ORGANIC LETTERS

2011
Vol. 13, No. 9
2464–2467

A Dual-Catalysis/Anion-Binding Approach to the Kinetic Resolution of Allylic Amines

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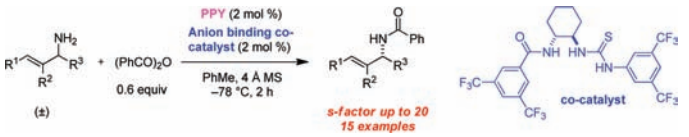
Received March 16, 2011

ABSTRACT



A dual-catalysis approach enables the small-molecule catalyzed kinetic resolution of allylic amines by acylation. By employing 2 mol % of each 4-(pyrrolidino)pyridine (PPY) and a readily available chiral hydrogen-bonding cocatalyst, the first nonenzymatic kinetic resolution of allylic amines was accomplished with *s* factors of up to 20.

Allylic amines are useful building blocks for the synthesis of amino acids,[1] alkaloids,[2] and therapeutic agents.[3] Enantioenriched allylic amines[4] have been prepared via aza-Claisen rearrangement,[1d,5] allylic amination,[1a,c,e,6] vinylation of protected imines,[7] and aza-Baylis–Hillman reaction,[8] in addition to other methods.[9] Many of these approaches produce secondary or tertiary allylic amines. Access to enantioenriched primary allylic amines may be achieved via kinetic resolution of the corresponding racemic amines, but this process has remained elusive. This is despite considerable efforts that have been devoted to the kinetic resolution of allylic alcohols.[10] Here we report the kinetic resolution of allylic amines via a dual-catalyst approach.

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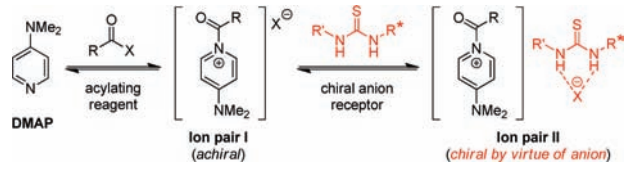
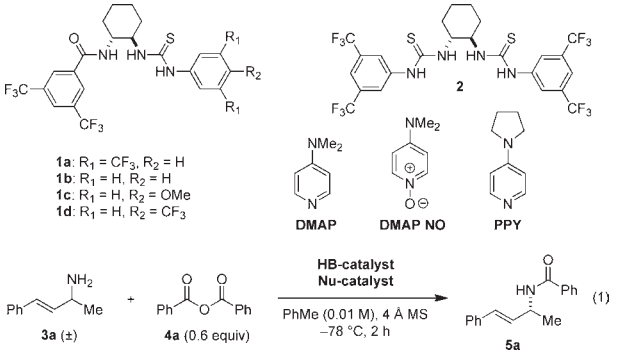
10.1021/ol200712b
Published on Web 04/08/2011

Scheme 1. Anion-Binding Concept for Asymmetric Nucleophilic Catalysis



The high nucleophilicity of many primary amines poses a significant challenge for their kinetic resolution by acylation, specifically in the context of small-molecule catalysis.[11] Several elegant approaches to the kinetic resolution of certain amines and some of their less nucleophilic derivatives have been reported,[12] but there is still no general solution that is applicable to a broad range of unmodified and highly reactive amines, including primary allylic amines. We have recently reported a new concept for asymmetric nucleophilic catalysis,[13] along with its application to the kinetic resolution of benzylic[13a] and propargylic amines.[13b] This concept is outlined in Scheme 1. Upon combining a simple nucleophilic catalyst[14] such as DMAP with an acylating reagent, an equilibrium is set up in which achiral ion pair **I** is formed. The addition of a chiral catalyst, capable of binding to the anion of ion pair **I** via hydrogen-bonding (HB) interactions, establishes a second equilibrium that results in the formation of chiral ion pair **II**.[15−17] On the basis of our previous studies, it appears that chiral ion pair **II** is more reactive and/or present in higher concentrations than achiral ion pair **I**. This favors a scenario in which amines preferentially react with chiral ion pair **II** over achiral ion pair **I** or unmodified acylating reagent, thereby allowing for kinetic resolution.

Table 1. Evaluation of Reaction Parameters[a]



entry	HB catalyst (mol %)	Nu catalyst (mol %)	conversion (%)	*s* factor
1	**1a** (5)	DMAP (5)	55	12
2	**1a** (5)	DMAP NO (5)	57	12
3	**1a** (5)	PPY (5)	55	14
4	none	none	8	N/A
5	none	DMAP (5)	8	N/A
6	none	PPY (5)	8	N/A
7[b]	none	none	<2	N/A
8[b]	none	DMAP (5)	<2	N/A
9[b]	none	PPY (5)	<2	N/A
10[b]	**1a** (5)	PPY (5)	55	13
11[b]	**1a** (5)	DMAP (5)	33	9.5
12[b]	**1a** (5)	none	29	1.6
13	**1a** (2)	PPY (2)	56	14
14	**1a** (1)	PPY (1)	53	12
15	**1b** (5)	PPY (5)	55	4.5
16	**1c** (5)	PPY (5)	58	3.5
17	**1d** (5)	PPY (5)	55	8.1
18	**2** (5)	PPY (5)	58	8.4

[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 30 min.

We initiated our efforts to develop an efficient resolution procedure for primary allylic amines by exposing **3a** to the optimized resolution conditions previously developed for propargylic amines.[13b]

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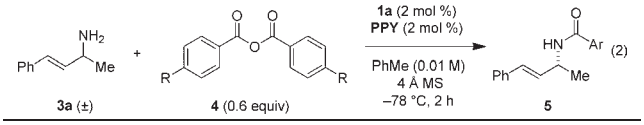
Specifically, the combination of 5 mol % of each of the two catalysts, **1a** and DMAP, in addition to 0.6 equiv of benzoic anhydride, resulted in the kinetic resolution of amine **3a** with an *s* factor[18] of 12 at 55% conversion (Table 1, entry 1). Other achiral nucleophilic cocatalysts were subsequently evaluated. Interestingly, DMAP *N*-oxide gave virtually identical results (entry 2), whereas the more nucleophilic PPY led to an improved *s* factor of 14 (entry 3). Reactions in the absence of any catalyst or with DMAP or PPY as the only catalyst under otherwise identical conditions led to 8% conversion after 2 h. This observation indicates that allylic amines are more nucleophilic than benzylic or propargylic amines, as the latter two substrates typically give less than 2% conversion under the same conditions.[13]

In order to better understand background rates and how they affect selectivities, we performed a number of experiments in which the reaction time was reduced from 2 h to 30 min (entries 7–12). Under these conditions, in the absence of any catalyst or with DMAP or PPY as the only catalyst, less than 2% conversion was observed. The superiority of PPY over DMAP becomes apparent when entries 10 and 11 are compared.[19] In combination with catalyst **1a**, PPY led to 55% conversion and an *s* factor of 13, whereas DMAP only gave 33% conversion (*s* factor = 9.5). Consistent with our previous studies, catalyst **1a** was capable of catalyzing the reaction by itself, presumably through direct activation of benzoic anhydride via HB. However, this process was unselective (*s* factor = 1.6, entry 12).

Attempts to lower catalysts loadings in an effort to increase the overall efficiency of the resolution were met with success. The use of 2 mol % of each **1a** and PPY produced results similar to those obtained at 5 mol % catalyst loadings (entry 13). The efficiency decreased slightly when only 1 mol % of both catalysts was used (entry 14). Nevertheless, a respectable *s* factor of 12 was still observed. Other HB catalysts were also evaluated but found to give poorer results (entries 15–18).

Table 2. Evaluation of Different Anhydrides[a]

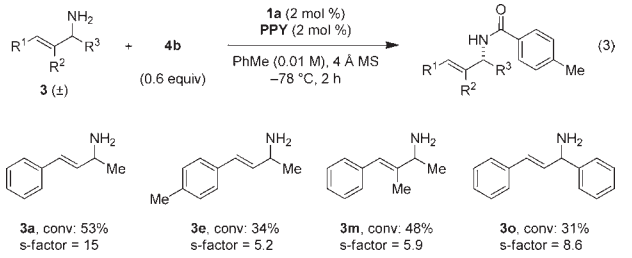


entry	anhydride	conversion (%)	*s* factor
1	**4a** (R = H)	55	14
2	**4b** (R = Me)	54	16
3	**4c** (R = OMe)	18	9.2
4	**4d** (R = *t*Bu)	53	5.6

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

We hypothesized that a reduction in background rate may be achieved by employing a less reactive acylating reagent. To this end, several modified benzoic anhydrides were tested under the optimized conditions (Table 2). Indeed, the use of the more electron-rich anhydride **4b** led to an increased *s* factor of 16 (entry 2). However, a further reduction in reactivity by using *p*-MeO-benzoic anhydride led to lower conversion and selectivity (entry 3). The bulkier *tert*-butyl-substituted anhydride **4d** also gave a lower *s* factor, although the reactivity remained high for this acylating reagent.

Scheme 2. Scope of the Resolution with Anhydride **4b**[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).

Given the improved results obtained with anhydride **4b** over benzoic anhydride (**4a**), we initially used **4b** to explore the scope of the allylic amine resolution. Some results of this survey are shown in Scheme 2. Whereas in some cases better *s* factors were indeed obtained with **4b** than with **4a**, this trend proved not to be general. In many cases, conversions were low with **4b**, and more importantly, selectivities also suffered.

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(18) *s* factor = rate of faster reacting enantiomer/rate of slower reacting enantiomer. *s* factors were calculated according to: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249 See the Supporting Information for details.

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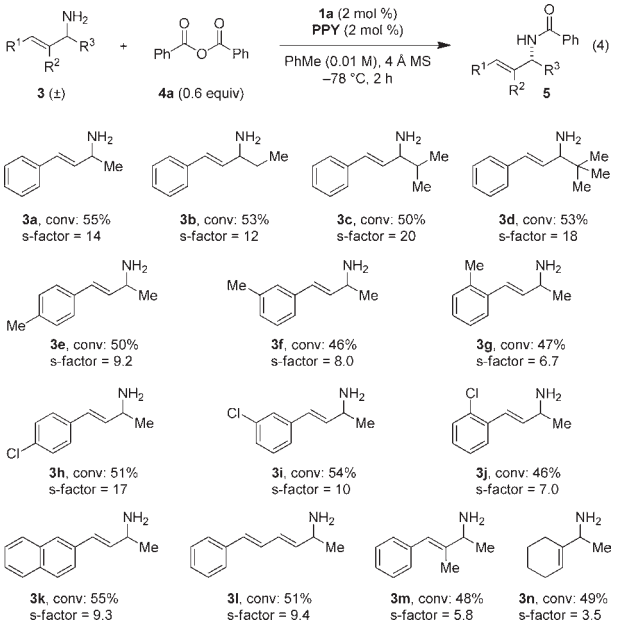
(20) The requisite racemic allylic amines were conveniently obtained in one step from the corresponding α,β-unsaturated ketones by following a modified literature procedure: Miriyala, B.; Bhattacharyya, S.; Williamson, J. S. *Tetrahedron* **2004**, *60*, 1463. See the Supporting Information for details.

A broader range of allylic amines[20] were resolved by utilizing the optimized reaction conditions with benzoic anhydride (**4a**) as the acylating reagent (Scheme 3). Whereas an exchange of methyl for ethyl in the parent substrate led to a slight drop in *s* factor, substrates bearing the bulkier substituents isopropyl and *tert*-butyl were resolved with higher *s* factors. Introduction of a methyl substituent in either the para, meta, or ortho position of the phenyl ring of the parent substrate led to lower *s* factors. In contrast, a chloro substituent in the para position had a positive effect on the efficiency of the resolution, while the same substituent in the meta or ortho position led to a drop in selectivity.

Scheme 3. Scope of the Allylic Amine Resolution[a]

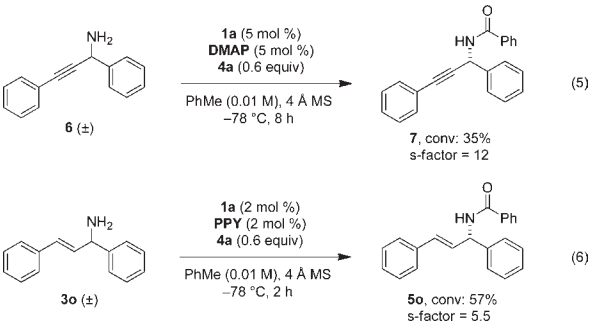


[a] See footnote in Scheme 2.

Substrates with further extended π-systems, such as **3k** and **3l**, were resolved with *s* factors approaching 10. The trisubstituted allylic amine **3m** gave a modest level of selectivity (*s* factor = 5.8). Amine **3n** gave a poor result (*s* factor = 3.5), suggesting the importance of conjugation of the allylic amine to another π- system.

We had previously observed that propargylic amines that are also benzylic are significantly less reactive than propargylic amines with aliphatic side chains (Scheme 4, eq 5).[13b] Nevertheless, compound **6** was resolved with an *s* factor of 12, indicating that the catalytic system is capable of distinguishing between two different π-systems. Furthermore, the corresponding product **7** was obtained with the same absolute configuration as other products, establishing control of propargyl over phenyl.

Scheme 4. Comparison of Allylic and Propargylic Amines[a]



[a] See footnote in Scheme 2.

In the present study, the analogous allylic amine **3o** was found to be significantly more reactive than **6**. Although the overall selectivity was lower for substrate **3o** (*s* factor = 5.5), our catalytic system again was found to be capable of distinguishing between two different π-systems, with apparent control of allyl over phenyl. The absolute configurations of **5o** and recovered, enantioenriched **3o** were independently determined on the basis of literature precedents.[1a,21]

In summary, we have reported the first small-molecule catalyzed kinetic resolution of racemic allylic amines. These substrates were resolved with *s* factors of up to 20 by using a dual catalyst approach that utilizes an achiral nucleophilic catalyst in combination with a chiral HB catalyst. Further applications of this strategy are currently being developed in our laboratory.

Acknowledgment. Financial support from Rutgers, The State University of New Jersey, is gratefully acknowledged. We thank Dr. Tom Emge (Rutgers University) for crystallographic analysis. E.G.K. thanks the US Department of Education for a GAANN fellowship. T.K.S. acknowledges support from the Aresty Research Center for Undergraduates. D.S. is a fellow of the A. P. Sloan Foundation.

Supporting Information Available. Experimental procedures and characterization data, including an X-ray crystal structure of product **5h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Bishop, J. A.; Lou, S.; Schaus, S. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 4337.