JOC Article

The Design of Novel *N*-4′-Pyridinyl-α-methyl Proline Derivatives as Potent Catalysts for the Kinetic Resolution of Alcohols

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A novel family of chiral acylation catalysts based on a *N*-4′-pyridinyl-α-methyl proline structure has been studied. A set of 31 compounds has been easily prepared and screened in the kinetic resolution of racemic alcohol **33** resulting in high enantioselectivities in most cases. From results obtained, H-bonding interactions between the catalyst and the substrate would appear essential to afford high enantioselectivity during the catalytic acylation. Additional solvent dependence and anhydride studies have been made to better identify the mechanism. This work has been further extended to the study of a number of structurally different alcohols. Ethanolamine derivatives in particular were found to be highly effective substrates (up to $S = 18.8$) in the kinetic resolution.

Introduction

Since DMAP and 4-pyrrolidinopyridine (PPY) were discovered as potent nucleophilic acylation catalysts,[1] many investigations have targeted the use of chiral DMAP derivatives for enantioselective acylations.[2,3] One particularly extensive area of work is the study of chiral DMAP analogues as catalysts for the nonenzymatic kinetic resolution (KR) of racemic alcohols.[4−8] Some existing nucleophilic chiral catalysts act as DMAP mimetics although their structure is not derived from DMAP,[9−11] e.g. chiral phosphine catalysts **A** (Vedejs),[9] small peptide catalysts **B** (Miller),[10] and Oriyama's catalyst[11] based on a chiral diamine **C** (Figure 1). Other families of catalysts such as **D**, **E** and **F** contain the DMAP or PPY skeleton in their structure (Figure 1). Fu's catalyst **D** leads to high enantioselectivities in the KR of allylic and propargylic alcohols (96% ee, selectivity index (S) = 20).[4b] Spivey's catalyst **E** proves highly enantioselective in the acylation of arylalkylcarbinols (69% ee, $S = 24$).[5c]

With Fuji's catalyst **F** high enantioselectivities have been reported in the KR of racemic alcohols or amino alcohol derivatives (>99% ee, $S > 13$).[6,7] In Fuji's approach, the stereogenic centers are positioned distant from the catalytic site (the nitrogen atom of the pyridinyl group), hence avoiding the selectivity−reactivity problem encountered with some other catalysts where the stereogenic center is close to the pyridine nitrogen.[5c]

A "closed conformation" resulting from $\pi-\pi$ interactions between the naphthyl ring and the *N*-acylated pyridinyl moiety has been suggested as the active conformation of catalyst **F** (Figure 2). These stacking interactions hold the catalyst in one preferential conformation and also provide stereoselection during the catalytic process.[6] We were interested in Fuji's catalyst **F** and felt

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(1) (a) Litvinenko, L. M.; Kirichenko, A. I. *Chem. Abstr.* **1968**, *68*, 68325u. (b) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

(2) For a general review see: Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.

(3) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.

(4) (a) Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637. (b) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 5091. (c) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 10452. (d) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230.

(5) (a) Spivey, A. C.; Maddaford, A.; Leese, D. P.; Redgrave, A. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1785. (b) Spivey, A. C.; Maddaford, A.; Fekner, T.; Redgrave, A.; Frampton, J. C. S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3460. (c) Spivey, A. C.; Fekner, T.; Spey, S. E. *J. Org. Chem.* **2000**, *65*, 3154. (d) Spivey, A. C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39*, 8919. (e) Spivey, A. C.; Charbonneau, P.; Fekner, T.; Hochmuth, D. H.; Maddaford, A.; Malardier-Jugroot, C.; Redgrave, A. J.; Whitehead, M. A. *J. Org. Chem.* **2001**, *66*, 7394. (f) Spivey, A. C.; Fekner, T.; Spey, S. E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9430.

(6) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169.

(7) Kawabata, T.; Yamamoto, K.; Momose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Commun.* **2001**, 2700.

(8) Naraku, G.; Shimomoto, N.; Hanamoto, T.; Inanaga, J. *Enantiomer* **2000**, *5*, 135.

(9) (a) Vedejs, E.; Rozners, E. *J. Am. Chem. Soc.* **2001**, *123*, 2428. (b) Vedejs, E.; MacKay, J. A. *Org. Lett.* **2001**, *3*, 535. (c) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813. (d) Vedejs, E.; Daugulis, O.; Diver, S. T. *J. Org. Chem.* **1996**, *61*, 430.

(10) (a) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11638. (b) Copeland, G. T.; Jarvo, E. R.; Miller, S. J. *J. Org. Chem.* **1998**, *63*, 6784. (c) Vasbinder, M. M.; Jarvo, E. R.; Miller, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 2824. (d) Miller, S. J.; Copeland, G. T.; Papaioannou, N.; Hortsmann, T. E.; Ruel, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 1629.

(11) (a) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chem. Lett.* **1999**, *3*, 265. (b) Oriyama, T.; Imai, K.; Sano, T.; Hosoya, T. *Tetrahedron Lett.* **1998**, *39*, 3529. (c) Oriyama, T.; Hori, Y.; Imai, K.; Sazaki, R. *Tetrahedron Lett.* **1996**, *37*, 8543.

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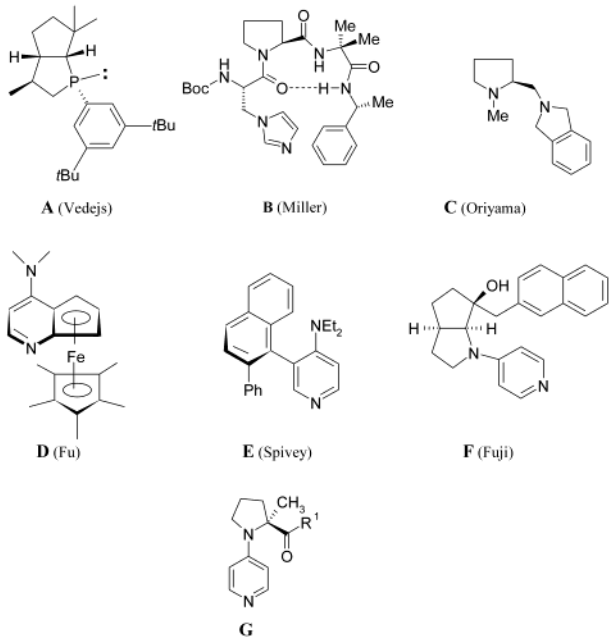


FIGURE 1. Catalysts used in the kinetic resolution of racemic alcohols.

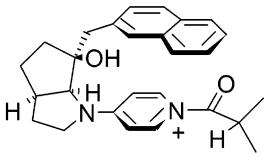


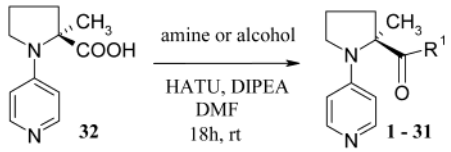
FIGURE 2. Active "closed conformation" of Fuji's catalyst **F**.

that opportunities may exist to develop highly accessible novel catalytic systems based around this structural motif.

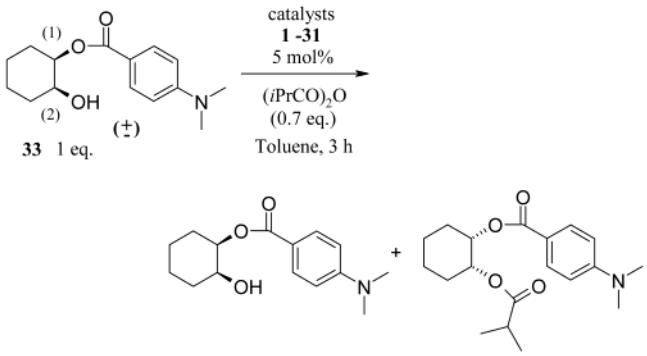
A very attractive approach to discovering chiral catalysts for enantioselective acylation is to obtain a versatile intermediate late in the synthesis, which can allow the preparation of diverse arrays of potential catalysts for screening in the reaction of choice. An elegant example of such an approach is the polymer-bound library of nonenantioselective acylation catalysts described by Taylor and Morken.[12] Included in this library are PPY derivatives; however, under the reaction conditions for preparing the library, racemization of the chiral center can occur.

Our work has been focused on the design and synthesis of a novel family of chiral PPY derivatives based on a *N*-4′-pyridinyl-α-methyl proline structure **G** (Figure 1), and the study of these in the KR of racemic alcohols. We envisaged that our highly accessible PPY derivatives **G** could behave similarly to Fuji's catalyst **F**. In contrast to the synthesis of previously described catalysts which generally require multistep asymmetric reactions, the fast and easy synthesis of **G** allows facile structural modifications. Although previous studies have described the use of *N*-4′-pyridinyl proline compounds as acylating reagents,[12,13] this is the first time such an approach has been described for an enantioselective acylation with nonpeptidic catalysts and appears ideally suited for rapid iterations aimed at increasing enantioselectivity for a given substrate.

SCHEME 1. Synthesis of the Library of Potential Catalysts 1−31



SCHEME 2. Kinetic Resolution of Alcohol 33 with a Library of Potential Catalysts 1−31



Results and Discussion

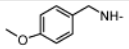
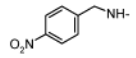
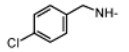
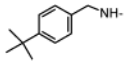
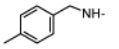
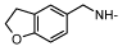
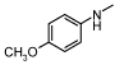
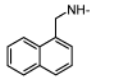
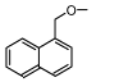
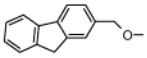
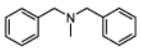
A first library of PPY derivatives (compounds **1**−**31**) based on structure **G** has been synthesized (Scheme 1). This new family of compounds contains a methyl group in the α position of the carbonyl group of the proline residue, hence avoiding racemization problems encountered during the synthesis of the α-hydrogen-containing analogues.[14]

Only two synthetic steps are required to prepare each potential catalyst **1**−**31** from commercially available starting materials. A coupling reaction between previously prepared precursor **32**[14] and a selection of amines or alcohols, in the presence of HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate), gave the 31 desired compounds. Each of these potential catalysts was then examined in the KR of racemic *cis*-(±)-(*p*-*N*′,*N*′-dimethylbenzoyl)cyclohexan-1,2-diol (**33**, Scheme 2). According to Fuji, this alcohol provides high enantioselectivity for acylation.[6] The catalytic reaction was run in dry toluene with 0.7 equiv of isobutyric anhydride and 5 mol % of catalyst and analyzed at 3 h, since a kinetic study with catalyst **6** (Table 1) showed that the reaction was highly enantioselective toward alcohol **33** after 3 h (see Supporting Information).

Results for the most representative catalysts **1**−**16** are given in Table 1 (see Supporting Information for the complete study with the 31 potential catalysts). Inspired by Fuji's mechanistic theory, we began our study with catalysts containing an aromatic R^1 group (entries 1−13). Within the benzylamide series (entries 1−6), the substituent in the para position of the aromatic ring does

(12) Taylor, S. J.; Morken, J. P. *Science* **1998**, *280*, 267.
(13) Delaney, E. J.; Wood, L. E.; Klotz, I. M. *J. Am. Chem. Soc.* **1982**, *104*, 799.
(14) Priem, G.; Anson, M. S.; Macdonald, S. J. F.; Pelotier, B.; Campbell, I. B. *Tetrahedron Lett.* **2002**, *43*, 6001.

TABLE 1. Kinetic Resolution of Alcohol 33 with Catalysts 1−16[e]

Entry	R^1-	catalyst	%conversion[a]	%ee[b] of recovered (1*R*,2*S*)[c] **33**	S[d]
1		**1**	64	93	10.1
2		**2**	62	88	9.2
3		**3**	60	88	10.6
4		**4**	67	93	8.3
5		**5**	62	89	9.6
6		**6**	62	95	13.2
7		**7**	66	86	6.6
8		**8**	60	84	8.9
9		**9**	67	91	7.6
10		**10**	40	3	1.1
11		**11**	50	1	1.0
12		**12**	51	32	2.5
13		**13**	67	33	1.8
14		**14**	66	89	7.4
15		**15**	64	89	8.4
16		**16**	70	21	1.4

[a] Calculated from the crude material by HPLC calibration. [b] Determined from the purified alcohol by chiral HPLC (Chiralcel OD-H column). [c] Absolute configuration of the recovered alcohol determined by comparison with the optical rotation of the pure (1*R*,2*S*) alcohol: $[\alpha]_D^{20}$ −6.8 for ee >99% (ref 6). [d] The selectivity index (*S*) represents the ratio of rate constants for the more reactive to the less reactive enantiomer (ref 15). [e] conditions: Alcohol **33** (1 equiv; 0.1 M), isobutyric anhydride (0.7 equiv), catalyst (0.05 equiv), dry toluene, 3 h, rt.

not induce any electronic effect, since electron-withdrawing as well as electron-donating groups give approximately the same enantioselectivity for the acylation. Of the catalysts studied, compound **6** (entry 6) is the most promising with $S = 13.2$.[15] The presence of a more conjugated aromatic R^1 substituent also does not improve the enantioselectivity of the reaction (entries 8 and 9). Surprisingly, when the R^1 substituent is not an aromatic group the catalyst is still highly enantioselective toward acylation. Both a bulky group (*t*Bu-CH_2-, entry 14) and a less sterically demanding group (Et-, entry 15) also give high selectivities. These results clearly require a different mechanism from that suggested by Fuji for his catalyst (Figure 2) as even a nonaromatic R^1 substituent leads to a highly enantioselective catalyst.[16] Another relevant observation is the loss of enantioselectivity observed when the catalyst contains either an ester or a tertiary amide group (entries 10−13 and 16). The presence of a N−H bond seems therefore crucial for the enantioselectivity during the catalytic process, which finds precedence in the work of Miller.[10] One mechanism consistent with data presented here would involve favorable complexation by H-bonding between the catalyst and the faster reacting enantiomer of the substrate.

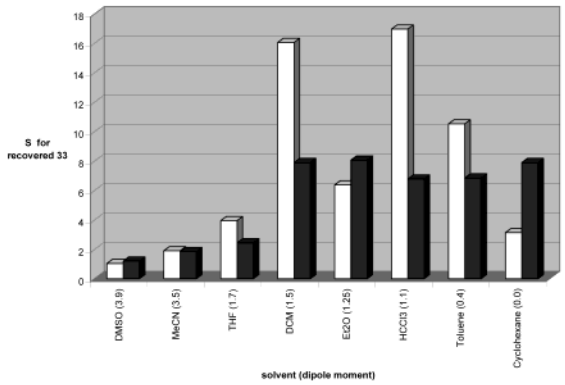


FIGURE 3. Solvent studies with catalysts **6** and **15**. Conditions: Alcohol **33** (1 equiv; 0.1 M), isobutyric anhydride (0.7 equiv), **6** or **15** (0.05 equiv), 12 h, rt. In white: Study with catalyst **6**. In black: Study with catalyst **15**. *X*-axis: Solvents studied with respective dipole moments in parentheses. *Y*-axis: Selectivity index for the KR of alcohol **33**.

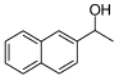
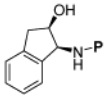
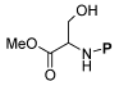
Further studies have been carried out to better understand the reaction mechanism. First, we studied the influence of the solvent toward the enantioselectivity of the reaction (Figure 3). Catalysts **6** and **15** were selected for this study. For both catalysts, the highest enantioselectivities (*S* factor) were observed with less dissociative solvents (lower dipole moments) such as toluene, chloroform, diethyl ether, and dichloromethane. Chloroform and dichloromethane seem the best solvents for KR studies with catalyst **6** (up to $S = 17.0$). Lower *S* values obtained with catalyst **6** in cyclohexane and diethyl ether are probably due to lack of solubility of this catalyst. The obvious explanation for selectivity enhancement with nonpolar solvents would be the strengthening of intermolecular H-bonding between the catalyst and the substrate.

In a second study, the nature of the anhydride species was investigated. Reactions were run with catalyst **6** for 12 h under conditions reported in Scheme 2. TFAA is too reactive to induce enantioselectivity (1% ee, $S = 1.0$). The use of benzoic anhydride leads to moderate selectivity (35% ee, $S = 2.8$). From a bulky anhydride such as trimethylacetic anhydride the reaction is highly enantioselective but the reaction rate is very slow (6% ee, $S = 34.2$). Extending the reaction time to 7 days increases the ee of recovered **33** (96% ee) but diminishes the enantioselectivity ($S = 12.6$). Finally, acetic anhydride (99% ee, $S = 12.7$) and isobutyric anhydride (95% ee, $S = 13.2$) provide the highest enantioselectivities after 12 h.

(15) The selectivity index (*S*) was calculated from Kagan's rule: Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249.

(16) NOEs calculated from the nonacylated and acylated forms of catalysts **8** and **17** have demonstrated no differences in NOEs whether the catalyst does or does not contain an aromatic group.

TABLE 2. Kinetic Resolution with Alcohols 34−40[f]

Alcohol **P** = *p*-(Me)$_2$N-C$_6$H$_4$-CO-		%conversion[a]	% ee[b] of recovered alcohol	S[c]
34		44[d]	14	1.6
35		34[d]	2	1.1
36		65[d]	11	1.2
37		74[d]	22	1.4
38[e]		(74)	(99)	(9.0)
39[e]		59(64)	96(99)	18.8(17.0)
40[e]		69(69)	>99(99)	>12.0(12.0)

[a] % conversion = 100 × ee(recovered alcohol)/[ee(recovered alcohol) + ee(ester formed)]. [b] Enantiomeric excess (ee) was determined by HPLC, using a Chiralcel OD-H column for alcohols **34** and **37** and a Chiralpak AD column for alcohols **35**, **36**, and **38**−**40**. [c] The selectivity index (*S*) represents the ratio of rate constants for the more reactive to the less reactive enantiomer (ref 15). [d] Ratios of recovered alcohol and ester were calculated by ^{1}H NMR integration of the respective peaks, assuming that all the reactive alcohol has been converted into the ester. [e] Chloroform as solvent, 12 h. [f] Standard conditions: alcohol (1 equiv; 0.1 M), isobutyric anhydride (0.7 equiv), catalyst **6** (0.05 equiv), toluene, 3 h, rt. Results after purification are given in parentheses.

This study has been further extended to other alcohols (Table 2). Compound **34**, the anti-isomer of **33**, proves a significantly poorer substrate toward acylation (14% ee, $S = 1.6$). In this anti-conformation, H-bonding to the catalyst would not place the reactive hydroxyl group of the alcohol in a favorable orientation for acylation to occur. Moreover, the presence of a carbonyl group in proximity to the hydroxyl function of the alcohol seems crucial to induce high enantioselectivities. Compounds **35**−**37** which do not contain this carbonyl group give low *S*. Enantioselectivities obtained with predictably good substrates[17] such as compounds **38**−**40** are very high (up to $S = 18.8$). The *cis*-aminoindanol derivative **38** has a highly rigid structure and provides high enantioselectivity (99% ee, $S = 9.0$). Compound **39**, which contains an amide group instead of the ester group in **33**, proves a highly effective substrate (96% ee, $S = 18.8$). Even a more flexible noncyclic alcohol such as **40** leads to high enantioselectivity (>99% ee, $S > 12.0$). In summary to the above experiments, two key structural components seem to promote a high degree of enantiomer differentiation during acylation: the catalyst should contain an N−H amide bond, and highly effective substrates would contain a carbonyl group in proximity to the reactive hydroxyl group. Moreover, less polar solvents would reinforce favorable complexation by H-bonding between the catalyst and the substrate.

Conclusions

In conclusion, we have developed a novel approach to chiral PPY derivative catalysts based on a *N*-4′-pyridinyl-α-methyl proline structure **G**. Most of the 31 compounds screened in the kinetic resolution of racemic alcohol **33** gave high enantioselectivities. Experiments with solvent dependence and a variety of alcohols have provided us with more information for the determination of a mechanism. Ethanolamine derivatives (compounds **38**−**40)** give high enantioselectivities for acylation (up to $S = 18.8$). Thus, although many of these substrates are also effectively resolved with Fuji's catalyst **F**, the data presented here with our system are consistent with a different mechanistic H-bond based hypothesis. The formulation of this hypothesis has demonstrably been aided by the very simple access to structurally different catalysts. We hope to further use the power of the synthetic accessibility of these catalysts for discovery of tailored catalysts for important enantioselective acylations in drug synthesis. This new approach to highly accessible and easily modified chiral PPY derivative catalysts is very promising for the kinetic resolution of various classes of alcohols and may have applications in other asymmetric processes.[18]

Experimental Section

General Experimental Procedures. Commercially available compounds were used without further purification. All dry solvents were used as purchased. Melting points (mp) were determined on an Electrothermal Digital apparatus from the nonrecrystallized purified compounds. IR spectra (cm^{-1}) were recorded on a FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were measured as solutions in $CDCl_3$ or CD_3OD, and chemical shifts are expressed in ppm relative to internal Me_4Si (0.00 ppm), and were recorded on a 250- or 400-MHz spectrometer. Accurate masses were measured from an electrospray mass spectrometer with <5-ppm tolerance. Chiral separations were performed by HPLC with Chiralcel OD-H and Chiralpak AD columns. The library of compounds **1**−**31** was purified by Liquid Chromatography/Mass Directed Preparative apparatus and in parallel, using the CombiFlash Optix 10 machine with 4 g silica columns.

Materials. The synthesis of *N*-4′-pyridinyl-α-methyl proline **32** has been previously described.[14] Alcohols **36**−**38** are commercially available. Alcohol **35** was prepared from alcohol **36** in two steps. First, a Mitsunobu reaction (PPh_3, DEAD, *p*-NO_2-C_6H_4-CO_2H) gave the corresponding syn-ester. This intermediate was converted into alcohol **35** with use of sodium azide in MeOH/CH_3CN.[19]

General Procedure for the Preparation of Racemic Alcohols Containing a *p*-(*N*′,*N*′-Dimethylamino)benzoyl Group: Compounds 33, 34, and 38−40. To a solution of *p*-(*N*′,*N*′-dimethylamino)benzoic acid (1 equiv) in DMF was added HATU (1.2 equiv) at 0 °C. The mixture was stirred for 1 h before addition of the starting racemic alcohol (3 equiv). DIPEA (2.5 equiv) was then added and the reaction was stirred overnight for 12 h. DMF was removed. The crude material was dissolved in EtOAc and washed with a 10% citric acid solution,

(17) **Note**: Alcohols **38**−**40** have also been described by Fuji as effective substrates for enantioselective acylation reactions (>99% ee, $S > 13$) in refs 6 and 7.

(18) (a) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131. (b) Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2002**, *124*, 2870. (c) Hodous, B. L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578.

(19) Gomez-Vidal, J.; Forrester, M. T.; Silvermann, R. B. *Org. Lett.* **2001**, *3*, 2477.

(20) Byun, Y. S.; Lightner, D. A. *Tetrahedron* **1991**, *47*, 9759.

water, and brine. The organic phase was dried on $MgSO_4$ before removal of EtOAc under vacuum. The crude material was purified by flash chromatography on silica column, using consecutively Toluene, DCM, EtOAc, and MeOH as eluents.

Physicochemical characterization of alcohols **34**,[20] **38**,[7] and **39**[7] has been previously described in the literature.

***cis*-(±)-(*p*-*N*′,*N*′-Dimethylbenzoyl)cyclohexan-1,2-diol (33):** white solid; mp 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 9 Hz, 2H), 6.65 (d, ^3J = 9 Hz, 2H), 5.22 (d, J = 8 Hz, 1H), 3.92 (d, J = 8 Hz, 1H), 3.03 (s, 6H), 2.00−1.40 (m, 8H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.7, 153.5, 131.4, 119.6, 117.0, 110.7, 69.9, 40.1, 30.4, 27.6, 21.9; IR (film, cm^{-1}) ν 3425 (OH), 3059, 2970, 2939, 1500, 1446, 1368 (CH); 1731, 1605, 1526 (C═C), 1700 (C═O), 1274 (C−O), 829, 768, 698 (CH_{arom}); HPLC (25 cm Chiralcel OD-H, heptane/ethanol: 95/5) retention times 13.6 and 22.3 min for the two cis enantiomers (1*R*,2*S*) and (1*S*,2*R*).

(±)-*N*-(*p*-*N*′,*N*′-Dimethylbenzoyl)methyl serine ester (40): colorless oil; ^{1}H NMR (400 MHz, CD_3OD) δ 7.75 (d, J = 9 Hz, 2H), 6.72 (d, J = 9 Hz, 2H), 4.72 (m, 1H), 4.00 (dd, J = 5, 12 Hz, 1H), 3.95 (dd, J = 4 Hz, J(H,H) = 11 Hz, 1H), 3.77 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (400 MHz, CD_3OD) δ 173.0, 170.5, 154.7, 130.2, 121.3, 112.3, 63.2, 56.9, 53.0, 50.0, 40.4; IR (film, cm^{-1}) ν 3367 (OH), 2953, 1440, 1347 (CH), 1736, 1603 (CO), 1507 (C═C), 830, 766 (CH_{arom}); HPLC (25 cm Chiralpak AD, heptane/ethanol: 85/15) retention times 35.7 and 48.6 min for the two enantiomers.

Procedure for the Synthesis of *N*′-(4′-Pyridinyl)-α-methyl Proline Amides (1−9 and 12−31) and *N*-(4′-Pyridinyl)-α-methyl Proline Esters (10 and 11). In 31 tubes, compound **32** (30 × 16.5 mg, 1 equiv, 0.08 mmol) was dissolved in 31 × 0.25 mL of dry DMF. A solution of HATU (31 × 0.096 mmol, 1.2 equiv) in 31 × 0.25 mL of dry DMF was added. The mixture was stirred for 20 min, and then the corresponding amine or alcohol (31 × 0.096 mmol; 1.2 equiv) was added, followed by DIPEA (31 × 0.035 mL; 2.5 equiv) previously dissolved in 31 × 0.5 mL of dry DMF. The reactions were stirred overnight. The solvents were removed. Purification was carried out in parallel by semipreparative LC/MS and on silica columns (gradient of eluents: DCM/MeOH/Et_3N:10/0/0.5 at t = 0 min to DCM/MeOH/Et_3N 9.5/0.5/0.5 at t = 10 min).

***N*-(2′,3′-Dihydrobenzo[*B*]furan-5-ylmethyl)-*N*′-(4′-pyridinyl)-α-methylproline amide (6)**: 32% yield; colorless crystals (recrystallization in toluene); mp 156−158 °C; $[\alpha]_D^{20}$ −13.2 (*c* 0.8 in ethanol); ^{1}H NMR (250 MHz, CD_3OD) δ 7.85 (d, J = 6 Hz, 2H), 6.92 (s, 1H), 6.85 (d, J = 8 Hz, 1H), 6.50 (d, J = 8 Hz, 1H), 6.30 (d, J = 6 Hz, 2H), 4.40 (t, J = 9 Hz, 2H), 4.22 (d, J = 16 Hz, 1H), 4.07 (d, J = 16 Hz, 1H), 3.60 (m, 2H), 3.00 (t, J = 8 Hz, 2H), 2.25−1.90 (m, 4H), 1.42 (s, 3H); IR (film, cm^{-1}) ν 3324, 1511 (NH), 2926, 2503, 1378 (CH), 1646, 1491, 1461 (C═C), 1597 (C═O), 1228 (C−O), 806, 755 (CH_{arom}); MS m/z $(M + H)^+$ calcd 338.1869, obsd 338.1870.

***N*-Methyl-*N*-ethyl-*N*′-(4′-pyridinyl)-α-methylproline amide (15)**: 36% yield; yellow oil; $[\alpha]_D^{20}$ −46.7 (*c* 0.9 in ethanol); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.05 (d, J = 7 Hz, 2H), 6.53 (d, J = 7 Hz, 2H; ArH), 3.80−3.70 (m, 1H), 3.60−3.50 (m, 1H), 3.30−3.20 (q, J = 7 Hz, 2H), 1.55 (s, 3H), 1.05 (t, J = 7 Hz, 3H); IR (film, cm^{-1}) ν 3332, 1516 (NH), 2975, 2878, 1461, 1380 (CH), 1642 (C═C), 1600 (C═O), 831 (CH_{arom}); MS m/z $(M + H)^+$ calcd 234.1606, obsd 234.1605.

See Supporting Information for the characterization of all 31 compounds.

Procedure for the Kinetic Resolution of Racemic *cis*-(±)-(*p*-*N*′,*N*′-Dimethylbenzoyl)cyclohexan-1,2-diol (33). In 31 tubes, 5 mol % (0.02 mmol) of each of compounds **1**−**31** was dissolved in 31 × 1 mL of dry toluene. A solution of isobutyric anhydride (31 × 0.2 mmol, 0.7 equiv) in 31 × 1 mL of dry toluene was added successively. After 15 min, *cis*-(±)-(*p*-*N*′,*N*′-dimethylbenzoyl)cyclohexan-1,2-diol (**33**; 31 × 0.3 mmol, 1 equiv) was introduced. The volume was completed in each tube to 3 mL by addition of dry toluene. The reaction was stirred for 3 h at room temperature. A 200-μL sample of each reaction mixture was then sampled for the determination of the percentage of conversion (see Supporting Information). Toluene was removed from the 31 tubes. Purification was made in parallel on silica columns (gradient of eluents: DCM/MeOH/Et_3N 10/0/0.5 at t = 0 min to DCM/MeOH/Et_3N 9/1/0.5 at t = 10 min). The fractions corresponding to the recovered alcohol **33** and the corresponding ester were collected and solvent was removed.

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Supporting Information Available: Kinetic study with catalyst **6**, characterization of compounds **1**−**31**, HPLC retention times of alcohols **34**−**40**, calculation of percentages conversion, yield, and ee for the KR of alcohol **33**, and results of the KR of **33** with catalysts **1**−**31**. This material is available free of charge via the Internet at http://pubs.acs.org.

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