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Kinetic Resolution of Amines via Dual Catalysis: Remarkable Dependence of Selectivity on the Achiral Cocatalyst

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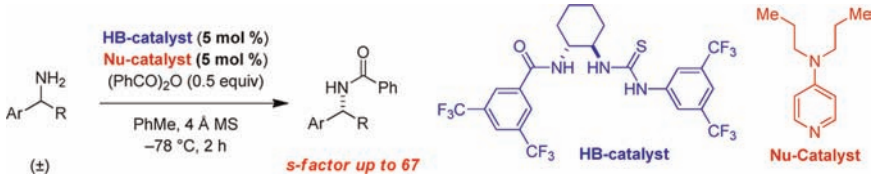
ABSTRACT



A dual-catalysis/anion-binding approach with a chiral hydrogen bonding (HB) catalyst and an achiral nucleophilic cocatalyst was applied to the kinetic resolution of amines. Out of a structurally diverse collection of 22 nucleophilic species, 4-di-*n*-propylaminopyridine emerged as the most efficient cocatalyst, allowing for the kinetic resolution of benzylic amines with *s*-factors of up to 67.

The discovery of 4-dimethylaminopyridine (DMAP) by Litvinenko/Kirichenko[1] and independently Steglich/Höfle[2] has enabled the development of many synthetically valuable acyl-transfer processes.[3] Pioneering contributions by Vedejs,[4] Fu,[5] Kawabata/Fuji,[6] and others[7] have resulted in the identification of powerful chiral DMAP analogues and related nucleophilic catalysts. Among the various asymmetric reactions that have been studied with chiral nucleophilic catalysts, the kinetic resolution of alcohols has received much attention.[8] In contrast, the corresponding kinetic resolution of amines with small-molecule catalysts has remained in its infancy.[9] This fact is readily explained by the difficulties associated with this substrate class, as the high reactivity of unmodified amines results in high background reaction rates with many acylating reagents. The first small-molecule catalysis approach to the kinetic resolution of unmodified primary amines, specifically benzylic amines, was reported by Fu et al. in 2001.[10] In this landmark study, an azlactone derived acylating reagent was utilized with a planar chiral 4-pyrrolidinopyridine catalyst (PPY*). Other important contributions were

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reported by Birman[11] and Miller,[12] who successfully devised methods to resolve amine derivatives with attenuated reactivities. Very recently, a unique dual-catalysis redox approach to the kinetic resolution of secondary amines was reported by Bode et al.[13–15] Our group has advanced a dual-catalysis approach in which a chiral acylating reagent is generated in situ via the interplay of a chiral anion receptor/H-bonding (HB) catalyst,[16] DMAP as an achiral nucleophilic cocatalyst, and a stoichiometric amount of benzoic anhydride as the acylating reagent.[17–19] Here we report the results of a systematic study aimed at identifying the ideal nucleophilic cocatalyst for this process.

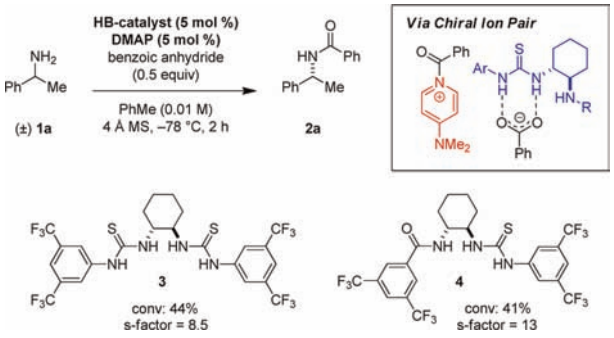

Figure 1. Dual-catalysis/anion-binding approach to amine resolution.

Previous results for the kinetic resolution of benzylic amines are summarized in Figure 1. Our initial study with known urea and thiourea catalysts revealed that the readily available Nagasawa catalyst (**3**)[20] provides good selectivities in the kinetic resolution of benzylic amine **1a**.[17a] A subsequent evaluation of a range of previously unknown catalysts led to the development of thiourea-amide catalyst **4**, which enabled improved selectivities at lower catalyst loadings.[17b] Although either chiral catalyst **3** or **4** can catalyze the amine acylation in the absence of a nucleophilic cocatalyst, this leads to almost no resolution. Addition of the achiral nucleophilic cocatalyst DMAP is required in order to obtain high levels of selectivity. The reaction is thought to involve an in situ formed chiral ion pair in which the benzoate anion of the acylpyridinium salt is bound to the HB catalyst (Figure 1). The crucial role of DMAP led us to consider that its replacement by other nucleophilic cocatalysts might present an avenue for further selectivity improvement. In addition to the changes in selectivity that could be brought about by simple structural modifications, we hypothesized that an increase in nucleophilicity may lead to more efficient catalysis. Furthermore, as **4** displays relatively poor solubility in toluene, a nucleophilic cocatalyst more soluble than DMAP was thought to potentially

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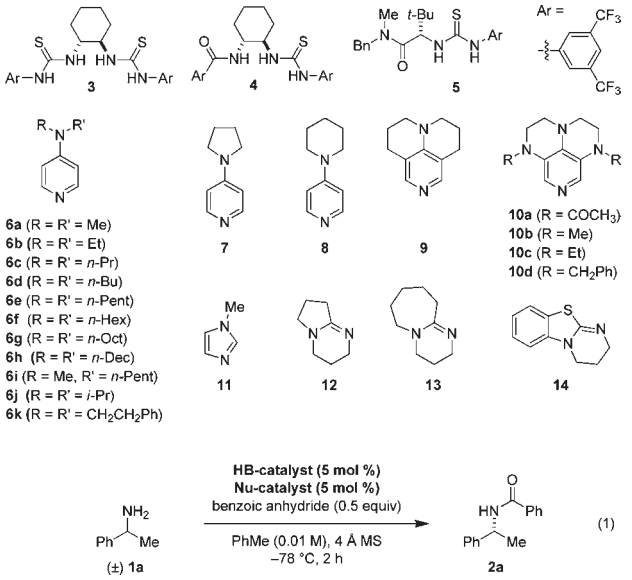
improve the overall efficiency of the process by enabling the formation of a more soluble chiral ion pair.

Table 1. Evaluation of Nucleophilic Cocatalysts[a]



entry	HB-catalyst (5 mol %)	Nu-catalyst (5 mol %)	conversion (%)	*s*-factor
1	**4**	–	34	1.9
2	**4**	**6a**	41	13
3	**4**	**6b**	50	24
4	**4**	**6c**	49	27
5	**4**	**6d**	49	22
6	**4**	**6e**	50	22
7	**4**	**6f**	46	18
8	**4**	**6g**	50	19
9	**4**	**6h**	49	18
10	**4**	**6i**	44	17
11	**4**	**6j**	48	25
12	**4**	**6k**	46	8.9
13	**4**	**7**	50	15
14	**4**	**8**	38	12
15	**4**	**9**	50	6.6
16	**4**	**10a**	<5	ND
17	**4**	**10b**	50	7.7
18	**4**	**10c**	45	6.0
19	**4**	**10d**	46	4.1
20	**4**	**11**	30	1.3
21	**4**	**12**	17	1.0
22	**4**	**13**	21	1.0
23	**4**	**14**	26	1.1
24	**3**	**6c**	49	11
25	**5**	**6c**	36	1.3

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

A structurally diverse collection of 22 nucleophilic cocatalysts encompassing a broad range of nucleophilicities[21] was evaluated in combination with amide-thiourea catalyst **4** (Table 1). All experiments were conducted with 5 mol % catalyst loadings. As alluded to earlier, **4** was active in the absence of any cocatalysts but led to very poor resolution (*s*-factor = 1.9, entry 1).[22] On the other hand, the combination of DMAP and **4** gave an *s*-factor of 13 at 41% conversion (entry 2). Remarkably, the simple switch from DMAP to 4-diethylaminopyridine (**6b**) led to a dramatic increase in selectivity (*s*-factor = 24, entry 3). Another incremental increase in selectivity was observed upon switching to 4-di-*n*-propylaminopyridine (**6c**) (*s*-factor = 27, entry 4).[23] Further extension of the alkyl chain led to a drop-off in *s*-factors (entries 5–9). Interestingly, for alkyl groups beyond *n*-pentyl, the *s*-factor remained nearly constant at 18.

Two isomers of 4-di-*n*-propylaminopyridine (**6c**) were tested: 4-(*N*-methyl-*N*-pentylamino)pyridine (**6i**) and 4-diisopropylaminopyridine (**6j**). While the latter cocatalyst reached almost the same level of selectivity as **6c**, the former showed a selectivity similar to those of the longer chain analogues.[24] Just as we had observed in the kinetic resolution of allylic amines,[17c] PPY (**7**) offered a slight but measurable improvement over DMAP (entry 13). In contrast, 4-piperidinopyridine (**8**) gave inferior results. Analogues of DMAP with enhanced nucleophilicities[25] (**9** and **10a**–**d**) provided unsatisfactory results (entries 15–19). Amidine-type catalysts such as *N*-methylimidazole (**11**), DBN (**12**), and DBU (**13**) as well as isothiourea **14** were completely ineffective (entries 20–23).[26] When the best nucleophilic catalyst of this survey, **6c**, was paired with bisthiourea catalyst **3**, an *s*-factor of 11 was obtained (entry 24). This represents an improvement over DMAP (*s*-factor = 8.5, Figure 1) but one that is not nearly as pronounced as in the case of catalyst **4**. Thiourea **5**, developed by the Jacobsen group and previously shown to be an excellent anion-binding catalyst for a number of reactions, was inefficient in the amine resolution (entry 25).

As outlined in Figure 2, a number of benzylic amines were resolved efficiently via benzoylation with benzoic anhydride in the presence of 5 mol % of each catalyst **4** and cocatalyst **6c**. Dramatic improvements in selectivity were achieved over the previous catalytic system.[17a,b] While a range of alkyl groups were well tolerated, substrate **1c** bearing an isopropyl group was resolved most efficiently (*s*-factor = 67), providing the highest level of selectivity achieved with our approach thus far. Differentiation between phenyl and benzyl was readily achieved as shown by substrate **1e**, for which an *s*-factor of 24 was obtained. Substitution of the phenyl ring in different positions was also readily accommodated. An excellent result was achieved for substrate **1i** (*s*-factor = 64). Here, the presence of

(22) *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.

(23) In this specific example, product **2a** was isolated in 50% yield (82% ee). Starting material **1a** was recovered in 47% yield (85% ee).

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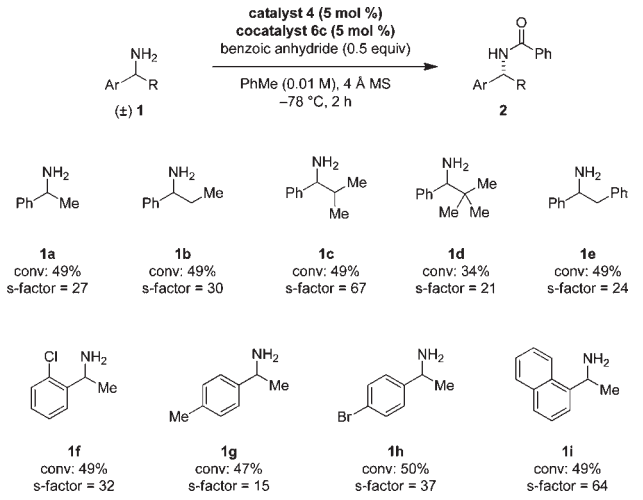


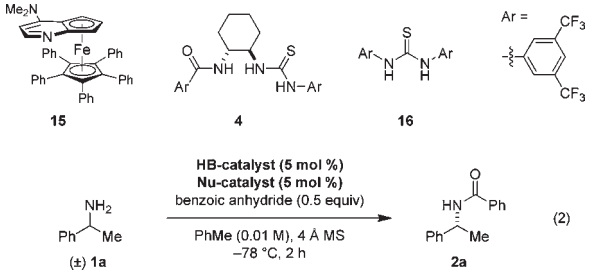
Figure 2. Scope of the kinetic resolution of benzylic amines.

an extended π-system might lead to additional stabilizing interactions of one substrate enantiomer with the intermediate ion pair.

Intrigued by the possibility of observing matched/mismatched scenarios, we decided to perform the kinetic resolution of amine **1a** by catalyst **4** in the presence of a chiral nucleophilic cocatalyst. For this purpose, we selected the commercially available Fu catalyst PPY* **15**. The results of this brief survey are summarized in Table 2. The combination of catalysts **4** and **15** provided an unfavorable result (*s*-factor = 1.8, Table 2, entry 1). Unfortunately, performing the same experiment with *ent*-**15** in place of **15** led to virtually identical results (*s*-factor = 1.9, Table 2, entry 2). In fact, both experiments match the result obtained when **4** was used as the sole catalyst (see entry 1 in Table 1), indicating that **15** or *ent*-**15** do not engage in cooperative catalysis with **4** under the reaction conditions. Catalyst *ent*-**15** by itself led to low conversion and no resolution (*s*-factor = 1.0, Table 2, entry 3).

The combined use of *ent*-**15** and the achiral Schreiner catalyst (**16**)[27] resulted in higher conversion but again no resolution (*s*-factor = 1.0, Table 2, entry 4). Other catalyst combinations may prove to be more efficient, and there are tremendous opportunities for future investigations of nucleophilic catalysis in the presence of anion-binding additives.

Table 2. Evaluation of PPY* as a Chiral Nucleophilic Cocatalyst[a]



entry	HB-catalyst (5 mol %)	Nu-catalyst (5 mol %)	conversion (%)	*s*-factor
1	**4**	**15**	36	1.8
2	**4**	*ent*-**15**	33	1.9
3	–	*ent*-**15**	20	1.0
4	**16**	*ent*-**15**	34	1.0

[a] Reactions were performed on a 0.2 mmol scale. The *s*-factors were determined by HPLC analysis, see the SI for details.

In summary, we have identified 4-di-*n*-propylaminopyridine (**6c**) as a highly efficient nucleophilic cocatalyst for the kinetic resolution of benzylic amines with *s*-factors of up to 67. Further applications of the dual catalysis approach are currently being explored in our laboratory.

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Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.