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Asymmetric Catalysis of the Carbonyl-Amine Condensation: Kinetic Resolution of Primary Amines

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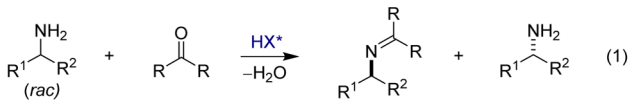
Supporting Information

ABSTRACT: A Brønsted acid catalyzed kinetic resolution of primary amines is described that is based on the condensation between an amine and a carbonyl compound. 1,3-Diketones react with racemic α-branched amines to furnish the corresponding enantioenriched enaminone and recovered starting material. Good to excellent enantioselectivity was observed with both aromatic and aliphatic primary amines. This process represents the first small-molecule catalyzed kinetic resolution of aliphatic amines.

The condensation of an amine with a carbonyl compound is not only a fundamental organic reaction by itself[1] but also key to enzymatic and organocatalytic cycles,[2] and to several important transformations including the Mannich, Petasis, Strecker, Pictet–Spengler, Paal–Knorr, Rodionov, and Kabachnik–Fields reactions.[3] Despite its significance and utility in chemical synthesis, however, a catalytic enantioselective variation of this reaction is unknown. Since the carbonyl-amine condensation is readily catalyzed by acids, we reasoned that an asymmetric version should be realizable using a chiral Brønsted acid catalyst. Such a process could be of significant utility in asymmetric synthesis, and we became particularly intrigued by the idea of utilizing it as a new approach for the kinetic resolution (KR) of racemic primary amines (eq 1).We



(1)

■ *concept: kinetic resolution via acid catalyzed carbonyl-amine condensation*

now report the realization of this general concept with the design and development of a highly enantioselective condensation of a 1,3-diketone with racemic primary amines to the corresponding enantioenriched enaminone via KR.

Enzymatic KRs of chiral amines are well advanced and technically utilized.[4] A particularly fascinating approach has been developed by Bäckvall et al., involving the dynamic KR of *rac*-amines using a ruthenium-based racemization catalyst in combination with a lipase.[5] In contrast, the KR of amines via small molecule catalysis is only emerging in recent years.[6–8] Pioneering contributions to this field came from Fu et al. using a ferrocene based chiral DMAP catalyst and an azlactone carbonate as an acylating reagent.[6a] Later, Seidel et al. reported a dual catalyst system consisting of a chiral thiourea catalyst and DMAP,[6f] and Bode et al. resolved cyclic amines using an N-heterocyclic carbene catalyst in combination with a chiral hydroxamic acid cocatalyst.[6i] Despite these advances, there is still no general organocatalytic approach available that is applicable to a broad range of chiral amines. In particular purely aliphatic amines could not previously have been resolved in organocatalytic asymmetric kinetic resolutions.

An inherent problem of small-molecule-based amine acylation catalysis is the high nucleophilicity of amines, which can lead to nonenantioselective background catalysis. We initially wondered if a Brønsted acid catalyzed imine formation could be used to address this problem. However, the reversibility of the reaction and the potential for trans-imination may yet lead to other new problems. We realized that an appropriate choice of the carbonyl compound was crucial in the design of such a process and specifically hoped that 1,3-diketones may be of utility, as they would lead to relatively stable enaminones, making the process much less reversible. Alternatively, 1,4-diketones may be used and lead to the corresponding pyrroles.[9]

Indeed, we commenced our studies by reacting racemic amine **1a** with 1,3-diketone **2a** in diethyl ether using (*S*)-TRIP (**3a**) as a catalyst at −5 °C and obtained the corresponding enaminone **4** (Table 1).[10] At 57% conversion, a low *s*-factor of 2.3 was achieved (entry 1). To improve the selectivity, β-ketoester **2b** and 1,3-diketones **2c** and **2d** were tested (entries 2–4), and of those, the best selectivity (s = 5.2) was observed with branched diketone **2c** (entry 3). Toward identifying an improved catalyst, a systematic study exploring its R^3-position was undertaken (entries 5–7). When R^3 is hydrogen (**3b**), the selectivity was lower than that of (*S*)-TRIP (**3a**) (entry 5), which led us to speculate that perhaps a more bulky group at this position may improve the enantioselectivity.[11] Gratifyingly, an additional 2,4,6-trisisopropylphenyl group at R^3 as in catalyst **3c** significantly increased the *s*-factor from 5.2 to 26.1 (entry 6). Modification of R^3 to 9-anthracenyl in catalyst **3d** gave lower conversion and selectivity than that displayed by catalyst **3c** (entry 7). Accordingly, catalyst **3c** was chosen in the following studies. The evaluation of different solvents (entries 8–11) showed that diethyl ether gave the best selectivity factor to resolve our model primary amine. The reaction was also performed at higher and lower concentrations (entries 12–13) with little to no effect on selectivity and conversion. Finally, in

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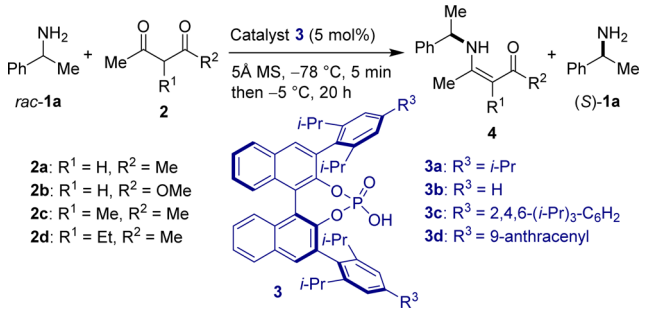
Table 1. Reaction Development[a]



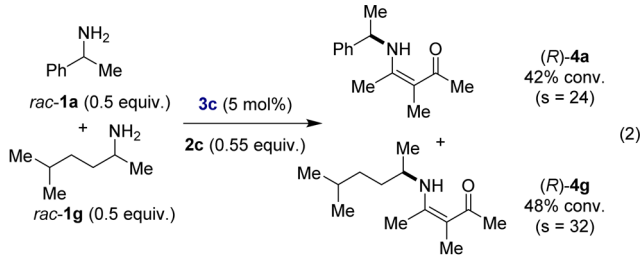
entry	solvent	diketone	catalyst	conv. (%)[b]	*s*
1	Et_2O	**2a**	**3a**	57	2.3
2	Et_2O	**2b**	**3a**	49	2.0
3	Et_2O	**2c**	**3a**	53	5.2
4	Et_2O	**2d**	**3a**	50	3.0
5	Et_2O	**2c**	**3b**	45	3.0
6	Et_2O	**2c**	**3c**	53	26.1
7	Et_2O	**2c**	**3d**	39	12.3
8	MTBE	**2c**	**3c**	50	23.8
9	EtOAc	**2c**	**3c**	31	18.3
10	PhMe	**2c**	**3c**	49	20.6
11	CH_2Cl_2	**2c**	**3c**	41	11.9
12[c]	Et_2O	**2c**	**3c**	48	24.7
13[d]	Et_2O	**2c**	**3c**	47	24.9
14	Et_2O	**2c**	–	0	NA

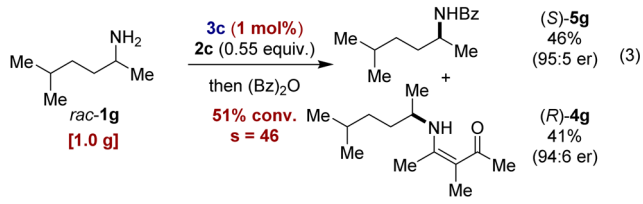
[a]0.025 mmol scale, 0.1 M. [b]Er, conv., and *s*-factor were determined by HPLC.[9] [c]0.125 M. [d]0.075 M. MTBE = methyl *tert*-butyl ether.

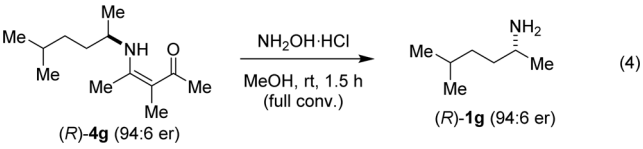
the absence of a catalyst, no conversion to product was obtained (entry 14).

The scope of the reaction was next explored using the optimized reaction conditions (Chart 1).[12] A broad range of *rac*-benzylic amines could be resolved. Irrespective of their electronics and sterics, and with different substituents at different ring positions, high selectivity factors were obtained (**1a**–**1f**). Excitingly, even aliphatic primary amines can be resolved with our method, displaying good to excellent selectivity (**1g**–**1l**). *To the best of our knowledge, this is the first example of a small molecule-catalyzed kinetic resolution of aliphatic primary amines.* Remarkably, the catalyst can even differentiate between an *n*-Pr and a Me group in aliphatic amine **1j**. Unfortunately, cyclic amines **1m** and **1n** did not furnish the desired product, even at elevated temperature. Furthermore, amino acid **1o** also did not provide the corresponding enaminone.

We also conducted a single flask competition experiment in which 0.5 equiv of *rac*-aromatic amine **1a** and 0.5 equiv of *rac*-aliphatic amine **1g** were subjected to our reaction conditions. Interestingly, the two different amines were independently resolved, each with good selectivity (eq 2). Further, to



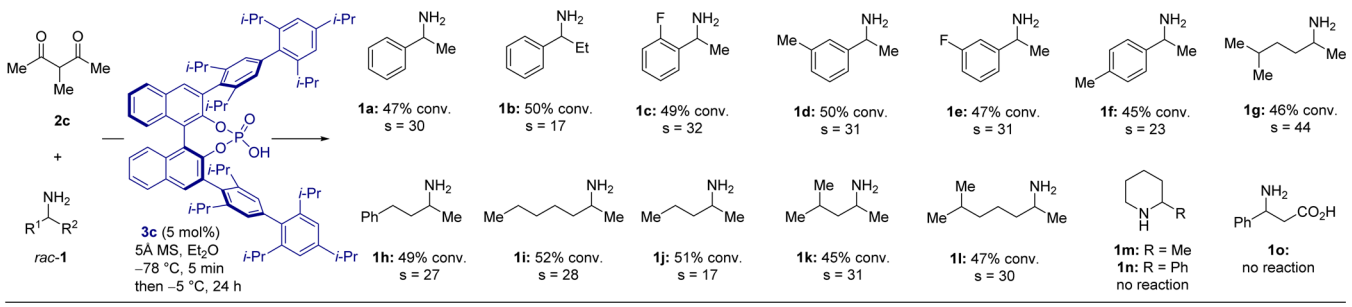




demonstrate the practicability of our method, a gram scale experiment was performed (eq 3). The reaction of 1 g of amine **1g** in the presence of only 1 mol % of catalyst **3c** (which was recovered from our scope studies shown in Chart 1) proceeded smoothly with an *s*-factor of 46 and gave at 51% conversion (*R*)-product (*R*)-**4g** in 41% yield and 94:6 er. The recovered amine **1g** was isolated as benzamide derivative **5g** in 46% isolated yield with an er of 95:5. Finally, removal of the enone moiety was readily accomplished and enaminone **4g**, upon treatment with hydroxylamine hydrochloride, was fully converted into free amine **1g** with preservation of enantiopurity (eq 4).[9] Our method therefore provides access to both amine enantiomers.

In summary, we have developed a Brønsted acid catalyzed kinetic resolution of primary amines that is based on their condensation with a diketone. This reaction is a proof-of-

Chart 1. Scope of the Kinetic Resolution of *rac*-Amines[a]



[a]0.1 mmol scale. er determined by HPLC.[9]

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principle for the general concept of catalyzing amine-carbonyl condensations enantioselectively, a concept which we assume to be widely applicable to many other transformations. Our methodology tolerates a wide variety of amines, and most remarkably, even aliphatic amines are resolved with good to excellent selectivity. Currently, we can only speculate on the origin of enantioselectivity of our reaction. In principle, any of the multiple steps of the condensation reaction, or combinations thereof, could govern the high selectivity. Even an enantiomer differentiating interaction of the catalyst with the amine enantiomers cannot be excluded at this point. Mechanistic studies and an expansion of the scope of our methodology are of high current interest in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b12176.

Experimental procedures, characterizations and analytical data of products, and spectra of NMR and HPLC (PDF)

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Notes

The authors declare no competing financial interest.

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(12) Under our optimized conditions, the unreacted free amine is derivatized in situ with benzoic anhydride to ease isolation and characterization. To isolate the free amine, the crude reaction mixture is directly loaded onto a silica gel column, which is initially eluted with 30% Et_2O–pentane (v/v) to obtain the enaminone product. Further elution with 0.1:1:9 (triethylamine/methanol/ethyl acetate) then provides the unreacted free amine.

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