-diketones via an aldolization−dehydration−conjugate reduction−reductive amination cascade that is catalyzed by a chiral Brønsted acid and accelerated by the achiral amine substrate, which is ultimately incorporated into the product.

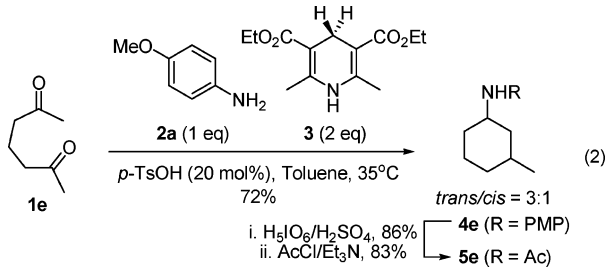
We have previously demonstrated that salts consisting of either an achiral or chiral ammonium cation and a chiral phosphate anion are powerful catalysts of transfer hydrogenations of α,β-unsaturated aldehydes and ketones with Hantzsch esters.[6,7] On the basis of this strategy, our experience in Brønsted acid catalyzed asymmetric imine reductions and reductive aminations,[8] and the well-known capacity of amine salts to catalyze aldolizations,[9] we designed a new triple organocatalytic cascade reaction for the synthesis of 3-substituted cyclohexylamines (eq 1).



(1)

Accordingly, treating a 2,6-diketone (**1**) with 1 equiv of an achiral amine (**2**), 2 equiv of a Hantzsch ester (**3**), and a catalytic amount of a chiral Brønsted acid should lead to the corresponding cyclohexylamines (**4**). The initial aldolization step involving intermediate **A** was expected to be catalyzed by the amine salt via enamine catalysis. The conjugate reduction step should proceed via a combination of iminium and Brønsted acid catalysis involving intermediate **B**. The terminating reductive amination of intermediate **C** would be Brønsted acid catalyzed.[10]

Indeed, a non-enantioselective variant could quickly be realized by treating 2,6-heptandione (**1e**) with *p*-anisidine (**2a**), Hantzsch ester **3**, and a catalytic amount of *p*-TsOH at 35 °C in toluene. The major product was the expected racemic 3-methylcyclohexylamine derivative **4e** as a mixture of diastereomers (eq 2). The PMP group can readily be removed in high yield using H_5IO_6.[11] Acetylation of the intermediate primary amine provided known amide **5e**.



(2)

Although 3-substituted cyclohexylamines are constituents of several pharmaceutically active compounds,[12] catalytic and highly stereoselective methods for their preparation are rare.[13] We therefore systematically screened various reaction conditions involving chial Brønsted acid catalysts (see Supporting Information) and found that treating different substituted 2,6-diketones **1**[14,15] with Hantzsch ester **3** (2.2 equiv), *p*-alkoxyanilines **2a** or **2b** (1.5 equiv), and (*R*)-3,3′-bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogen phosphate [(*R*)-**TRIP**][8a] (10 mol %) at 50 °C in cyclohexane and in the presence of molecular sieves afforded the corresponding *cis*-3-substituted (hetero)cyclohexylamine derivatives **4** in good yields, reasonable to very high diastereoselectivities, and in excellent enantioselectivities (Table 1). The er exceeds 95:5 (ee > 90%) in most of the studied reactions and is particularly high with aliphatic substituents. Heterocyclic products can also be obtained in high enantioselectivity (entries 11 and 12).

The initial aldolization is rapid, and diketones **1** were fully converted into the corresponding aldol condensation product within 5 min as monitored by GC−MS. This step seems to be kinetically controlled as regioisomeric products resulting from thermodynamic control were not formed (<3%). The aldolization is mediated by the amine substrate and the phosphoric acid; either reagent alone is inefficient in accelerating the aldolization. The formation of 2,6-disubstituted piperidines, which may have been expected from a double reductive amination, was not observed. Similarly, the conjugate reduction step is accelerated by the acid *and* by the amine. In the absence of either reagent, no further conversion of the enone intermediate is observed.

The regioselectivity in the conjugate reduction (1,4- vs 1,2-reduction) is excellent. Only in the case of 2-naphthyl-substituted diketone **1j**, we detected a small amount (<4%) of the 1,2-reduction product.

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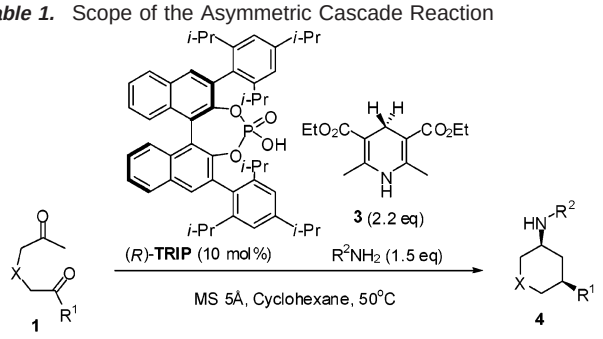
Table 1. Scope of the Asymmetric Cascade Reaction



Entry	R^1	R^2	X	Product	Yield [%]	dr^b	er^c
1		PEP[a]	CH_2	**4a**	75	10:1	95:5
2		PEP	CH_2	**4b**	79	12:1	98:2
3		PEP	CH_2	**4c**	77	6:1	93:7
4		PEP	CH_2	**4d**	82	24:1	98:2
5[d]	Me	PEP	CH_2	**4e**	88	6:1	92:8
6		PEP	CH_2	**4f**	72	24:1	98:2
7		PMP[a]	CH_2	**4g**	89	19:1	98:2
8		PEP	CH_2	**4h**	78	4:1	96:4
9		PMP	CH_2	**4i**	76	3:1	96:4
10		PEP	CH_2	**4j**	73	2:1	91:9
11	Me	PEP	O	**4k**	72	99:1	96:4
12	Me	PEP	S	**4l**	35	2:1	95:5

[a] PEP = *p*-ethoxyphenyl; PMP = *p*-methoxyphenyl. [b] Determined by GC−MS or ^{1}H NMR analysis of the crude product. [c] Determined by chiral stationary phase HPLC analysis. [d] The relative configuration of products **4** was determined by NMR analysis. The absolute configuration of product **4e** was assigned via conversion to known amide (1*R*,3*S*)-**5e** (see eq 2).

In the final reductive amination step, **TRIP** is crucial for the observed *cis*-selectivity. Alternative phosphoric acids typically gave the corresponding *trans*-isomer. Similarly, the reductive amination of the intermediate 3-alkyl cyclohexanones generally provides the corresponding *trans*-isomer under a variety of reductive amination conditions (see Supporting Information).

We conclude that combining enamine catalysis and iminium catalysis with Brønsted acid catalysis constitutes a powerful strategy for organocatalytic cascade reactions. The combination of a "self-sacrificing" achiral amine in combination with a chiral Brønsted acid has been used in a highly enantioselective triple organocatalytic cascade reaction for the synthesis of *cis*-3-substituted (hetero)-cyclohexylamines from 2,6-diones. Further explorations merging aminocatalysis with asymmetric Brønsted acid catalysis and a detailed mechanistic investigation are under investigation in our laboratory.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC traces (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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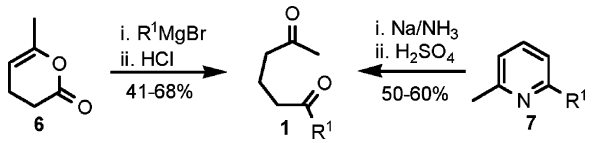
(14) Most diketones **1** can be obtained from commercially available lactone **6** or from pyridines **7** (see Supporting Information):



(15) As expected, 2,5-diketones gave the corresponding pyrroles.

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