Synthesis of *trans*-3-Substituted Cyclohexylamines via Brønsted Acid Catalyzed and Substrate-Mediated Triple Organocatalytic Cascade Reaction

Jian Zhou, Benjamin List*

Max-Planck-Institut für Kohlenforschung, Kaiser-Wilhelm-Platz 1, 45470 Mülheim an der Ruhr, Germany
Fax +49(208)3062999; E-mail: list@mpi-muelheim.mpg.de

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Abstract: We report a new organocatalytic cascade reaction. A combination of the amine substrate with a catalytic amount of a Brønsted acid merges enamine and iminium catalysis with Brønsted acid catalysis in a new organocatalytic cascade reaction. We found that the aniline substrate itself in combination with a catalytic amount of PTSA·H_2O can function as an aminocatalyst accomplishing an aldol condensation–conjugate reduction cascade, which terminates in a Brønsted acid catalyzed reductive amination incorporating the amine substrate into the final product. This transformation furnishes *trans*-3-substituted cyclohexyl amines in good yields and good diastereoselectivities.

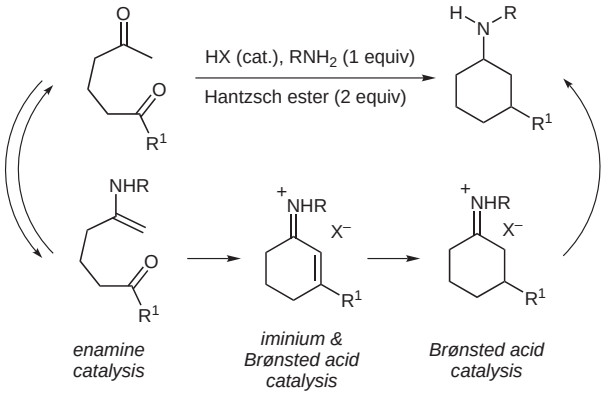
Key words: organocatalytic cascade reaction, substrate co-catalyzed, 3-substituted cyclohexyl amine, organocatalysis

The design of new catalytic cascade reactions is at the forefront of modern organic synthesis because such processes can effectively save time, energy, and materials.[1] Especially, the modular combination of different organocatalytic reactions into cascades has recently become a fruitful concept for complex molecule synthesis.[2] This approach fundamentally relies on the reaction compatibility, often realized in organocatalysis.[3]

Amines and their salts are particularly versatile for the design of organocatalytic cascade reactions because they can trigger reactions either via enamine or iminium ion formation.[4] Combining enamine and iminium catalysis in different sequences paves a facile way for the creation of new carbon–carbon bonds and stereogenic centers in a highly controlled fashion from readily available precursors in one-pot operations.[5] Meanwhile, Brønsted acid catalysis have already found many applications in organic synthesis, and been shown to be compatible with amine substrates and products.[6] However, the combination of Brønsted acid catalysis with amine catalysis is largely undeveloped. In this communication, we wish to report a new strategy for organocatalytic cascade reactions. We found that the amine substrate itself in combination with a catalytic amount of a Brønsted acid can function as both enamine and iminium catalyst accomplishing an aldol condensation–conjugate reduction cascade, which terminates in a Brønsted acid catalyzed reductive amination and the incorporation of the amine into the final product. This transformation provides a useful access to *trans* 3-substituted cyclohexyl amines in good yields and diastereoselectivities (Scheme 1).

We have previously demonstrated that salts consisting of 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.[7,8] We have also developed Brønsted acid catalyzed imine reductions and reductive aminations with Hantzsch esters.[9] Based on these results, together with the well-established capacity of amine salts to catalyze aldolizations,[10] we designed a new triple organocatalytic cascade process which integrates enamine catalysis, iminium catalysis, and Brønsted acid catalysis. Accordingly, treating 2,6-heptanediones with an amine, a catalytic amount of a Brønsted acid, and two equivalents of a Hantzsch ester (HE), the corresponding saturated amines should be formed via an aldol condensation–conjugate reduction–reductive amination cascade (Scheme 1). The first two steps of this reaction would be catalyzed by the amine salt via enamine catalysis and via a combination of iminium and Brønsted acid catalysis. The amine would finally be incorporated into the product in a Brønsted acid catalyzed reductive amination.[11]

This concept was realized by treating 2,6-heptanedione (**1a**) with 1.5 equivalents of *p*-ethoxy aniline (PEP-NH_2, **2**), 2.2 equivalents of Hantzsch ester **3**, and 5 mol% of PTSA·H_2O, in toluene at 40 °C. After 48 hours, cyclohexyl amine **4a** was isolated in 72% yield (Scheme 2). The relative configuration of **4a** was confirmed by NMR analysis, the *trans* isomer being the major product (dr = 4:1).[12] We have investigated various solvents without significantly affecting the diastereoselectivity.



Scheme 1

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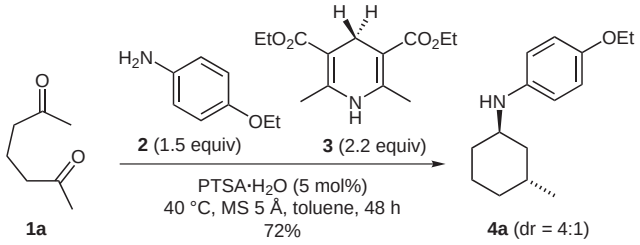
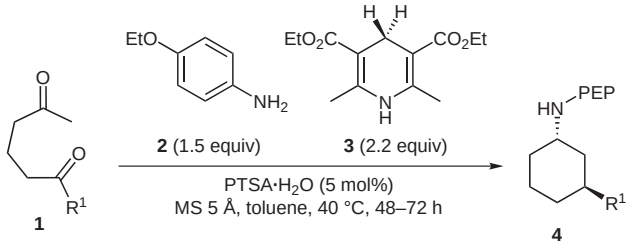
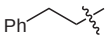
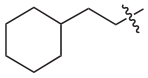
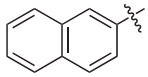
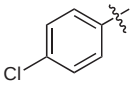


Scheme 2

The highest reactivity was observed in toluene. The use of 1.5 equivalents of the amine was found to minimize the amount of byproduct 3-methylcyclohexanone **6a**. This intermediate serves as the precursor for the terminating reductive amination. Molecular sieves (5 Å) accelerated the reaction. The substrate scope was then examined under the optimized reaction conditions (Table 1).

Table 1 Substrate Scope[13]



Entry	R^1	Product **4**	Yield (%)	dr[a]
1	Me	**4a**	72	4:1
2		**4b**	65	4:1
3		**4c**	72	3:1
4		**4d**	73	6:1
5		**4e**	86	5:1
6		**4f**	75	4:1
7		**4g**	68	5:1
8		**4h**	83	4:1
9		**4i**	63	8:1
10	Ph	**4j**	60	5:1
11		**4k**	66	5:1

[a] Determined by GC-MS or ^{1}H NMR analysis.

Several substituted 2,6-diones (**1a**–**k**) react smoothly to the desired products **4** (Table 1). All the substrates afforded good to high yield and the *trans*-diastereomer was the major product with selectivities of up to 8:1.

The initial aldol condensation is fast and seems to be kinetically controlled. This reaction almost exclusively takes place between the 1-methyl- and the 6-carbonyl group of the substrate.[14] Even in the case of substrate **1b** and **1c**, apt to give regioisomeric mixtures, less than 5% of the regioisomers could be detected in a careful GC-MS study. The aldolization is catalyzed by the amine substrate and the acid catalyst; either reagent alone is inefficient in catalyzing the reaction. The formation of 2,6-disubstituted piperidines, which may have been expected from a double reductive amination, was not observed.

The conjugate reduction step is Brønsted acid and amine co-catalyzed and in the absence of either catalyst, no further conversion of the enone intermediate is observed. That the amine is a true catalyst of at least the initial two steps of the cascade reaction is revealed when the reaction is carried out in the presence of only one equivalent of the Hantzsch ester and a substoichiometric amount of the amine. Under these conditions the product of the aldol–conjugate reduction sequence is observed as the major product after passing the crude mixture through a short pad of silica gel. The regioselectivity in the conjugate reduction step (1,4- vs. 1,2-reduction) is excellent. Only when R^1 is aromatic (entries 9–11), small amounts of the 1,2-reduction products **7i**–**k** (Figure 1) are formed as byproducts in 10–15% yield. Similar electronic effects have been observed in reductions of preformed α,β-unsaturated iminium ions.[15]

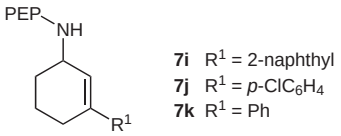
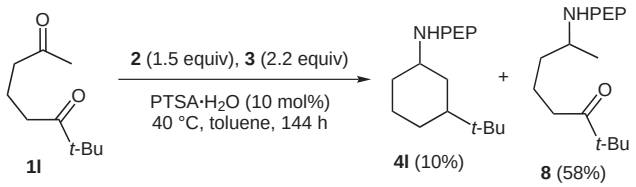


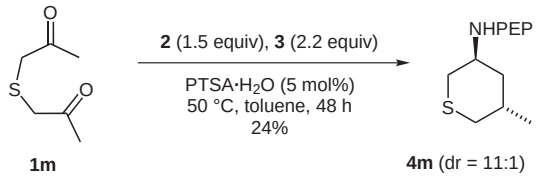
Figure 1

Interestingly, with *t*-Bu-substituted diketone **1l**, the desired product **4l** could be obtained in only 10% (Scheme 3). In this case, compound **8** was formed as major product. Presumably reductive amination is faster than aldol condensation in this case.



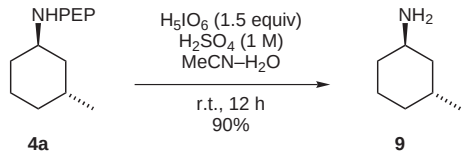
Scheme 3

This method can also be used for the synthesis of heterocyclic compounds. For example, thiodiketone **1m** could be transformed to the corresponding heterocyclic compound **4m** in excellent diastereoselecitivity (92:8) and in moderate yield (Scheme 4).



Scheme 4

The PEP group can be readily removed in high yield using H_5IO_6, a method recently reported by researchers at DSM (Scheme 5).[17]



Scheme 5

In conclusion, we demonstrate that combining enamine catalysis and iminium catalysis with Brønsted acid catalysis constitutes a powerful strategy for developing organocatalytic cascade reactions. Based on this strategy, we have developed a new triple organocatalytic cascade reaction for preparing *trans*-3-substituted (hetero) cyclohexyl amines from 2,6-diones, which are constituents in several pharmaceutically active compounds.[17] The use of a catalytic amount of Brønsted acid in combination with a stoichiometric amount of an achiral amine as self-sacrificing aminocatalyst is a new concept for organocatalysis. Further extensions of this strategy are under investigation in our laboratory.

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(13) Typical Procedure: To a Schlenk tube was added 2,6-dione **1** (0.2 mmol), *p*-ethoxyphenyl amine **2** (0.3 mmol), Hantzsch ester **3** (0.45 mmol) and PTSA·H_2O (2 mg, 0.01 mmol), and then charged with argon, followed by adding MS 5 Å (50 mg) and anhyd toluene (0.5 mL). The mixture was stirred at 40 °C for 24–72 h. To determine the ratio of *trans*- to *cis*-product, 20 μL of the reaction mixture was taken for GC-MS analysis, or 0.2 mL of crude mixture for ^{1}H NMR analysis. The sample for analysis and the rest were emerged together for column chromatography purification using hexane–EtOAc (96:4) or CH_2Cl_2 as eluent. Compound *trans*-**4a** was obtained as colorless liquid (0.144 mmol, 72%) after chromatography with hexane–EtOAc (96:4). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 6.4 Hz, 3 H), 0.99–1.10 (m, 1 H), 1.27–1.37 (m, 1 H), 1.36 (t, *J* = 6.9 Hz, 3 H), 1.47–1.78 (m, 7 H), 3.20–3.50 (s, br, 1 H), 3.56–3.60 (m, 1 H), 3.95 (q, *J* = 6.9 Hz, 2 H), 6.53–6.58 (m, 2 H), 6.74–6.79 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.05, 20.52, 21.69, 27.13, 30.54, 33.98, 38.96, 48.54, 64.17, 114.60, 115.88, 141.68, 151.04. MS (EI): *m/z* (%) = 233 (100) [M^+], 234 (14) [M + H]$^+$, 190 (40), 108 (39), 176 (32), 204 (22), 137 (18), 97 (10). HRMS (EI): *m/z* calcd for $C_{15}H_{24}NO$ [M + H]$^+$: 234.1852; found: 234.1852.

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