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Merging Nucleophilic and Hydrogen Bonding Catalysis: An Anion Binding Approach to the Kinetic Resolution of Propargylic Amines

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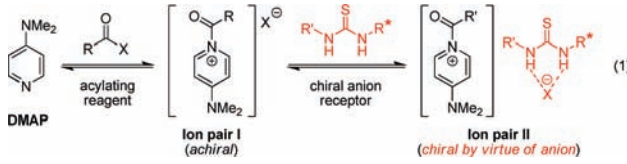
Abstract: An efficient kinetic resolution of primary propargylic amines with s-factors of up to 56 is reported. The strategy is based on a dual catalytic approach, namely the use of a newly developed and easy-to-make thiourea-amide anion binding catalyst in combination with 4-(dimethylamino)pyridine (DMAP), both employed at a 5 mol % catalyst loading. Benzylic amines are also resolved with s-factors of up to 38.

Propargylic amines constitute versatile synthetic intermediates and are found as substructures in natural products and medicinal drugs.[1] Consequently, significant efforts have been devoted to synthesize propargylic amines in enantioenriched form.[2] The majority of catalytic enantioselective approaches have focused on the addition of alkynes to imines.[3] In most cases, the resulting secondary propargylic amines cannot be readily transformed into the often synthetically more useful primary amines. A practical approach to enantioenriched primary propargylic amines would be the kinetic resolution of the corresponding and readily available racemic amines. Although small-molecule catalyzed kinetic resolutions of propargylic alcohols have been reported,[4] the equivalent reaction with propargylic amines has remained elusive. Here we report the first example of such a process.

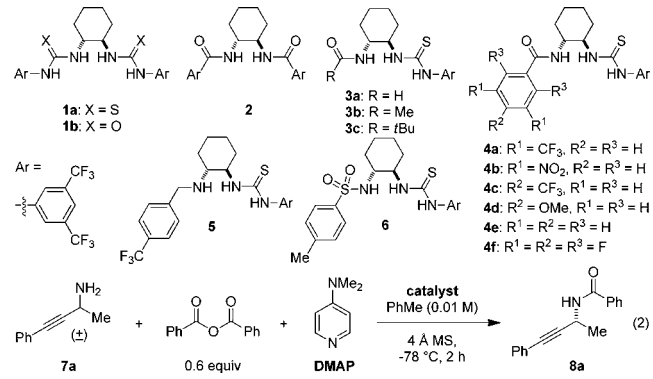
The inherent nucleophilicity of primary amines presents a significant challenge for their kinetic resolution by small-molecule based chiral nucleophilic catalysts.[5] In fact, the nucleophilicity of the amine substrate is often comparable to that of potential catalysts. Although a few elegant approaches to the kinetic resolution of amines and some of their less nucleophilic derivatives have been reported,[6,7] there is still no general solution that is applicable to a broad range of unmodified and highly reactive amines.



We have recently reported a new concept for asymmetric catalysis that provides an alternative to the use of chiral nucleophilic catalysts (eq 1).[8−11] A simple achiral acyl pyridinium salt (e.g., ion pair **I**), formed in situ from DMAP and an acylating reagent, is rendered chiral upon binding of the associated anion to a chiral thiourea compound. The latter functions as an anion receptor to form chiral ion pair **II**. Conditions were identified under which primary benzylic amines react predominantly with ion pair **II** over ion pair **I** or a free acylating reagent. This approach enabled the kinetic resolution of benzylic amines.[8]

Gratifyingly, our previously optimized conditions with catalyst **1a**[12] (20 mol %) and DMAP (20 mol %) allowed for the kinetic resolution of propargylic amine **7a** with an s-factor[13] of 11 (Table 1, entry 1). In order to determine what structural parameters affect catalyst performance and to ultimately identify a more efficient catalyst, we performed a systematic modification of the basic catalyst framework. Exchanging both of the thiourea moieties for 3,5-bis(CF_3)benzamide groups resulted in the ineffective catalyst **2** (entry 3). Replacement of only one of the thiourea functions with a simple acetyl group led to the improved catalyst **3b** (entry 5). A significantly more efficient catalyst (**4a**) resulted from the replacement of one thiourea subunit for 3,5-bis(CF_3)benzamide (entry 7). This catalyst performed equally well at a 10 mol % loading (entry 10) and, remarkably, even better if used in only 5 mol % (entry

Table 1. Evaluation of Reaction Parameters[a]



entry	catalyst (mol %)	DMAP (mol %)	conversion (%)	s-factor
1	**1a** (20)	20	49	11
2	**1b** (20)	20	42	9
3	**2** (20)	20	30	1
4	**3a** (20)	20	48	8.6
5	**3b** (20)	20	50	14
6	**3c** (20)	20	51	9.2
7	**4a** (20)	20	50	33
8	**5** (20)	20	27	1
9	**6** (20)	20	38	1.5
10	**4a** (10)	10	47	33
11	**4a** (5)	5	46	38
12	**4a** (2)	2	41	35
13[b]	**4a** (2)	2	46	35
14[b]	**4a** (1)	1	24	18
15	none	5	<5	N/A
16	none	none	<2	N/A
17	**4a** (5)	none	26	1.6
18	**4b** (5)	5	43	18
19	**4c** (5)	5	42	28
20	**4d** (5)	5	42	14
21	**4e** (5)	5	41	13
22	**4f** (5)	5	39	3.0

[a] Reactions were performed on a 0.2 mmol scale. The s-factors were determined by HPLC analysis; see the Supporting Information for details. [b] Reactions were run for 4 h.

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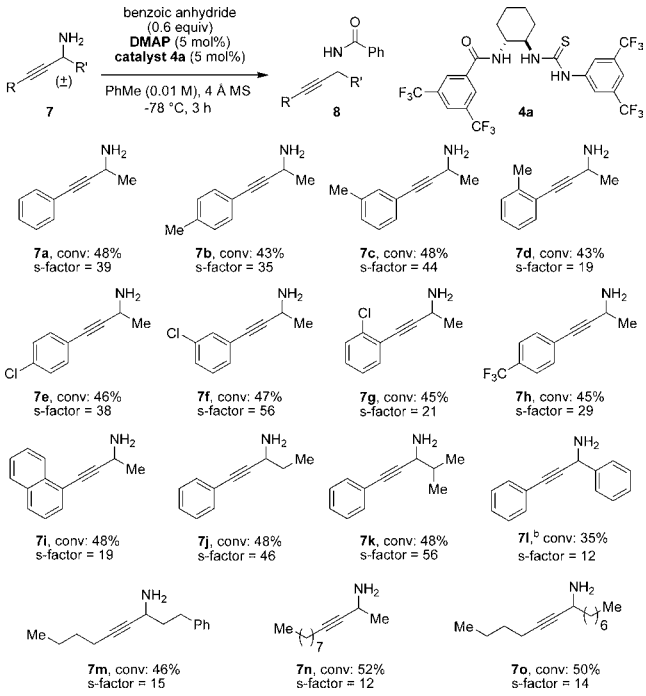
Chart 1. Scope of the Propargylic Amine Resolution[a]



[a] Reactions were performed on a 0.25 mmol scale. The s-factors are averages of two runs (determined by HPLC analysis, see the Supporting Information for details). [b] The reaction was run for 8 h.

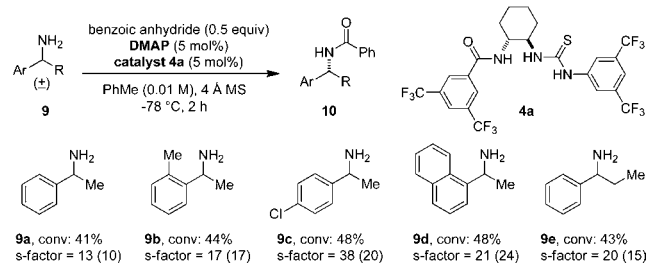
11). Under these conditions, **7a** was resolved with an s-factor of 38. The efficiency was still high at a 2 mol % catalyst loading but diminished markedly when only 1 mol % of each, DMAP and **4a**, were used. Very little conversion occurred in the absence of **4a** or both, DMAP and **4a** (entries 15 and 16). Catalyst **4a** in the absence of DMAP catalyzed the reaction but led to much lower conversion and essentially no resolution (s-factor = 1.6, entry 17). Benzylthiourea **5** and sulfonamide-thiourea **6** proved to be inefficient catalysts (entries 8 and 9). Other benzamide-thiourea catalysts were also evaluated but gave inferior results with regard to selectivity (entries 18−22).[14]

The scope of the reaction was explored under the optimized conditions (Chart 1). A number of propargylic amines were resolved with good to excellent selectivities. Arylpropargylic amines bearing substituents on different ring positions were readily accommodated. Substitution in the 3-position of the aromatic ring gave rise to the highest s-factors, regardless of the electronic nature of the substituent. Substrates **7j** and **7k**, with alkyl groups other than methyl, were resolved with even better selectivities as compared to the parent substrate **7a**.

Remarkably, our catalytic system is capable of distinguishing between two different π-systems, as exemplified by the resolution of substrate **7l**. The corresponding product **8l** was obtained with the same absolute configuration as compared to the other products, establishing control of propargyl over phenyl. Propargylic amines with two aliphatic residues were also viable substrates for kinetic resolution (e.g., **7m**−**7o**).[15]

In order to further evaluate the potential of catalyst **4a** to serve as a general kinetic resolution catalyst for amines, we tested its effectiveness for benzylic amines (Chart 2). With the exception of substrate **9d**, which was resolved with a respectable s-factor of 21, catalyst **4a** at a 5 mol % loading provided equal or better results than catalyst **1a** at a 20 mol % loading.[8] In the case of substrate **9c**, a dramatic improvement in s-factor from 20 to 38 was achieved.

Chart 2. Kinetic Resolution of Benzylic Amines[a]



[a] See footnote in Chart 1. Numbers in parentheses correspond to results obtained with 20 mol % of each, catalyst **1a**, and DMAP.

In summary, we have introduced a new and easy-to-make thiourea-amide anion binding catalyst that, in combination with catalytic amounts of simple DMAP, enables the efficient kinetic resolution of propargylic and benzylic amines with s-factors of up to 56. The use of catalyst **4a** is currently being explored in other reactions that could proceed through chiral anionic intermediates.

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Supporting Information Available: Experimental procedures and characterization data, including X-ray crystal structures of catalyst **4a** and product **8e** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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