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2,3-Dihydroimidazo[1,2-a]pyridines: A New Class of Enantioselective Acyl Transfer Catalysts and Their Use in Kinetic Resolution of Alcohols

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Enantioselective acyl transfer provides a convenient method for kinetic resolution of racemic alcohols[1a,b] and desymmetrization of meso-diols.[1c] Traditionally, both of these types of transformations have been accomplished by using natural enzymes. In recent years, a number of nonenzymatic chiral catalysts were developed which, in some cases, exhibit practically useful levels of enantioselectivity.[2,3] However, their preparation is typically difficult, often requiring multistep sequences and resolution of racemates. We have recently set out to develop a new class of asymmetric acyl transfer catalysts that would be both effective and easily accessible. In this communication, we describe our first successful results.

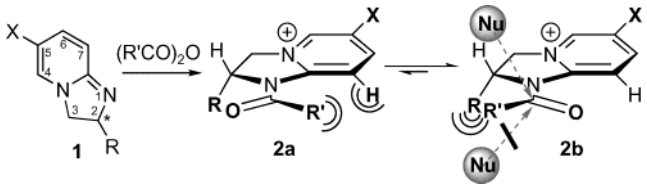
We have envisioned the possibility of using 2,3-dihydroimidazo-[1,2-a]pyridine (**1**, X = R = H, hereinafter abbreviated as DHIP; see Scheme 1) as a potential new core structure for designing asymmetric acylation catalysts. First, the imine nitrogen was expected to be highly nucleophilic. Second, a variety of DHIP derivatives with a chiral center α- to the nucleophilic nitrogen (cf. **1**, R = aryl or alkyl) would be easily accessed by N-arylation of chiral 2-amino alcohols with 2-halopyridines followed by cyclization. The electronic properties of this structure could be tuned simply by varying substituent X in the pyridine ring.

The acylated species was expected to exist predominantly in conformation **2b**, because of the greater steric interaction of the hydrogen at C7 with the R′ group than with the carbonyl oxygen.[4] The R group would then block the approach of nucleophiles from the bottom face, thus effectively discriminating the two faces of the carbonyl. However, there still remained a question: will the acylated species **5** be a competent acylating agent?

Although the parent compound, **1**, has been known since 1936[5a] and a number of its derivatives have been prepared over the years,[5d] no information regarding possible catalytic activity of DHIPs could be glimpsed from the literature. Nevertheless, the expected properties of DHIP were so attractive, and its preparation so easy, that we decided to satisfy our curiosity experimentally. Unsubstituted DHIP **1** was prepared by a modified literature procedure.[5a−c] Its catalytic activity in the acetylation of methanol with Ac_2O was clearly established by NMR experiments. Only the acylated form of the catalyst was observed during the reaction, indicating that the initial acylation step is considerably faster than the acyl transfer to MeOH. The first chiral derivative to be prepared and tested was (*R*)-2-phenyl-2,3-dihydroimidazo[1,2-a]pyridine **1a** (PIP), derived from *R*-phenylglycinol **3** (Scheme 2). Acetylation of (±)-phenylethylcarbinol in the presence of 20 mol % of **1a** produced (*R*)-acetate in 49% ee at 21% conversion, which corresponds to 3.3:1 selectivity (Table 1, entry 1).

Before proceeding with the optimization of enantioselectivity, it was deemed important to increase the reactivity of the catalyst. Introduction of electron-withdrawing substituents in the pyridine ring was expected to increase the electrophilicity of the acylated intermediate and therefore the rate of acyl transfer. Br-PIP **1b** was prepared by bromination of **4a** with NBS[6] (93%) followed by

Scheme 1



Scheme 2

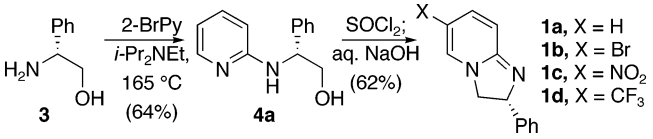
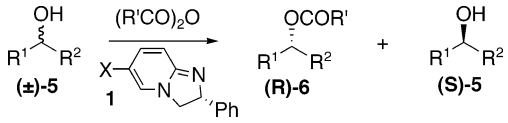


Table 1. Kinetic Resolution Catalyzed by PIP Derivatives



entry	R^1	R^2	R′	X	*t* (h)	C%[c]	s[c]
1[a]	Ph	Et	Me	H	1	21	3.3
2[a]	Ph	Et	Me	Br	1	25	8.6
3[a]	Ph	Et	Me	NO_2	1	14	11
4[a]	Ph	Et	Me	CF_3	1	38	14
5[b]	Ph	Me	Me	CF_3	8	21	7.7
6[b]	Ph	Et	Me	CF_3	8	43	17
7[b]	Ph	*i*-Pr	Me	CF_3	30	47	24
8[b]	Ph	Me	Et	CF_3	8	32	26
9[b]	Ph	Et	Et	CF_3	8	39	36
10[b]	Ph	*i*-Pr	Et	CF_3	30	55	41
11[b]	Ph	*t*-Bu	Et	CF_3	52	48	85
12[b]	1-naphthyl	Me	Et	CF_3	8	51	56
13[b]	*m*-Me-C_6H_4	Me	Et	CF_3	8	36	27
14[b]	*m*-MeO-C_6H_4	Me	Et	CF_3	8	40	34
15[b]	*m*-Br-C_6H_4	Me	Et	CF_3	8	44	32
16[b]	*o*-Me-C_6H_4	Me	Et	CF_3	8	44	26
17[b]	2,4,6-$Me_3C_6H_2$	Me	Et	CF_3	30	53	20
18[b]	*c*-C_6H_{11}	Me	Et	CF_3	50	<4	nd
19[b]	1-indanol		Et	CF_3	50	16	≈1

[a] 1 M (±)-5, 1 M Ac_2O, 0.2 M **1**, $CDCl_3$, room temperature. [b] 1 M (±)-5, 0.75M $(R'CO)_2O$, 0.75 M *i*-Pr_2NEt, 0.02 M **1d**, $CHCl_3$, 0 °C. [c] Averages of two runs; calculated from ee's of **(*R*)-6** and **(*S*)-5** obtained by chiral HPLC, except conversions in entries 18 and 19 determined by ^1H NMR.

cyclization (91%). When tested under the same conditions, it catalyzed the acylation somewhat faster than PIP (25% conversion after 1 h). Much more interestingly, the enantioselectivity also increased to 8.6:1 (entry 2). Intrigued by this result, we prepared the most electron-deficient analogue, NO_2-PIP **1c**.[7] It also catalyzed the esterification, albeit at a slower rate than Br-PIP. The selectivity increased moderately (s = 11, entry 3). The decreased catalytic activity of **1c** was attributed to its lower nucleophilicity. Therefore,

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we expected that choosing a substituent with an intermediate σ value[8] would be optimal both for the overall catalytic activity and for the enantioselectivity. Indeed, CF_3-PIP **1d**[9] fulfilled our expectations ($s = 14$ and 38% conversion after 1 h, entry 4).

Addition of *i*-Pr_2NEt as an auxiliary base significantly increased the reaction rate, so that it became possible to use only 2 mol % catalyst loadings and lower the reaction temperature to 0 °C. Under these conditions, acetylation of PhCH(OH)Et proceeded with 17:1 selectivity and reached 43% conversion after 8 h. Selectivity was lower in the case of PhCH(OH)Me and higher in the acetylation of PhCH(OH)-*i*-Pr (entries 5−7). Judging from these data, the discrimination appeared to take place between the hydrogen and the alkyl group of the substrate, rather than between the phenyl and the alkyl. As a working hypothesis, we proposed that the aryl group of the substrate stacks on top of the pyridinium ring of the catalyst,[10] while the alkyl group is repelled from the acyl portion for steric reasons (Figure 1).

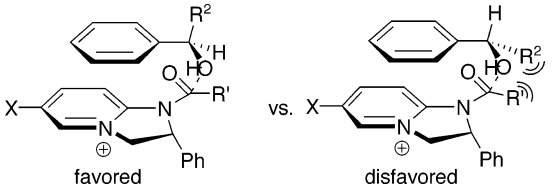

Figure 1. Transition state model.

On the basis of this model, increasing the size of R′ was expected to result in a greater steric repulsion of the R^2 group. Indeed, the use of propionic anhydride instead of Ac_2O resulted in a considerable improvement of selectivity (entries 8−10).[11] Under these conditions, phenyl *t*-butyl carbinol was resolved with selectivity factor of 85 (entry 11). Substitution of the aromatic ring was varied to investigate the influence of the electronic and steric factors on the selectivity and the reaction rates (entries 12−17). Not unexpectedly, cyclohexyl methyl carbinol containing no aromatic ring and 1-indanol, which cannot adopt the required conformation in the transition state, proved to be ineffective substrates (entries 18 and 19).[12] Chloroform is currently the solvent of choice, producing both high reaction rates and selectivities (Table 2). Kinetic resolutions using CF_3PIP can be easily scaled up[13] and are carried out using reagent grade solvents under air atmosphere.

Table 2. Selectivities in Different Solvents[a]

entry	solvent	conversion %	selectivity
1	$CHCl_3$	39	36
2	Et_2O	27	40
3	PhMe	30	36
4	CH_2Cl_2	30	24
5	*tert*-amyl alcohol	18	23
6	MeCN	20	11

[a] Conditions: 1M (±)-PhCH(OH)Et, 0.75 M $(EtCO)_2O$, 0.75 M *i*-Pr_2NEt, 0.02M **1d**, 0 °C, 8 h.

In conclusion, we have developed a new class of effective enantioselective acylation catalysts based on the previously unexplored 2,3-dihydroimidazo[1,2-a]pyridine structure. The ease of preparation of chiral derivatives of the DHIP core make it valuable not only as a novel structural basis for rationally designing new catalysts, but also as a tool for probing the details of the mechanism of asymmetric recognition. Further studies aimed at refining the current model and exploration of the use of DHIP-based catalysts in asymmetric catalysis are currently underway in our laboratory.

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

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(7) Prepared by arylation of **3a** with 2-chloro-5-nitropyridine (NEt_3, EtOH, reflux, 92% yield) followed by cyclization (98%).

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(9) Prepared by arylation of **3a** with 2-chloro-5-trifluoromethylpyridine (*i*-Pr_2NEt, neat, 110 °C, 66% yield) followed by cyclization (85%). Both reagents are available from Aldrich. (*R*)-Phenylglycinol costs $215.30/25 g and 2-chloro-5-trifluoromethylpyridine costs $58.70/50 g.

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(11) Further increase in the size of R′ (using $(n\text{-PrCO})_2O$, $(i\text{-BuCO})_2O$, and $(i\text{-PrCO})_2O$) led to lower selectivities than with $(EtCO)_2O$.

(12) Similar observations have been made using Vedejs's phosphine catalyst[3c] and Fu's planar-chiral catalyst: Ruble, J. C. Ph.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1999.

(13) Preparative-scale resolution of 1-naphthyl methyl carbinol (2.416 g, 14.0 mmol) gave the ester in 52% yield and 82.5% ee and the unreacted alcohol in 45% yield and 98.8% ee, which corresponds to 54% conversion and 52:1 selectivity. 68% of the catalyst was recovered. See Supporting Information for more details.

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