# 新世代求核触媒の設計と選択的反応

（課題番号　14370721）

平成１４年度～１６年度科学研究費補助金「基盤研究 (B)(2)」

研究成果報告書

平成１８年３月

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１、研究課題　　新世代求核触媒の設計と選択的反応

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３、研究組織


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４、研究費

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| 平成１１年度 | ５、９００ | 千円 |
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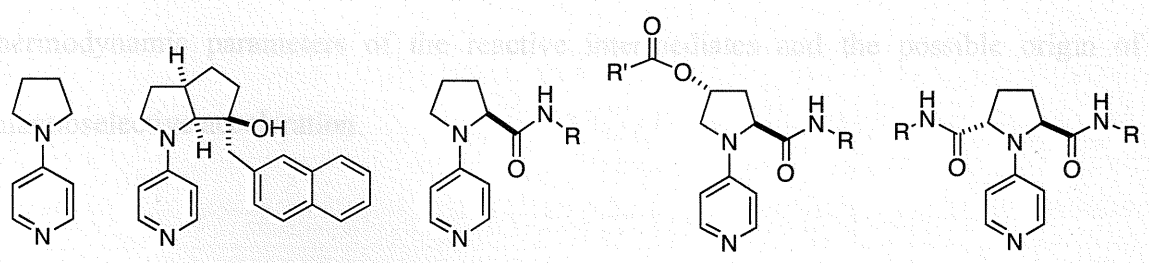
| 計 | １３、８００ | 千円 |

研究成果

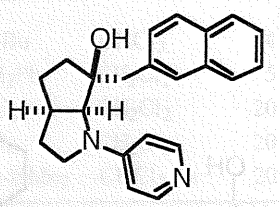
２０世紀後半に不斉合成は長足の進歩を遂げたが、その中心的役割を担ってきたのが有機金属触媒である。金属の持つルイス酸性とキラルリガンドから成る不斉場を利用する方法は不斉誘導の方法論として既に確立され成熟している。一方、最近では環境調和性の観点から金属を含まない有機触媒が注目されているが、有機触媒は不斉誘導の方法論そのものが未発達で、この観点からもチャレンジングな分野である。本研究では有機触媒として求核触媒に着目し研究を行なった。4-ジメチルアミノピリジン(DMAP) や 4-ピロリジノピリジン(PPY) に代表される求核触媒は水酸基のアシル化触媒としてよく知られているが、この他にもラクトン化などの C-O 結合形成や多くの C-N、C-C 結合形成を温和な条件下に触媒する。PPY 型不斉求核触媒の開発はこれら一連の反応の不斉触媒化を可能にし、常温、常圧で有効に働く環境調和型触媒的不斉プロセスへの展開が期待される。

このような背景のもと、本研究では以下の研究を行なった。（1）触媒 **1** を用いるアミノアルコール類の速度論的分割とその加速性を伴う選択性発現機構の解明、（2）$C_2$ 対称 PPY 型不斉求核触媒 **4** の開発とメソージオール類の不斉非対称化への利用、および触媒 **2**、**3** との不斉触媒能の比較。

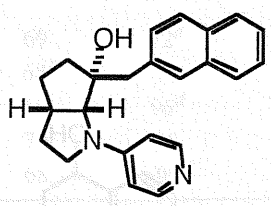


# Enantioselective Acceleration in Kinetic Resolution of Amino Alcohol Derivatives with a Chiral Pyrrolidinopyridine

An important goal of current research in organic chemistry is to design an artificial low-molecular-weight catalyst with enzymatic functions.[1] Chiral pyrrolidinopyridine **1** was developed to mimic the properties of an enzyme such as lipase to enantioselectively acylate alcohols.[2] A unique feature of **1** is that there are no chiral elements near the catalytically active pyridine nitrogen. The high catalytic activity of **1** is expected to be due to the low steric interaction, where **1** readily forms an acylpyridinium reactive intermediate with acid anhydride.[3] On the other hand, **1** shows high enantioselectivity (selectivity factor,[4] $s$=10-54) in the kinetic resolution of racemic amino alcohols with a *p*-dimethylaminobenzoyl protective group.[5] We describe here the scope and mechanistic aspects of the kinetic resolution of racemic alcohols promoted by **1**, ***ent*-1**, and the analogues. Kinetic studies of acylation indicate that ***ent*-1** is as active as 4-pyrrolidinopyridine (PPY) and the selectivity in the kinetic resolution with ***ent*-1** is due to enantioselective acceleration. We also address the structural thermodynamic parameters of the reactive intermediates and the possible origin of the enantioselective acceleration.



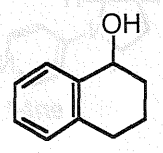

**1**



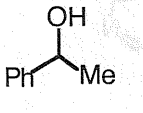

***ent*-1**

**Kinetic Resolution of Racemic Alcohols with Catalysts 1 and *Ent*-1**

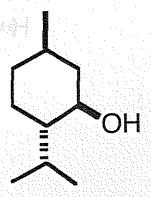
Since the pioneering work by Vedejs,[6] several chiral nucleophilic catalysts for enantioselective acylation have been developed.[7-9] Some of these catalysts show high enantioselectivity for the kinetic resolution of racemic arylalkylcarbinols,[8] while others are suitable for the enantioselective acylation of diol- and amino alcohol derivatives.[9] Catalyst **1** is a typical example in the latter category. For example, the acylative kinetic resolution of *racemic* mono-functional alcohols **2-4** with isobutyric anhydride in the presence 5 mol% of **1** proceeds without noticeable enantioselectivity ($s \leq 1.1$), while kinetic resolution of *racemic* diol monoesters with **1** proceeds with moderate to high selectivity depending on the ester moiety (Table 1). Kinetic resolution of *racemic* cyclohexane-1,2-diol mono-isobutyrate **(5)** proceeds with $s$=4.3 upon treatment with 5 mol % of **1** and 70 mol % of isobutyric anhydride in toluene at 20 °C. The enantioselectivity increased to $s$=8.3 with pivaloate **6**. When benzoate and substituted benzoates **7-10** were used as substrates, a clear tendency was observed: the enantioselectivity of acylation increased with an increase in the electron donating ability of the aromatic ring (entries 3-6, $s$=2.4~12.3). An enantiomerically pure (>99% ee) alcohol was recovered from the kinetic resolution of *racemic p*-dimethylaminobenzoate **10** with 5 mol % of **1** at 72% conversion (entry 6). The kinetic resolutions of several *racemic* mono(*p*-dimethylaminobenzoate) of diols were examined with 5 mol % of **1**. For both cyclic diol-monoesters **11-13** and the acyclic variant **14**,




**2**




**3**




**4**

enantioselective acylation proceeded to give the recovered alcohols in 92 ~ 97% ee at 70 ~ 77% conversion (entries 7-10, $s$=4.7~8.3).[2]

Next, the kinetic resolution of *racemic* β-amino alcohol derivatives was investigated, since a β-amino alcohol functionality is present in numerous biologically active compounds and, is therefore an important pharmacophore.[10] *cis*-2-Aminocyclohexanol was chosen as the standard substrate for optimizing the conditions for kinetic resolution, and the effects of the protective group of the amino group on kinetic resolution were examined (Table 2). *Racemic*-**15** with typical carbamate-protective groups such as Boc and Cbz was resolved with moderate enantioselectivity ($s$=4.0~4.5) *via* acylation with ***ent*-1** (entries 1 and 2), while **15** with amide-protective groups showed better selectivity ($s$=8.7~>13, entries 3-5). Enantiomers of a substrate with a *p*-(dimethylamino)benzoyl group, **15e**, were most effectively differentiated by ***ent*-1** ($s$ > 13, entry 5). The effects of acylating agents were then investigated, and are shown in Table 3. Among commercial acid anhydrides, isobutyric anhydride gave the highest selectivity ($s$=6.2~17, entries 1-4). Although the corresponding pentafluorophenyl ester resulted in selectivity comparable to that with isobutyric anhydride,

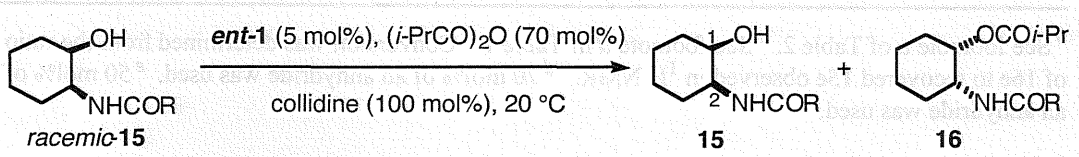



**Table 2.** Effects of protective group on the kinetic resolution of *racemic*-**15** with ***ent*-1**

| entry | substrate | R | solvent | reaction time (h) | conversion[a] (%) | ee of recovered **15** (%) | ee of **16** (%) | $s^b$ |
|---|---|---|---|---|---|---|---|---|
| 1 | **15a** | O*t*-Bu | $CHCl_3$ | 24 | 69 | 72[d] | 33 | 4.0 |
| 2 | **15b** | $OCH_2Ph$ | $CH_2Cl_2$ | 5 | 68[c] | 76 | – | 4.5 |
| 3 | **15c** | $CH_3$ | $CH_2Cl_2$ | 20 | 69 | 96[d] | 43 | 8.7 |
| 4 | **15d** | Ph | $CH_2Cl_2$ | 20 | 70 | 98 | 42 | 9.4 |
| 5 | **15e** | $C_6H_4$-*p*-$NMe_2$ | $CHCl_3$ | 20 | 68 | >99[d] | 47 | >13 |

[a] Conversion was determined by the following equation; conversion (%) = ee (recovered **15**) / ee (recovered **15**) + ee (**16**). [b] See footnote d of Table 1. [c] Conversion was determined from the ratio of **16b** to recovered **15b**. [d] Absolute configuration is (1*R*, 2*S*).

the kinetic resolution was much less effective due to the low reactivity ($s$=17, **15e** in 29% ee and **16e** in 86% ee at 25% conversion after 2 days, entry 5). The presence of an *ortho*-substituent in the benzoic anhydride derivatives increased the efficiency of the kinetic resolution (entries 7 vs. 4 and 6). While 2,4,6-trifluorobenzoic anhydride gave the highest selectivity ($s$=19, entry 8), isobutyric anhydride was used in further investigations because it is readily available.

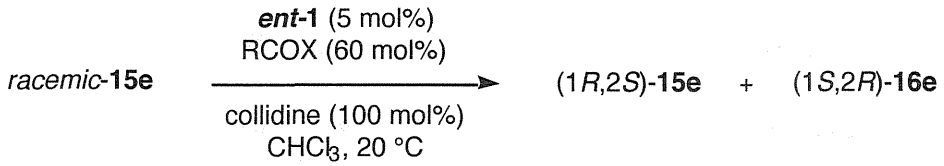



**Table 3.** Effects of acylating agent on the kinetic resolution of *racemic*-**15e** with ***ent*-1**

| entry | RCOX | reaction time (h) | conversion[a] (%) | ee of recovered (1*R*,2*S*)-**15e**, (%) | ee of (1*S*,2*R*)-**16e** (%) | $s^b$ |
|---|---|---|---|---|---|---|
| 1 | $(CH_3CO)_2O$ | 9 | 60 | 93 | 60 | 12 |
| 2 | $(i\text{-PrCO})_2O$ | 9 | 61 | 97 | 61 | 17 |
| 3 | $(t\text{-BuCO})_2O$ | 96 | 17 | 14 | 69 | 6.2 |
| 4 | $(PhCO)_2O$ | 9 | 60 | 75 | 51 | 6.6 |
| 5 | $i\text{-PrCO-OC}_6F_5$ | 48 | 25 | 29 | 86 | 17 |
| 6 | $(4\text{-MeO-C}_6H_4CO)_2O$ | 96 | 64[c,d] | 82 | – | 6.5 |
| 7 | $(2\text{-MeO-C}_6H_4CO)_2O$ | 72 | 57 | 88 | 66 | 14 |
| 8 | $(2,4,6\text{-F}_3\text{-C}_6H_2CO)_2O$ | 24 | 49[e] | 76 | 79 | 19 |

[a] See footnote *a* of Table 2. [b] See footnote *d* in Table 1. [c] Conversion was determined from the ratio of **16e** to recovered **15e** observed in $^1$H NMR. [d] 70 mol% of an anhydride was used. [e] 50 mol% of an anhydride was used.

Table 4 shows the kinetic resolution of several cyclic amino alcohol derivatives **15e** and **17**– **20**. Treatment of *racemic*-**15e** with 60 mol% of isobutyric anhydride in chloroform in the presence of 5 mol% of ***ent*-1** at 20 °C led to the recovery of (1*R*,2*S*)-**15e** in 93% ee at 58% conversion ($s$=17, entry 1). Increasing the amount of acid anhydride to 65 mol% resulted in the recovery of enantiopure **15e** with minimal loss of chemical yield (entry 2).

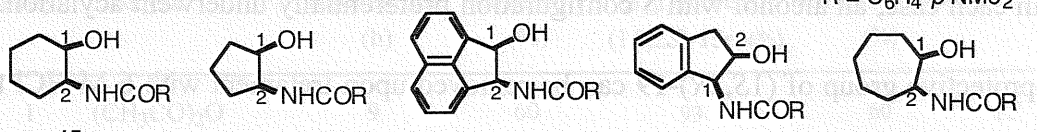
Even with 0.5 mol% of the catalyst (catalyst/substrate=0.9 mg/131 mg), the acid anhydride was completely consumed within 24 h and enantiopure **15e** was recovered (entry 3). The enantioselectivity of the kinetic resolution of **15e** with ***ent*-1** reached $s$=54 when the reaction was performed at –40 °C (entry 4). However, we believe that the kinetic resolution at 20 °C with $s$=17 is better from a practical viewpoint because enantiopure materials are readily obtained by the reaction at 20 °C and the reaction conditions are more convenient. While the addition of a stoichiometric amount of collidine does not affect the efficiency of the kinetic resolution with 5 mol% of ***ent*-1** (entries 2 *vs.* 5), it does affect the efficiency with 0.5 mol% of ***ent*-1** (entries 3 *vs.* 6). Nearly enantiopure amino alcohol derivatives **17** – **20** were recovered at 64~73% conversion by a similar treatment of the racemates ($s$=10~21, entries, 7-11). In each case, an alcohol with *S* configuration preferentially underwent acylation. The amide-protective group of (1*S*,2*R*)-**19** can be removed upon tretament with 6 M HCl to give (1*S*,2*R*)-1-aminoindan-2-ol (68% yield), a key component of the orally active HIV protease inhibitor, indinavir.[11,12]

**Table 4.** Kinetic resolution of racemic amino alcohol derivatives **15e** and **17-20** with ***ent*-1**[a]

| entry | substrate | ***ent*-1** (mol%) | $(i\text{-PrCO})_2O$ (mol%) | reaction time (h) | conversion[b] (%) | ee of recovered substrate[c], (%) | ee of acylated product, (%) | *s* |
|---|---|---|---|---|---|---|---|---|
| 1 | **15e** | 5 | 60 | 9 | 58 | 93 | 68 | 17 |
| 2[d] | **15e** | 5 | 65 | 44 | 63 | >99 | 59 | >18 |
| 3 | **15e** | 0.5 | 70 | 24 | 66 | >99 | 52 | >15 |
| 4[d,e] | **15e** | 5 | 50 | 19 | 30 | 40 | 95 | 54 |
| 5[f] | **15e** | 5 | 70 | 9 | 67 | >99 | 48 | >14 |
| 6[f] | **15e** | 0.5 | 70 | 24 | 60 | 89 | 59 | 11 |
| 7 | **17** | 5 | 70 | 9 | 69 | >99 | 44 | >12 |
| 8[g] | **18** | 5 | 60 | 24 | 59 | 97 | 67 | 21 |
| 9[g] | **18** | 5 | 70 | 24 | 68 | >99 | 46 | >13 |
| 10[h] | **19** | 5 | 70 | 3 | 64 | 99 | 56 | 17 |
| 11 | **20** | 5 | 75 | 9 | 73 | 99 | 37 | 10 |

[a] A 0.17 M solution of substrate (0.5 mmol) in $CHCl_3$ was treated with isobutyric anhydride at 20 °C in the presence of catalytic amount of ***ent*-1** and 100 mol% of collidine, unless otherwise stated. [b] See footnote *a* of Table 2. [c] Absolute configuratuion of **15e**, **17**, **18**, and **20** is (1*R*,2*S*) in each case and that of **19** is (1*S*,2*R*). [d] Run in 0.05 M solution of substrate. [e]Run at −40 °C. [f] Run in the absence of collidine. [g] Run in 0.03 M solution of substrate. [h] Run in $CH_2Cl_2$.

R = $C_6H_4$-*p*-$NMe_2$

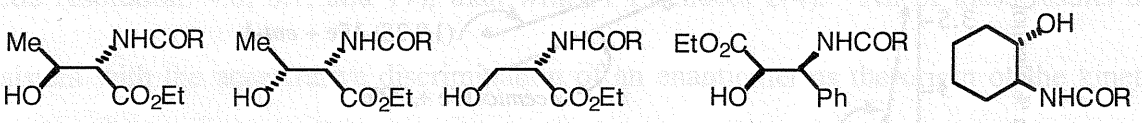



**15e** **17** **18** **19** **20**

The protocol for kinetic resolution was applied to acyclic amino alcohol derivatives. Acylation of an *anti*-amino alcohol derivative, *racemic*-**21**, under standard conditions (Table 4, footnote *a*) led to the recovery of **21** in 93% ee at 70% conversion (*s*=7.1), while the corresponding *syn*-derivative **22** showed negligible selectivity (*s*=1.0). Kinetic resolution of **23** with a primary hydroxyl group progressed with a selectivity factor of 6.8. Another *syn*-amino alcohol derivative **24** (taxol side-chain)[13] was poorly resolved with ***ent*-1** (28% ee at 71 conversion, *s*=1.6). Distinct differences in enantioselectivity were observed between the kinetic resolution of **15e** and that of its *trans*-isomer **25**. While acylation of *racemic*-**15e** with isobutyric anhydride in the presence of ***ent*-1** proceeds with *s*= 17 (Table 4, entry 1), that of **25** proceeds with *s*=1.5. Thus, the relative configuration of the β-amino alcohols critically

affects the enantioselectivity of the kinetic resolution promoted by ***ent*-1**.

Since the theoretical maximum yield of kinetic resolution is 50%, kinetic resolution is useful only when it can produce materials with high enantiomeric purity that would otherwise be unattainable by asymmetric synthesis. Toward this purpose, it is important to control the % conversion of kinetic resolution because the ee of the recovered substrate directly correlates with the conversion of the reaction. In the acylation with ***ent*-1**, the % conversion is readily controlled by the amount of acid anhydride, so that enantiopure compounds are readily obtained without the need to carefully monitor the progress of the reaction (Table 4), which is in contrast to enzymatic acylative kinetic resolution where excess acylating agent is used.[14] Even in the case of nonenzymatic acylative kinetic resolution, acylating agents are not always completely consumed within a reasonable reaction time.[8,9] In the acylation of **15** and **17-20** at 20 °C, acid anhydrides were complete consumed under conditions of 0.03-0.17 M substrate and 0.9-8.5 mM ***ent*-1** (Tables 2 and 4). These results indicate that ***ent*-1** has high catalytic activity.




**Relative Rates for Acylation with *Ent*-1 and PPY**

The catalytic activity of ***ent*-1** for the acylation of alcohols was investigated. Benzhydrol (**26**) was chosen as a standard achiral secondary alcohol for the kinetic study. The reaction rate for the acylation of **26** was monitored by 400 MHz $^1$H-NMR with a solution of 25 mM **26**, 0.25 mM catalyst, 500 mM isobutyric anhydride, 25 mM collidine, and 25 mM

methyl decanoate (internal standard) in $CDCl_3$ at 22±2 °C (Figure 1). Pseudo-first-order kinetics were observed under theses conditions and ***ent*-1** showed an acylation rate for **26** comparable to that of PPY {$k_{rel}$(***ent*-1**/PPY) = 0.88}. Thus, ***ent*-1** was found to be as active as PPY, the most powerful catalyst known for the acylation of alcohols.[15] Rates for the acylation of chiral alcohol **15e** were then investigated. The slow-reacting enantiomer in the acylation with ***ent*-1**, (1*R*,2*S*)-**15e**, underwent acylation at a rate comparable to that using PPY {$k_{rel}$(***ent*-1**/PPY) =0.76}. On the other hand, ***ent*-1** promoted acylation of the fast-reacting enantiomer, (1*S*,2*R*)-**15e**, 12 times faster than that with PPY. Thus, the origin of selectivity in the acylative kinetic resolution of **15e** by ***ent*-1** was due to enantioselective acceleration rather than enantioselective deceleration.[16,17]

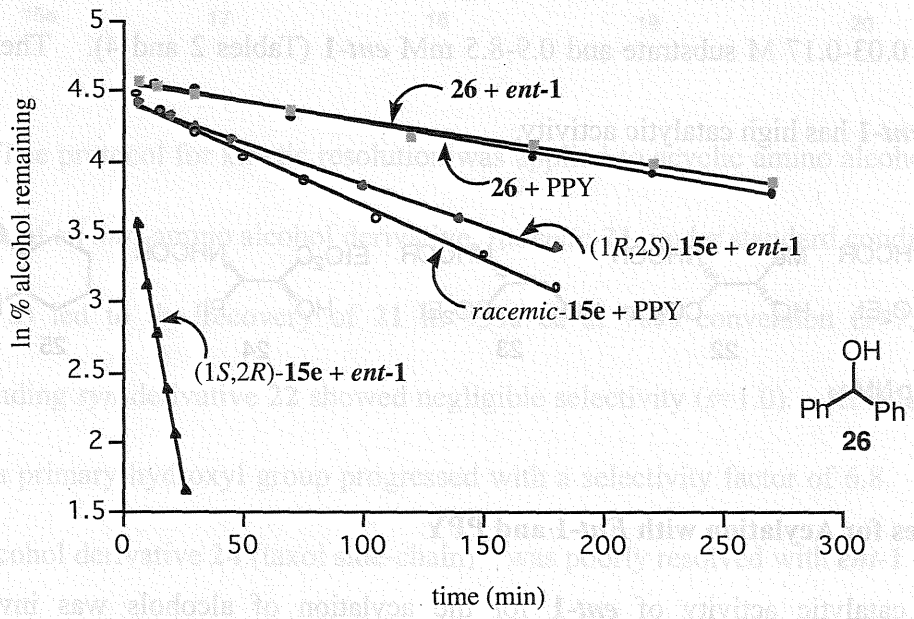



**Figure 1.** Kinetic plots for acylation of **26** and **15e** with isobutyric anhydride promoted by PPY and ***ent*-1**. See Suppotring Information for details.

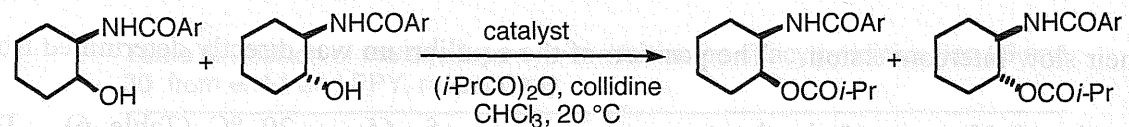
Similar kinetic phenomena were observed in the acylation of **15a** and **15c** with ***ent*-1**. Table 5 summarizes the kinetic profiles for the acylation of **15a** and **15c** as well as those of **26** and **15e** promoted by PPY or ***ent*-1**. Rates for the acylation of alcohols are shown relative to that for **26** using PPY. Acylation of *racemic*-**15a** with PPY proceeds slowly compared to that of **26** with PPY, whose relative rate for acylation is 0.16 ($k_{rel}$-PPY=0.16) (entry 2). The acylation of the slow-reacting enantiomer with ***ent*-1**, (1*R*,2*S*)-**15a**, proceeds at a rate comparable to that with PPY ($k_{rel}$-***ent*-1**=0.18; accordingly, the ratio of $k_{rel}$-***ent*-1** to $k_{rel}$-PPY {$k_{rel}$(***ent*-1**/PPY)}=0.18/0.16=1.1, entry 2). On the other hand, the fast-reacting enantiomer, (1*S*,2*R*)-**15a**, underwent acylation with ***ent*-1** 5.3 times as fast as that with PPY ($k_{rel}$(***ent*-1**/PPY) = 5.3, entry 2). Similarly, the $k_{rel}$(***ent*-1**/PPY) values for the fast-reacting (1*S*,2*R*)-**15c** and the slow-reacting (1*R*,2*S*)-**15c** are 7.7 and 1.0, respectively (entry 3). ***Ent*-1** promoted the acylation of the slow-reacting enantiomer at rates similar to those with PPY for **15a**, **15c** and **15e**, while acylation of the fast-reacting enantiomer with ***ent*-1** proceeded 5.3, 7.7, and 12 times faster, respectively (which are comparable to the respective *s* values of kinetic resolution: 4.0, 8.7, and 17), than with PPY (entries 2-4). All of these results are consistent with the accelerative discrimination of an enantiomer as the origin of the kinetic resolution.

**Table 5.** Correlation between relative rates for acylation and *s* value of the kinetic resolution[a]

| entry | substrate | $k_{rel}$-PPY[b] | $k_{rel}$-***ent*-1**[c] | $k_{rel}$(***ent*-1**/PPY)[d] | $k_{(S/R)}$[e] | *s*[f] |
|---|---|---|---|---|---|---|
| 1 | **26** | 1.0 | 0.88 | 0.88 | | |
| 2 | (1*S*,2*R*)-**15a** | 0.16 | 0.85 | 5.3 | 4.8 | 4.0 |
| | (1*R*,2*S*)-**15a** | | 0.18 | 1.1 | | |
| 3 | (1*S*,2*R*)-**15c** | 5.3 | 41 | 7.7 | 7.7 | 8.7 |
| | (1*R*,2*S*)-**15c** | | 5.3 | 1.0 | | |
| 4 | (1*S*,2*R*)-**15e** | 2.5 | 31 | 12 | 16 | 17 |
| | (1*R*,2*S*)-**15e** | | 1.9 | 0.76 | | |

a) Rates are shown as relative rates to a rate for acylation of **26** with PPY. Kinetic measurements of acylation were done by 400 MHz $^1$H NMR at 22±2 °C in $CDCl_3$ and the kinetic resolution was performed in $CHCl_3$ at 20 ±2 °C. See Supporting Information for details. b) Rate for acylation of a substrate promoted by PPY relative to that of **26** by PPY. Racemic **15a**, **15c**, and **15e** were used for the kinetic study with PPY. c) Rate for acylation of a substrate with isobutyric anhydride promoted by ***ent*-1** relative to that of **26** by PPY. d) Ratio of $k_{rel}$-***ent*-1** to $k_{rel}$-PPY. e) Ratio of $k_{rel}$-***ent*-1** for (1*S*,2*R*)-isomer to $k_{rel}$-***ent*-1** for (1*R*,2*S*)-isomer. f) *S*-value experimentally determined by the kinetic resolution of the racemate.

Accelerative behavior was also observed in the competitive acylation of different substrates. Acylation of a 1:1 mixture of (5 equiv. of each relative to isobutyric anhydride) of *cis*- and *trans*-amino alcohol derivatives **15e** ($s$=17 with ***ent*-1**) and **25** ($s$=1.5 with ***ent*-1**) with isobutyric anhydride in the presence of ***ent*-1** gave **16e** (86% ee) and **25a** in a 90:10 ratio (Scheme 1). On the other hand, a similar treatment of the mixture with PPY gave **16e** and **25a** in a 54:46 ratio. Since the ratio obtained in the latter reaction promoted by PPY seems to reflect the intrinsic reactivity of the substrates toward acylation, the ratio obtained in the former reaction appears to be the result of a substrate-specific accelerative acylation caused by catalyst ***ent*-1**.




*racemic*-**15e** *racemic*-**25** **16e** **25a**

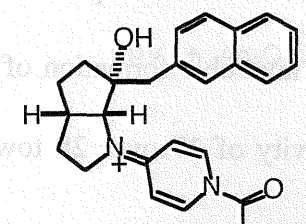
Ar = $C_6H_4$-*p*-$NMe_2$

catalyst ***ent*-1** : **16e** (90%, 86% ee), **25a** (10%)
PPY : **16e** (54%), **25a** (46%)

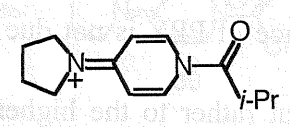
**Scheme 1**

**Thermodynamic Nature of Acylpyridinium Ions**

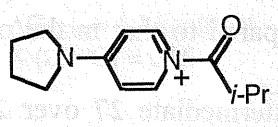
The observed accelerative acylation of **15a**, **15c**, and **15e** (Table 5) in the presence of ***ent*-1** could be due to either preferential formation of the acylpyridinium ion **27** from ***ent*-1** over the acylpyridinium ion **28** from PPY, and/or a higher reactivity of **27** toward the acylation of (1*S*,2*R*)-**15** than **28**. To clarify this issue and to investigate the nature of **27** and **28**, the equilibrium between the catalysts and their acylpyridinium ions was investigated. In this paper, the structure of the acylpyridinium ion is drawn as **28** and not as **28'** because of the reported X-ray structure of several *N*-acyl-4-dialkylaminopyridinim ions.[18]




**27**




**28**




**28'**

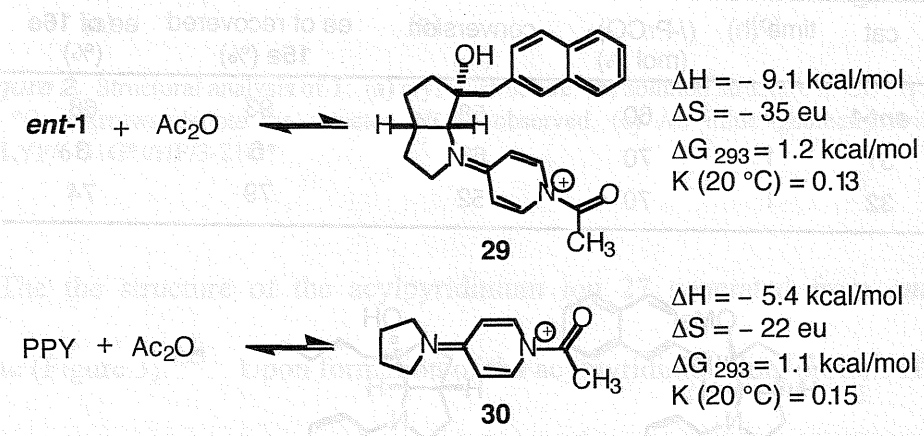
The process for the formation of the acylpyridinium ion from ***ent*-1** with acetic anhydride, instead of isobutyric anhydride, was investigated because of simplicity of the analysis.[19] The formation of acylpyridinium ion **29** from ***ent*-1** and acetic anhydride was monitored by variable-temperature $^1$H NMR of a $CD_2Cl_2$ solution of 0.1 M ***ent*-1** and 0.15 M

acetic anhydride (Scheme 2, Table 6). Signals of **29** appeared separately below –20 °C due to their slow interconversion. The position of the equilibrium was directly determined from the ratio of **29** to ***ent*-1** in the temperature range of –65 ~ –20 °C (Table 6). The thermodynamic parameters for the equilibrium between ***ent*-1** and **29** were determined from the data to be $\Delta H$ = –9.1 kcal/mol and $\Delta S$ = –35 eu. Similarly, those for the equilibrium between PPY and **30** were determined to be $\Delta H$ = –5.4 kcal/mol and $\Delta S$ = –22 eu.[20] The more-negative enthalpy and entropy for the formation of the acylpyridinium ion **29** than for **30** suggests that of the contribution of the naphthalene ring of ***ent*-1** may contribute to formation of the acylpyridinium ion. Although it was not possible to directly determine of the position of the equilibrium between ***ent*-1** and **29** at 20 °C due to rapid interconversion, the equilibrium constant (K) at 20 °C was estimated to be 0.13 based on the thermodynamic parameters. Similarly, the estimated equilibrium constant (K) for the formation of **30** at 20 °C was 0.15. Thus, under these conditions for kinetic resolution at 20 °C, the amount of the reactive acylpyridinium intermediate formed from ***ent*-1** seemed to be comparable to that from PPY. This suggests that the faster acylation of (1*S*,2*R*)-**15** observed in the presence of ***ent*-1** compared to that in the presence of PPY is not due to the favorable formation of the reactive intermediate **27** over **28**, but rather to the higher reactivity of **27** over **28** toward (1*S*,2*R*)-**15**.

**Table 6.** Position of the equlibrium for the formation of acylpyridinium ion **29** and **30** from ***ent*-1** and PPY, respectively

| entry | temp (°C) | formation of **29** (%) | ΔG (kcal/mol) | formation of **30** (%) | ΔG (kcal/mol) |
|---|---|---|---|---|---|
| 1 | –20 | 17 | –0.22 | | |
| 2 | –25 | 22 | –0.39 | | |
| 3 | –30 | 28 | –0.56 | | |
| 4 | –35 | 36 | –0.75 | | |
| 5 | –40 | 43 | –0.90 | 19 | –0.27 |
| 6 | –45 | 51 | –1.07 | 23 | –0.39 |
| 7 | –50 | 57 | –1.18 | 26 | –0.46 |
| 8 | –55 | 68 | –1.41 | 29 | –0.53 |
| 9 | –60 | 77 | –1.62 | 36 | –0.68 |
| 10 | –65 | 85 | –1.85 | 42 | –0.79 |
| 11 | –70 | | | 50 | –0.92 |
| 12 | –75 | | | 56 | –1.03 |
| 13 | –80 | | | 64 | –1.16 |
| 14 | –90 | | | 75 | –1.34 |

a) The ratio of the acylpyridinium was determined by variable temperature $^1$H NMR of a $CD_2Cl_2$ solution of 0.1 M catalyst and 0.15 M acetic anhydride. See Supporting Information for details




**Scheme 2**

## Functionality and Properties of Catalysts

To elucidate the effects of the hydroxyl group and the naphthalene ring in ***ent*-1** on its catalytic function, the corresponding methoxy derivative **31** and butyl derivative **32** were prepared and their catalytic properties were investigated. Kinetic resolution of *racemic*-**15e**

with isobutyric anhydride promoted by 5 mol % of **31** proceeded with *s*=1.1 (Table 7, entry 2). Surprisingly, the kinetic resolution of *racemic*-**15e** with **32** proceeded with high selectivity (*s*=16), comparable to that with ***ent*-1** (entries 1 and 3). *These results clearly indicate that the hydroxy group in **ent-1** is essential for enantioselective catalysis in the kinetic resolution of **15e**, while the naphthalene ring is not.* This observation contradicts a previously proposed mechanism involving π-π interaction caused by the naphthalene ring and the pyridinium ring.[2]

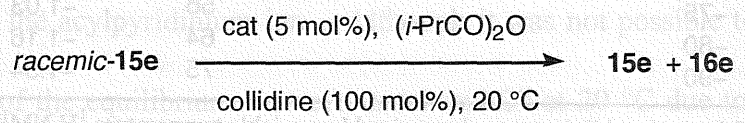
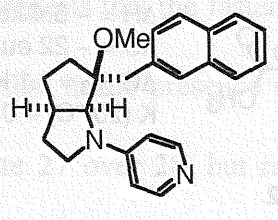
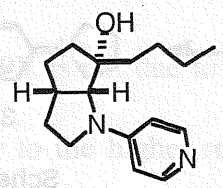



**Table 7.** Effects of functionality in chiral pyrrolidinopyridines, ***ent*-1**, **31**, and **32** on the enantioselectivity of kinetic resolution of *racemic*-**15e**

| entry | cat | time (h) | $(i\text{-PrCO})_2$ (mol %) | conversion (%) | ee of recovered **15e** (%) | ee of **16e** (%) | *s* |
|---|---|---|---|---|---|---|---|
| 1 | ***ent*-1** | 9 | 60 | 58 | 93 | 68 | 17 |
| 2 | **31** | 1 | 70 | 68 | 6 | 3 | 1.1 |
| 3 | **32** | 1 | 70 | 52 | 79 | 74 | 16 |




**31**




**32**

To clarify the origin of the enantioselective catalysis of ***ent*-1** and its derivatives, the structures of the catalysts and the acylpyridinium intermediates were further investigated.

**Structural Analysis of Nucleophilic Catalysts and Their Acylpyridinium Ions**

Figure 2 (a) shows the X-ray crystallographic structure of **1**. The naphthalene ring

and the pyridine ring are located far from each other, indicating that there is no interaction between them. A NOE study of **1** in $CDCl_3$ at 20 °C indicated a solution-structure (Figure 2, (b)) similar to the crystal structure. The optimized geometry obtained by ab initio MO calculation with B3LYP/6-31*//HF/3-21* was consistent with the crystal structure (Figure 2, (c)).

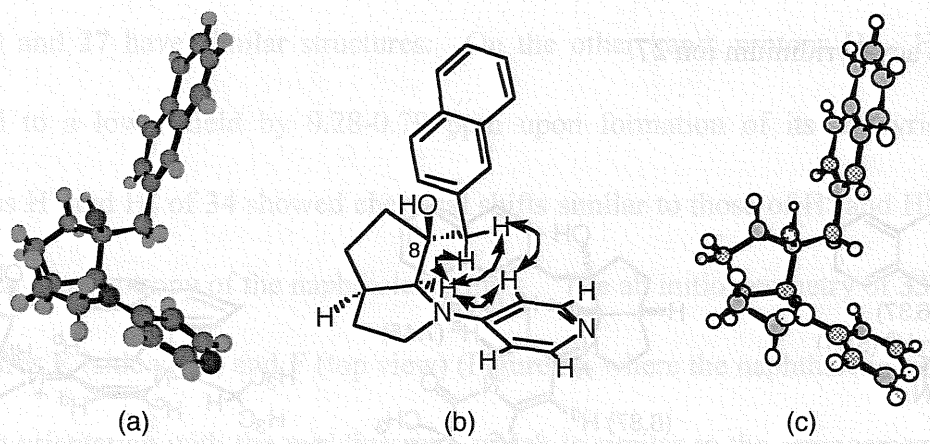



***Figure 2.*** Structural analysis of **1**: (a) crystal structure, (b) solution structure in $CDCl_3$ at 20 °C: Arrows denote the selected NOEs observed, (c) Ab initio geometry with B3LYP/6-31G*//HF/3-21G*

The the structure of the acylpyridinium ion **27** generated from ***ent*-1** was then investigate (Figure 3).[2,23] Upon formation of the acylpyridinium ion, protons $H^a$ and $H^b$ shift to a higher field by 0.56-0.68 ppm, whereas $H^c$ and $H^d$ shift to a lower field by 0.50-0.72 ppm (Figure 3, ***ent*-1** and **27**). Assuming that Δδ 0.85-1.08 ppm (Δδ value on the formation of **28** from PPY, see Figure 4) is the standard deviation in the chemical shifts for the forming the acylpyridinium ion, the observed Δδ for formation of the acylpyridinium ion **27** from ***ent*-1** indicates that protons $H^a$ and $H^b$ are strongly shielded while $H^c$ and $H^d$ are slightly shielded. Accordingly, we previously proposed structure **A**, where the naphthalene ring is located in an *offset* face-to-face orientation with the cationic pyridine ring via π-π interaction.[24] However,

alternative structure **B** is also possible based on the $^1$H NMR data, where the naphthalene ring is located perpendicular to the cationic pyridine ring via an edge-to-face π-π interaction.[25] It is not possible to discriminate between these two conformations solely on the basis of the $^1$H NMR. The ab initio optimized geometry of the acylpyridinium ion at the B3LYP/6-31G*//HF-/3-21G* level indicated an edge-to-face structure as shown in **C** (side view) and **D** (top view). Based on the NMR study and ab initio MO geometry, **B** is the more reliable structure of the acylpyridinium ion **27**.

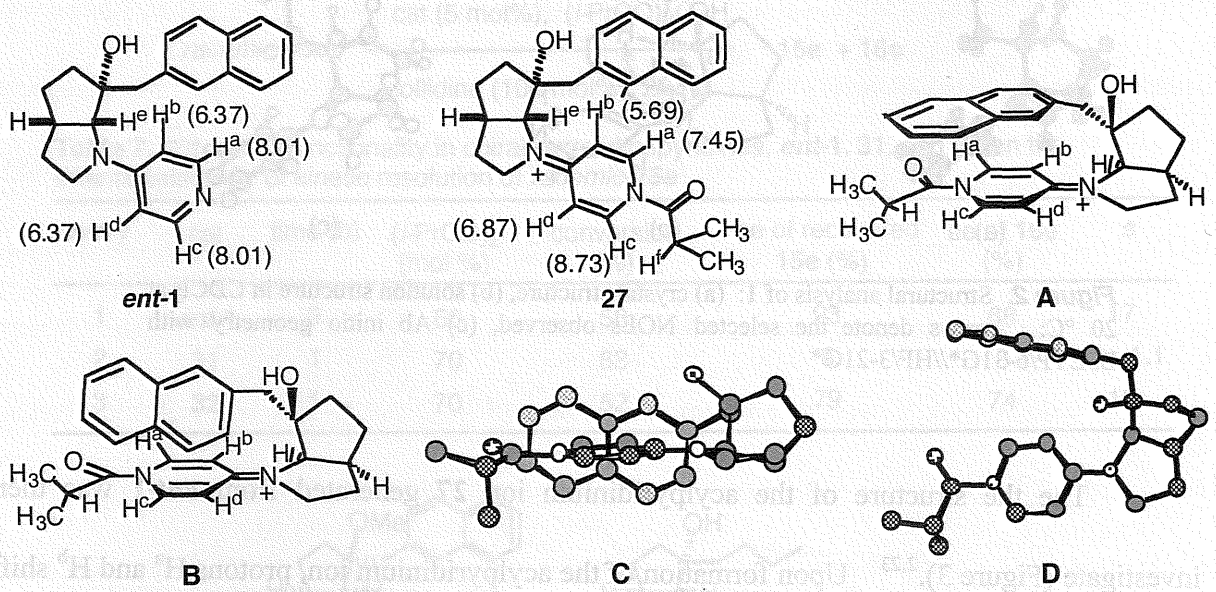



**Figure 3.** $^1$H NMR and structural analyses of ***ent*-1** and its acylpyridinium ion **27** : **A**: a previously proposed structure deduced by $^1$H NMR. Naphthalene and pyridinium rings are located in an offset face-to-face orientation via π–π interaction, see reference 2, **B**: proposed structure deduced by $^1$H NMR. Naphthalene and pyridinium rings are located in an edge-to-face orientation via π–π interaction, **C**: side view of the calculated structure at B3LYP/6-31G*//HF/3-21G* level. Protones are omitted and the naphthalen ring is colored green for clarity, **D**: top view of the calculated structure at B3LYP/6-31G*//HF/3-21G* level.

To understand the unexpected behavior in the enantioselective catalysis of **31** and **32**, we investigated the structurures of the acylpyridinium ions by $^1$H NMR and the ab initio MO method (Scheme 2). The acylpyridinium ions were prepared by mixing catalysts (PPY, **31**,

and **32**) and one equivalent of isobutyryl chloride in $CDCl_3$ in an NMR tube. Protons $H^a$-$H^d$ of acylpyridinium ion **33** generated from **31** appeared independently at 7.40, 5.27, 9.40, and 7.35 ppm, respectively, due to the fixed rotation of the $N^+$=C bond in an NMR time-scale.[22] Protons were unambiguously assigned based on COSY cross-peaks between $H^a$ and $H^b$, and $H^c$ and $H^d$ as well as a NOESY cross-peak between $H^b$ and $H^e$. As observed in **27**, protons $H^a$ and $H^b$ of **33** are strongly shielded and $H^c$ and $H^d$ are slightly shielded, which indicates that the **33** and **27** have similar structures. On the other hand, protons $H^a$ - $H^d$ of **32** are all shifted to a lower field by 0.28-0.79 ppm upon formation of its acypyridinium ion **34**. Protons $H^a$ and $H^b$ of **34** showed chemical shifts similar to those of $H^c$ and $H^d$ because of the absence of anisotropy of the naphthalene ring. The ab initio geometry of **33** again indicates structures **E** (side view) and **F** (top view) (Figure 5), where the naphthalene ring is in an edge-to-face orientation with the pyridine ring, which is similar to the arrangement in **27**. The ab initio geometry of **34** is also shown in **G** (side view) and **H** (top view) in Figure 5. These ab initio geometries **E-H** of **33** and **34** are compatible with observed $^1H$ NMR chemical shifts of acylpyridinium ions **33** and **34** shown in Figure 4.

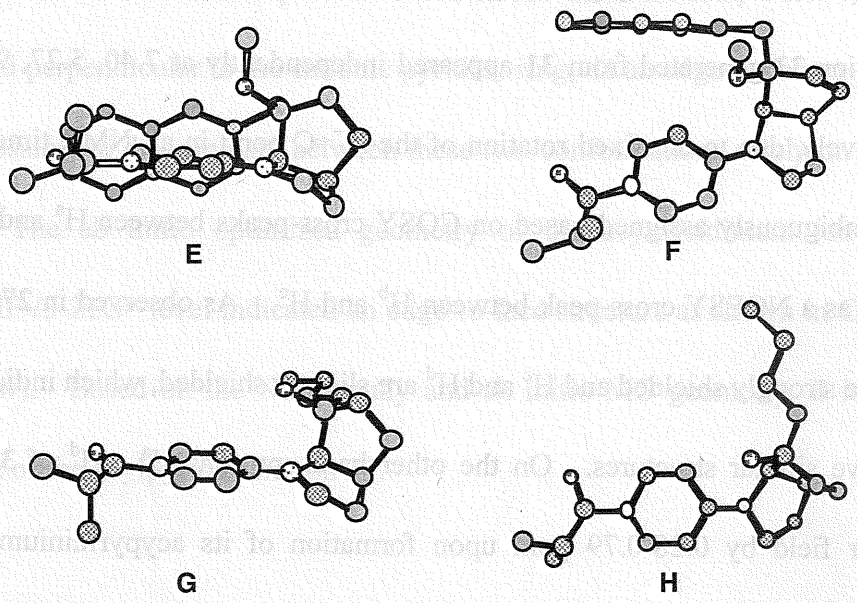



***Figure 5.*** Optimized structures of acylpyridinium ions **33** and **34** with B3LYP/6-31G*//HF/3-21G*. Protons are omitted for clarity **E**: side view of the opimized structure of **33**. The naphthalene ring is colored green for clarity, **F**: top view of the optimized structure of **33**, **G**: side view of the optimized structure of **34** , **H**: top view of the optimized structure of **34**.

Structures **C** - **H** provide a possible explanation for the observed accelerative acylation in the kinetic resolution of **15** and the differences in enantioselective catalysis between ***ent*-1**, **31**, and **32**. Figure 6 depicts a possible transition state assembly of **15e** and the acylpyridinium ion **27**. The fast-reacting enantiomer with ***ent*-1**, (1*S*,2*R*)-**15e**, would approach from the sterically more demanding concave face of **27** via transition state hydrogen bonding between C(8)-OH and the amide carbonyl of **15e** (Figure 6, **I** and **J**),[26] which may explain both the critical importance of the hydroxyl group in the catalyst for high enantioselectivity (Table 7, entries 1 vs. 2) and accelerative acylation (Figure 1 and Table 5, entry 4). Saturation behavior for the ***ent*-1**-catalyzed acylation of **15e** was investigated. Figure 7 (a) shows a plot of velocity constants for the acylation of (1*S*,2*R*)-**15e** with ***ent*-1**

versus its concentration, indicating saturation behavior and that the acylation follows the Michaelis-Menten equation with Vmax=0.8 x $10^{-5}$ M/sec and Km = 16 mM. This suggests the formation of complex **35** (Scheme 3) between (1*S*,2*R*)-**15e** and **27**, probably via hydrogen-bonding, prior to the acylation. On the other hand, hydrogen bonding is not beneficial for the transition state for the acylation of slow-reacting enantiomer, (1*R*,2*S*)-**15e**, with **27**, due to the severe steric interactions between the protective group of amine and the naphthalene ring (Figure 6, **K**, **L**). Thus, it would alternatively react with least steric interaction from the convex face of the acylpyridinium ion without hydrogen bonding between the substrate and the catalyst, as shown in **M**. Consistent with this hypothesis, (1*R*,2*S*)-**15e** did not show saturation behavior for the acylation with ***ent*-1** under the molar range within which (1*S*,2*R*)-**15e** did (Figure 7 (b)). The putative transition state structure, **M**, may be similar to that with PPY, **N**, which might account for the observation that the acylation of the slow-reacting enantiomer by ***ent*-1**, (1*R*,2*S*)-**15**, has a rate comparable to that by PPY (Figure 1 and and Table 4, entry 4).

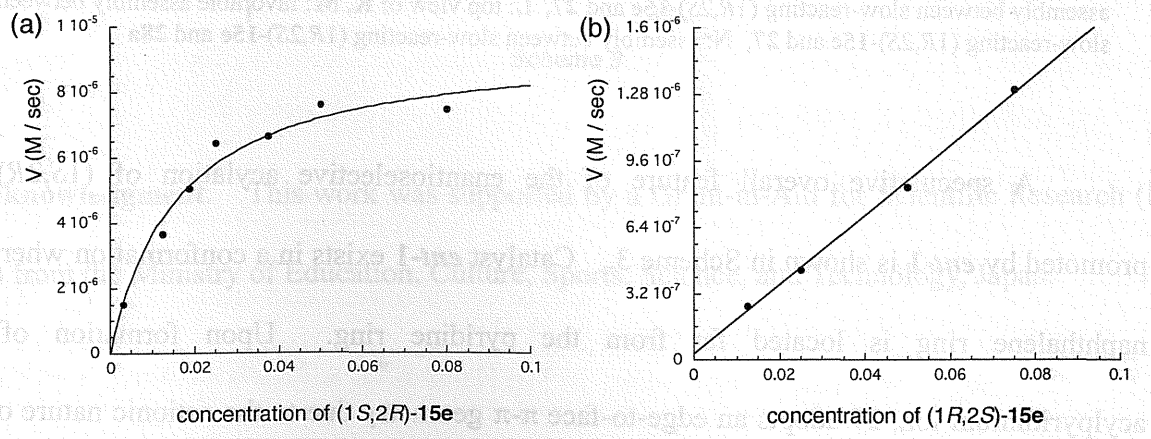



***Figure 7.*** Plot of velosity constant (V) for the ***ent*-1** catalyzed acylation versus concentration of (a) (1*S*,2*R*)-**15e** and (b) (1*R*,2*S*)-**15e** .

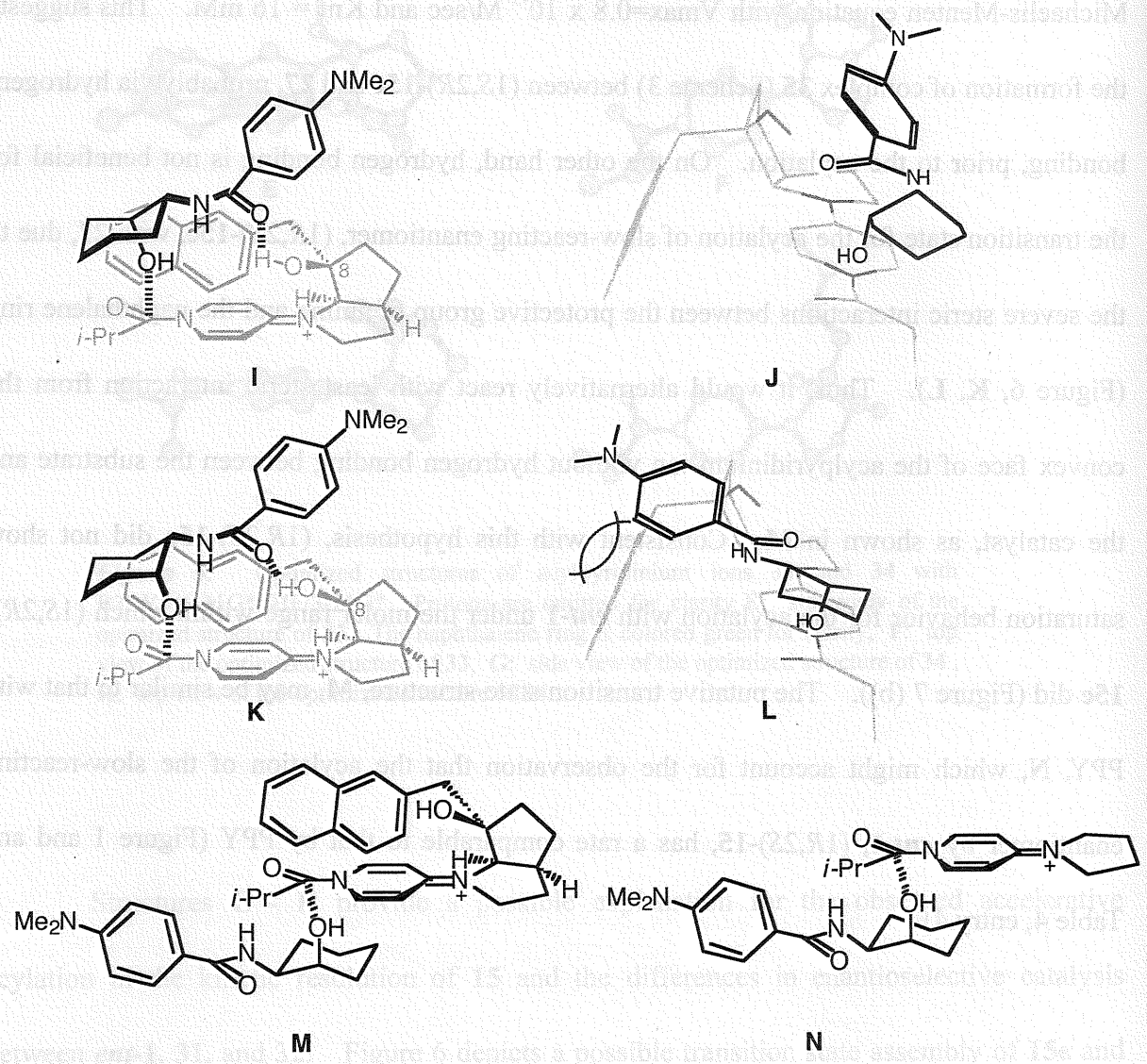
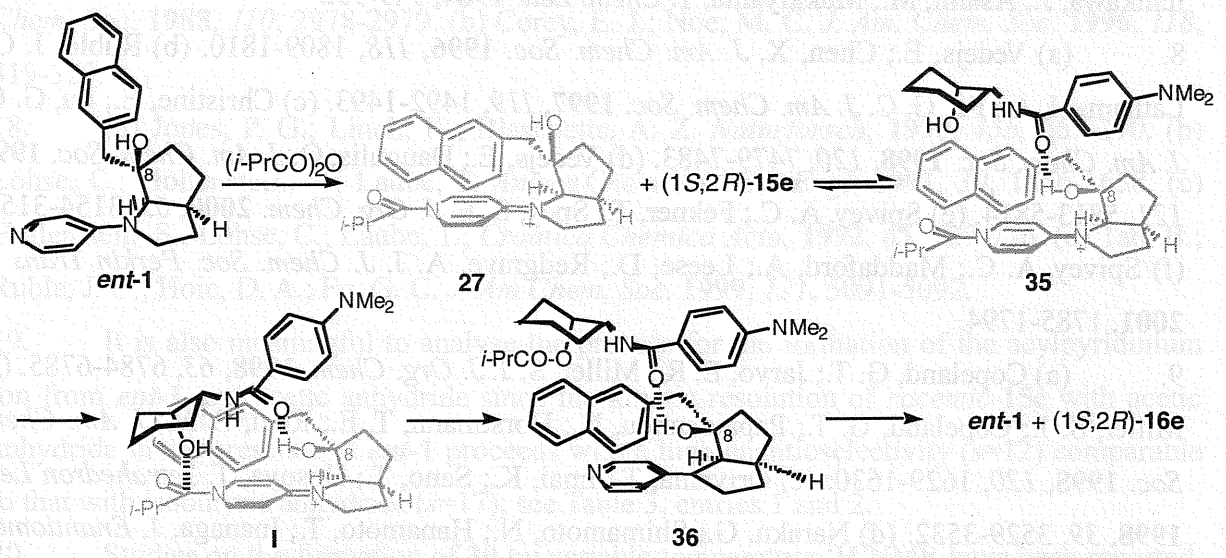



***Figure 6.*** Possible transition state assymbly betweem substrate **15e** and acylpyridinium reactive intermediate **27**. **I**: assembly between fast-reacting (1*S*,2*R*)-**15e** and **27**, **J**: top view of **I**, **K**: unfavorable assembly between slow-reacting (1*R*,2*S*)-**15e** and **27**, **L**: top view of **K**, **M**: favorable assembly between slow-reacting (1*R*,2*S*)-**15e** and **27**, **N**: assembly between slow-reacting (1*R*,2*S*)-**15e** and **28a**

A speculative overall feature of the enantioselective acylation of (1*S*,2*R*)-**15e** promoted by ***ent*-1** is shown in Scheme 3. Catalyst ***ent*-1** exists in a conformation where the naphthalene ring is located far from the pyridine ring. Upon formation of the acylpyridinium ion, **27** adopts an edge-to-face π-π geometry due to the cationic nature of the pyridine ring. This conformational change disposes the hydroxyl group at C(8) to substrate-

binding, resulting in the formation of a complex formation between (1*S*,2*R*)-**15e** and **27** via the hydrogen-bonding interaction, as shown in **35**. Immediately after the facile acylation takes place through transition state **I**, the naphthalene ring of **36** should change its geometry to the original one of ***ent*-1**, since the pyridine ring is no longer cationic. This change in the conformation of the naphthalene moiety would expel the acylated product (1*S*,2*R*)-**16e** from **36**, which may avoid product-inhibition of the catalytic cycle. This mechanism is highly speculative and is not based on concrete evidence. However, we believe that this must be closer to the nature of enantioselective catalysis promoted by ***ent*-1** than our previously proposed mechanism.[2]




***Scheme 3***

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16. Enantioselective acceleration in asymmetric acyl transfer catalysis has been reported previously; see reference 1.

17. Enantioselective acceleration was found in the kinetic resolution of allylic alcohols promoted by $[Ti(DIPT)(O\text{-}i\text{-}Pr)_2]_2$[a] and asymmetric dihydroxylation promoted by $OsO_4$-(bis-cinchona alkaloid).[b] (a) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978-2979. (b) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319-329.

18. (a) Jones, P. G.; Linoh, K.; Blaschette, A. Z. *Naturforsch*, **1990**, *45b*, 267-270. (b) Lohse, C.; Hollenstein, S.; Laube, T. *Angew.Chem. Int. Ed. Engl.* **1991**, *30*, 1656-1658. (c) Hollenstein, S.; Lohse, C.; Laube, T.; *Croatica Chemica Acta*, **1992**, *65*, 727-736. (d) Tao, B.; Ruble, J. C.; Hoic, D. A.; Fu, G. C. *J. Am.Chem. Soc.* **1999**, *121*, 5091-5092.

19. It is also meaningful to analyze the process for the formation of the acylpyridinium ion from ***ent*-1** and acetic anhydride since the kinetic resolution of *racemic*-**15e** with acetic anhydride in the presence of ***ent*-1** proceeds with a high enantioselectivity ($s$=12) comparable to that with isobutyric anhydride ($s$=17); see Table 3, entries 1 and 2.

20. Studies on the formation of **30** by variable-temperature $^1$H NMR have been reported, previously; see reference 15 (a).

21. $^1$H NMR spectrum of **28** in $CD_2Cl_2$ at 20 °C is similar to that in $CDCl_3$. Protons $H^a$ and $H^b$ appear at 9.23, 7.06 ppm, respectively.

22. The rotational barrier ($\Delta G^{\neq} > 21$ kcal/mol) of the corresponding $N^+$=C bond of an *N*-acylpyridinium ion has been reported; see reference 18 (d).

23. Structural analysis was performed with **1** and its acylpyridinium ion ***ent*-27** (see, reference 2). However, in the text, the enantiomeric forms, ***ent*-1** and **27**, are shown for easier comparison with **31**, **32** and their acylpyridinium ions.

24. Stereoselective synthesis based on face-to-face π-π interaction between a pyridinium

cation and an aromatic ring has been reported; see: (a) Yamada, S.; Saitoh, M.; Misono, T. *Tetrahedron Lett.* **2002**, *43*, 5853-5857. (b) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184-8185.

25. A favorable edge-to-face aromatic interaction between an pyridinium ion and aromatics has been reported; see: Hunter, C. A.; Low, C. M. R.; Vinter, J. G.; Zonta, C. *J. Am. Chem. Soc.* **2003**, *125*, 9936.

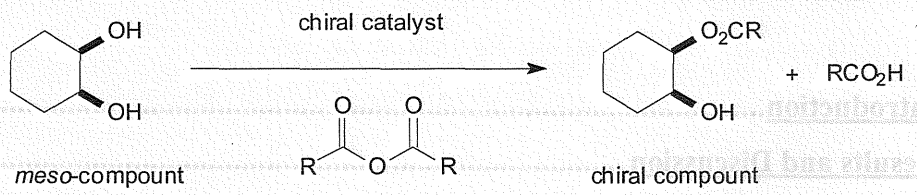
26. Campbell claimed hydrogen bonding between catalysts and a substrate in a similar acylative kinetic resolution; see reference 9i.

# $C_2$-Symmetric 4-Pyrrolidinopyridines as Stereoselective Nucleophilic Catalysts for Desymmetrisation of *meso*-Diols

# Table of Contents

# 1 Introduction

Nonenzymatic methods for stereoselective acyltransfer reactions are highly interesting tools for organic synthesis. Stereoselective acylation in this context is applied for kinetic resolution of racemic alcohols[1] and formation of quaternary carbon centres[2]. Recently the desymmetrisation of *meso*-diols by stereoselectiv acylation was reported with promising results[3]. As nucleophilic catalysts metal complexes[3c,d], tertiary phosphines[1g,4], tertiary amines[1a;3e] and pyridine derivatives are used.




Scheme 1: Desymmetrisation of *meso*-diols by partial acylation (e.g. 1,2-cyclohexanediol).

Since 4-pyrrolidinopyridine (PPY)[5] was discovered to be the most accelerating acylating catalyst a number of chiral PPY derivatives has been synthesised[6]. A challenge for the development of chiral PPY derivatives is to keep catalytic activity while introducing chirality. Because introduction of chiral centres nearby pyridine nitrogen strongly decreases catalytic reactivity.

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1 a) Priem, G.; Pelotier, B.; Macdonald, S.J.F.; Anson, M.S.; Campbell, I.B. *J. Org. Chem.* **2003**, *68*, 3844; b) Spivey, A.C.; Maddaford, A.; Fekner, T.; Redgrave, A.J.; Frampton, C.S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3460; c) Naraku, G.; Shimomoto, N.; Nanamoto, T.; Inanaga, J. *Enantiomer* **2000**, *5*, 135; d) Sano, T.; Imai, K.; Ohashi, K.; Oriyama, T. *Chemistry Letters* **1999**, 265; e) Somfai P. *Angew. Chem.* **1997**, *109*, 2849; f) Vedejs, E.; Chen, X. *J. Am. Chem. Soc.* **1996**, *118*, 1809; g) Vedejs, E.; Daugulis, O.; Diver, S.T. *J. Org. Chem.* **1996**, *61*, 430; h) Oriyama, T.; Hori, Y.; Imai, K.; Sasaki, R. *Tetrahedron Lett.* **1996**, *37*, 854; i) Evans, D.A.; Anderson, J.C.; Tayler, M.K. *Tetrahedron Lett.* **1993**, *34*, 5563; j) France, S.; Guerin, D.J.; Miller, S.J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985.

2 a) Fu, G.C.; Hills, I.D. *Angew. Chem. Int. Ed.* **2003**, *42*, 3921; b) Fu, G.C.; Mermerian, A.H. *J. Am. Soc.* **2003**, *125*, 4050; c) Shaw, S.A.; Aleman, P.; Vedejs, E. *J. Am. Chem. Soc.* **2003**, *125*, 13368.

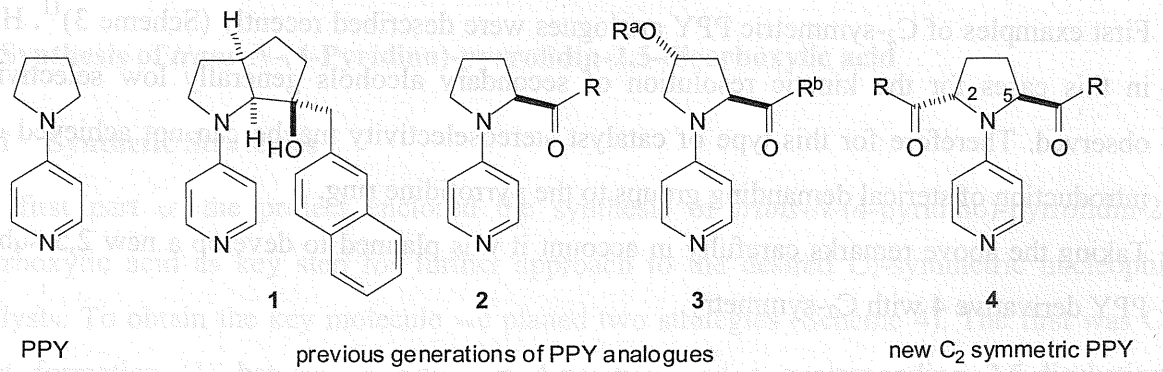
3 a) Vedejs, E.; Daugulis, O.; Tuttle,N. *J. Org. Chem.* **2004**, *69*, 1389; b) Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. *Angew. Chem. Int. Ed.* **2003**, *42*, 3383; c) Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052; d) Trost, B.M.; Mino, T. *J. Am. Chem. Soc.* **2003**, *125*, 2410; e) Oriyama, T.; Imai, K.; Hosoya, T.; Sano, T. *Tetrahedron Lett.* **1998**, *39*, 397.

4 Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166.

5 a) H fle, G.; Steglich, W.; Vorbr ggen, H. *Angew. Chem. Int. Ed.* **1978**, *17*, 569; b) Hassner, A.; Krepski, L.R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069; c) Murugan, R.; Scriven, E.F.V. *Aldrichimica Acta* **2003**, *36*, 21.

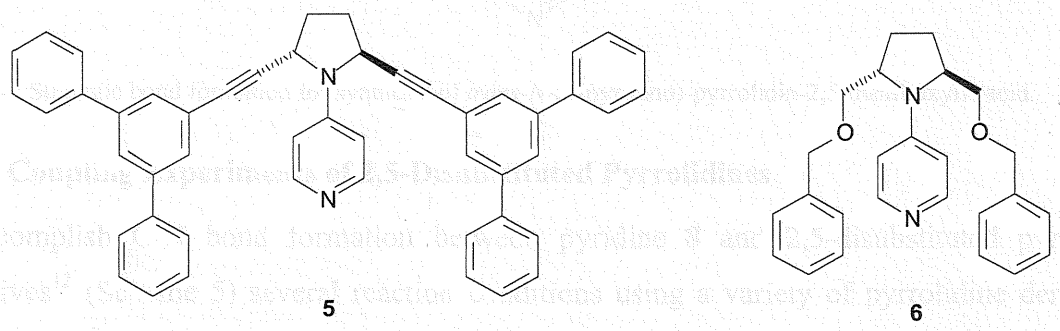
6 a) Spivey, A.C.; Fekner, T.; Spey, S.E. *J. Org. Chem.* **2000**, *65*, 3154; b) Spivey, A.C.; Fekner, T.; Spey, S.E.; Adams, H. *J. Org. Chem.* **1999**, *64*, 9438; c) Spivey, A.C.; Fekner, T.; Adams, H. *Tetrahedron Lett.* **1998**, *39*, 8919; see 1a, b, f; 2c; 11.

In our current project we gained wide ranged experience with introduction of chiral centers attached to the pyrrolidine moiety of PPY[7] **1-3**.




Scheme 2: PPY derivatives with chiral center on the pyrrolidine part.

A unique feature of this catalyst-design is that chiral elements are not present in the catalytical active pyridine ring. Because of no steric congestion around the nucleophilic nitrogen, very high catalytic activity is achieved (5-0.5 mol% catalyst). Additional advantage is that the PPY catalysis did not require any presence of metals to promote the reaction.




Scheme 3: Previously synthesized examples of $C_2$-symmetric PPY derivatives.

In the development of asymmetric synthesis the advantage of chiral auxiliaries having a $C_2$-axis of symmetry has been demonstrated by numerous examples[8]. Because of the $C_2$-symmetry the molecule get two equal sites[9], the number of competing diastereomeric transition states is

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7 a) Kawabata, T.; Stragies, R.; Fukaya, T.; Nagaoka, Y.; Schedel, H.; Fuji, K. *Tetrahedron Lett.* **2003**, *44*, 1545; b) Kawabata, T.; Stragies, R.; Fukaya, T.; Fuji, K. *Chirality* **2003**, *15*, 71; c) Kawabata, T.; Yamamoto, K.; Momose, Y.; Yoshida, H.; Nagaoka, Y.; Fuji, K. *Chem. Com.* **2001**, 2700; d) Kawabata, T.; Nagato, M.; Takasu, K.; Fuji, K. *J. Am. Chem. Soc.* **1997**, *119*, 3169.

8 a) ApSimon, J.W.; Seguin, R.P. *Tetrahedron* **1979**, *35*, 2797; b) Mukaiyama, T. *Tetrahedron* **1981**, *37*, 4111; c) Evans, D.A. *Aldrichimica Acta* **1982**, *15*, 23; d) Knowles, W.S. *Acc. Chem. Res.* **1983**, *16*, 106.

9 Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

reduced and atoms on the $C_2$ axis are chirotropic but not stereogenic centres[10], therefore the synthetic access usually should be easier.

First examples of $C_2$-symmetric PPY analogues were described recently (Scheme 3)[11]. However in this cases for the kinetic resolution of secondary alcohols generally low selectivity was observed. Therefore for this type of catalyst stereoselectivity maybe can not achieved only by introduction of sterical demanding groups to the pyrrolidine ring.

Taking the above remarks carefully in account it was planned to develop a new 2,5-substituted PPY derivative **4** with $C_2$-symmetry.

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10 Mislow, K.; Siegel, J. *J. Am. Chem. Soc.* **1984**, *106*, 3319.

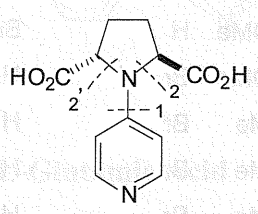
11 Naraku, G.; Shimomoto, N.; Nanamoto, T.; Inanaga, J. *Enantiomer* **2000**, *5*, 135; see 1b.

# 2 Results and Discussion

## 2.1 Synthesis of *trans*-*N*-(4-Pyridino)-pyrrolidin-2,5-dicarboxylic acid

### 2.1.1 Synthetic Strategies

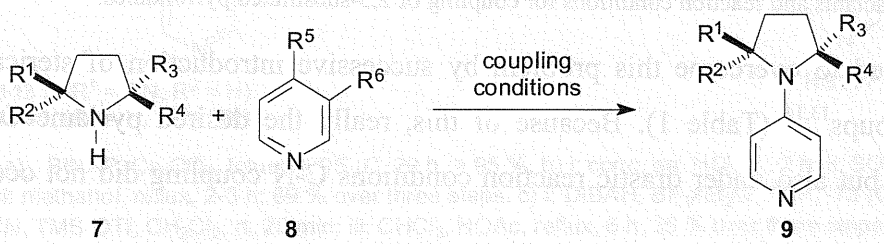
The first part of the project enclosed the synthesis of *trans*-*N*-(4-pyridino)-pyrrolidin-2,5-dicarboxylic acid as key step for further approach to the desired $C_2$-symmetric nucleophilic catalysts. To obtain the key molecule we planed two strategies (Scheme 4). The first was C-N bond formation (1) between pyridine in 4-position and a corresponding 2,5-disubstituted pyrrolidine. The second way was assembling of the pyrrolidine system around a nitrogen on pyridine in 4 position by simultaneous or successive formation of bonds 2 and 2«




Scheme 4: Strategic bond formation for synthesis of *trans*-*N*-(4-pyridino)-pyrrolidin-2,5-dicarboxylic acid.

### 2.1.2 Coupling Experiments of 2,5-Disubstituted Pyrrolidines

To accomplish C-N bond formation between pyridine **8** and 2,5-disubstituted pyrrolidine derivatives[12] (Scheme 5) several reaction conditions using a variety of pyrrolidine derivatives were investigated, however not any of them are able to provides the desired compound in a useful amount (Table 1).




Scheme 5: Coupling of 2,5-substituted pyrrolidines with 4-substituted pyridines

[12] For synthesis of *trans*-2,5-Pyrrolidinedicarboxylic acid dimethyl ester see 16b.

It is assumed that mainly the high sterical demanding circumstances of 2,5-disubstituted pyrrolidine nitrogen are causally connected to this type of difficulties.

| entry | **7, 9** | | | | **8** | | coupling conditions | yield |
|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | $R^6$ | | |
| **1** | H | $CO_2Me$ | H | $CO_2Me$ | Br | H | a) $Pd(OAc)_2$, BINAP, $Cs_2CO_3$, Toluene, 95 ¡C, 24 h | - |
| **2** | H | $CO_2Me$ | H | $CO_2Me$ | Br | H | b) DMSO, $(^iPr)_2NEt$, 120-150 ¡C | - |
| **3** | H | $CO_2Me$ | H | $CO_2Me$ | OPh | H | c) neat, 180 ¡C, 20 h | - |
| **4** | H | $CO_2Me$ | H | $CO_2Me$ | $NC_5H_5 \times HCl$ | H | d) neat, 170 ¡C, 1 h | - |
| **5** | H | $CO_2H$ | H | $CO_2H$ | OPh | H | c | - |
| **6** | H | $CH_2OMe$ | H | $CH_2OMe$ | Br | H | a | - |
| **7** | H | $CH_2OMe$ | H | $CH_2OMe$ | Br | H | THF, BuLi, rt. | 3 % |
| **8** | H | $CH_2OMe$ | H | $CH_2OMe$ | Br | H | THF, BuLi, CuI | - |
| **9** | H | $CH_2OMe$ | H | $CH_2OMe$ | H | Br | THF, BuLi, rt. | - |
| **10** | H | $CH_2OMe$ | H | $CH_2OMe$ | Br | H | THF, NaH, reflux, 20 h | - |
| **11** | CN | H | H | $CO_2Me$ | Br | H | a | 17 % *cis*-, 4 % *trans*- |
| **12** | H | CN | H | $CO_2Me$ | Br | H | a | traces |
| **13** | H | CN | H | $CO_2Me$ | Br | H | b | - |
| **14** | H | CN | H | $CO_2Me$ | OPh | H | c | - |
| **15** | H | CN | H | CN | Br | H | a | - |
| **16** | H | CN | H | CN | Br | H | b | - |
| **17** | H | CN | H | CN | OPh | H | c | - |
| **18** | H | CN | H | CN | Br | H | THF, NaH, reflux, 20 h | - |
| **19** | H | CN | H | CN | Br | H | DMF, NaH, 80 ¡C, 20 h | - |
| **20** | H | CN | H | CN | Br | H | $K_2CO_3$, NaI, DMF, 85 ¡C, 20 h | - |

Table 1: Reactants and reaction conditions for coupling of 2,5-substituted pyrrolidines.

It was tried to overcome this problem by successive introduction of sterical less demanding cyano groups[13,14] (Table 1). Because of this, really the desired pyridine derivative could be obtained, but also under drastic reaction conditions C-N coupling did not occurs in preparative

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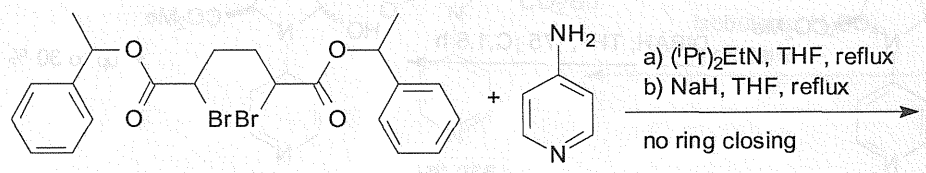
[13] a) For synthesis of 2-Cyanopyrrolidine-5-carboxylic acid methyl ester see Xia, Q.; Ganem, B. *Tetrahedron Lett.* **2002**, *43*, 1597; see also 19; for synthesis of 2,5-dicyanopyrrolidine see McIntosh, J.M. *J. Org. Chem.* **1988**, *53*, 447; Royer, J.; Husson, H.P. *Tetrahedron Lett.* **1987**, *49*, 6175; Takahashi, K.; Saitoh, H.; Ogura, K.; Iida, H. *Heterocycles* **1986**, *24*, 2905.

[14] For a example of successful palladium mediated coupling of 4-bromopyridine with a 2,5 alkine substituted pyrrolidine see 11.

useful yields. This kind of difficulties for coupling of 2,2[15]- and 2,5[1b]-disubstituted pyrrolidines and 4-substituted pyridines was also recently independently described.

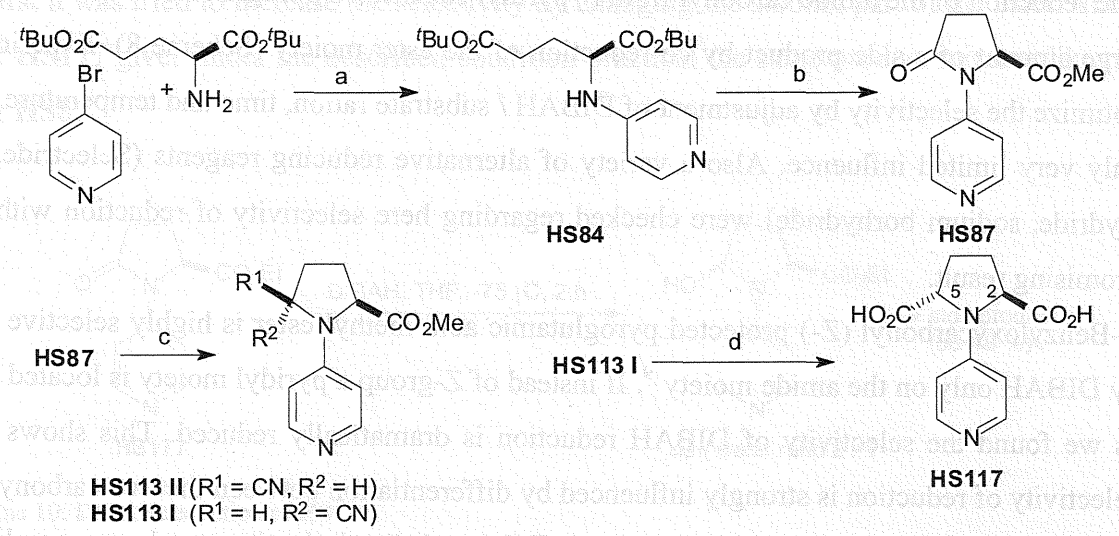
### 2.1.3 Assembling of the Pyrrolidine Ring System

The first experiment according to this strategy starts from α,α'-dibromo adipic acid ester closed to a standard approach to 2,5-disubstituted pyrrolidines[16] (Scheme 6). We found that because of the intrinsic properties of the 4-aminopyridine structure the nucleophilic character of the amino group is strongly decreased which prevents ring closing reaction under mild conditions. Using of the more reactive disodium amide[1b] leads to decomposition of the α-bromoester.




Scheme 6: Disubstitution of 4-aminopyridine.

### 2.1.4 Preparative Approach from L-Glutamic Acid




a) $Pd(OAc)_2$, BINAP, $Cs_2CO_3$, toluene, 95 ¡C, 20 h, > 95 %. b) i: conc. aq. HCl, rt., 2 h; ii: $SOCl_2$, TFA, rt, 20 h; iii: methanol, reflux, 2-3 h; 69 % over three steps. c) i: DIBAH, $BF_3xEt_2O$, THF, -73 ¡C, 40 min.; ii: TMS-CN, TMS-OTf, $CH_2Cl_2$, rt, 20 min; iii: $CHCl_3$, HOAc, reflux, 6 h, 35 % over three steps, *cis* / *trans* ration = 2/1. d) i: conc. aq. HCl, 85 ¡C, 5 h; ii: EtOH, propene oxide, 78 %.

Scheme 7: Synthesis of *trans-N*-(4-pyridino)-pyrrolidin-2,5-dicarboxylic acid (**HS117**).

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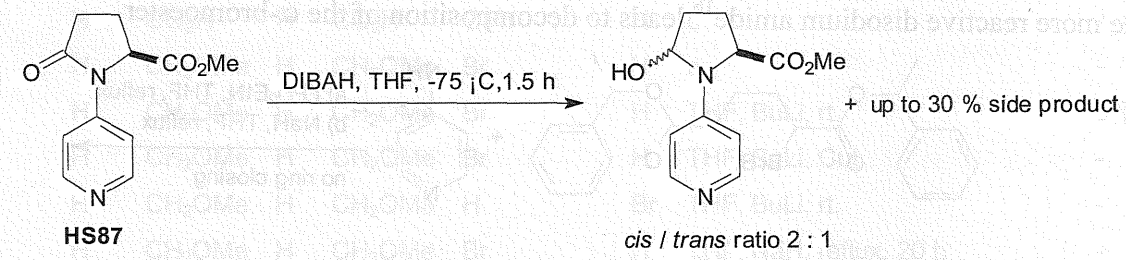
[15] Priem, G.; Anson, M.S.; Macdonald, S.J.F.; Pelotier, B.; Campbell, I.B. *Tetrahedron Lett.* **2002**, *43*, 6001.

[16] a) Koh, K.; Ben, R.N.; Durst, T. *Tetrahedron Lett.* **1994**, *35*, 375; b) Yamamoto, Y.; Hoshino, J.; Fujimoto, Y.; Ohmoto, J.; Sawada, S. *Synthesis* **1993**, 298.

A successful approach was developed starting from (*S*)-glutamic acid after its transformation to the di-*tert*-butyl ester[17]. (*S*)-Glutamic acid is a easily available starting material from chiral pool. The C-N bond formation with 4-bromopyridine using mild palladium mediated cross coupling conditions[18] occurs in excellent yield. After cleavage of the *tert*-butyl ester **HS84** with concentrated hydrochloric acid the resulting dicarboxylic acid was cyclised with thionyl chlorid in quantitative yield. The acid chloride was refluxed with methanol to obtain the methyl ester **HS87**. These conditions must be controlled carefully because also slowly ring opening occurs by acidic methanolysis.




**HS87**

*cis* / *trans* ratio 2 : 1

Scheme 8: DIBAH reduction of **HS87**.

The reduction of the amide carbonyl from *N*-pyridyl substituted pyroglutamic acid **HS87** forms a large amount of a side product by co-reduction of the ester moiety (Scheme 8). Experiments to optimize the selectivity by adjustment of DIBAH / substrate ration, time and temperature showed only very limited influence. Also a variety of alternative reducing reagents (Selectride, Super-Hydride, sodium borhydride) were checked regarding here selectivity of reduction without any promising result.

*N*-Benzyloxycarbonyl (Z-) protected pyroglutamic acid methyl ester is highly selective reduced by DIBAH only on the amide moiety[19]. If instead of Z-group a pyridyl moiety is located (**HS87**), as we found the selectivity of DIBAH reduction is dramatically reduced. This shows that the selectivity of reduction is strongly influenced by differentiation between the two carbonyl groups because of it different electronic properties. Enhanced discrimination can be accomplished by

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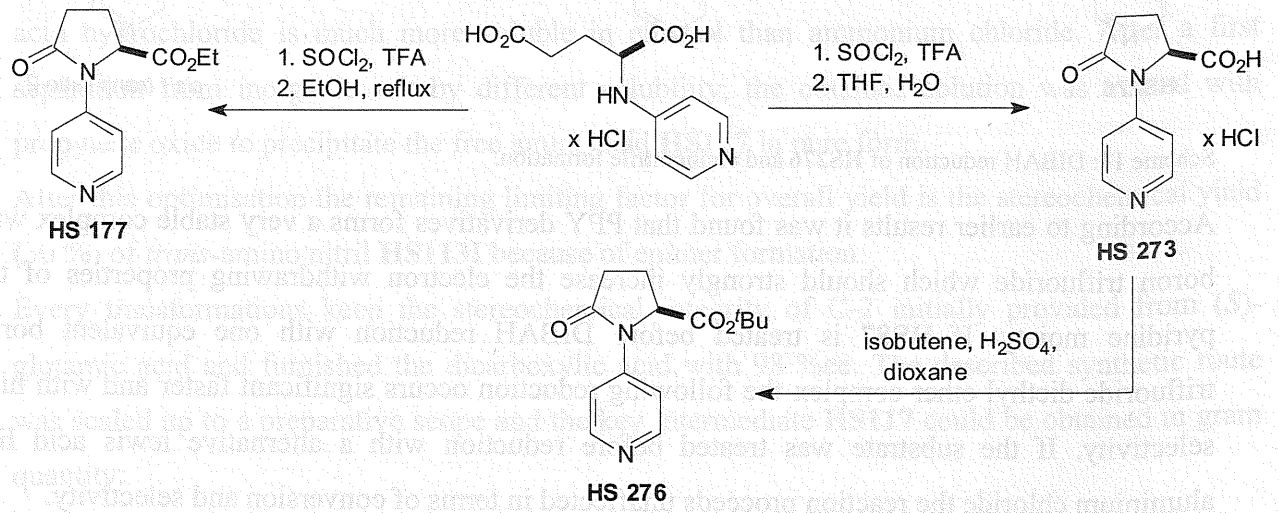
17 Anderson, G.W.; Callahan, F.M. *J. Am. Chem. Soc.* **1960**, *82*, 3359.

18 Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240.

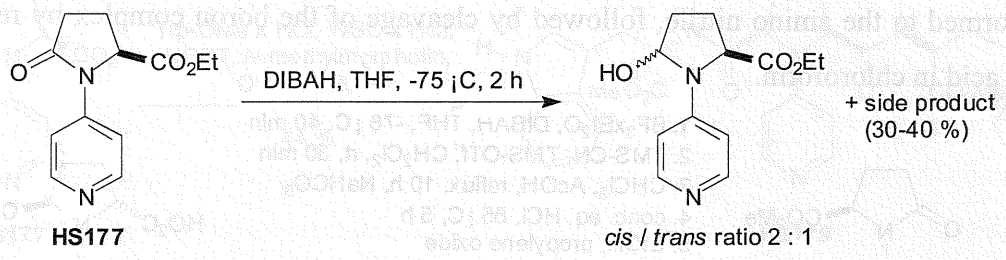
19 a) Katoh, T.; Nagata, Y.; Kobayashi, Y.; Arai, K.; Minami, J.; Terashima, S. *Tetrahedron* **1994**, *50*, 6221; b) Langlois, N.; Rojas-Rousseau, A.; Decavallas, O. *Tetrahedron Asymmetry* **1996**, *7*, 1095; c) Corey, E.J.; Yuen, P.; Hannon, F.J.; Wierda, D.A. *J. Org. Chem.* **1990**, *55*, 784.

changing the alcohol part of the ester to more electron pushing residues or by making the pyridine moiety stronger electron withdrawing.



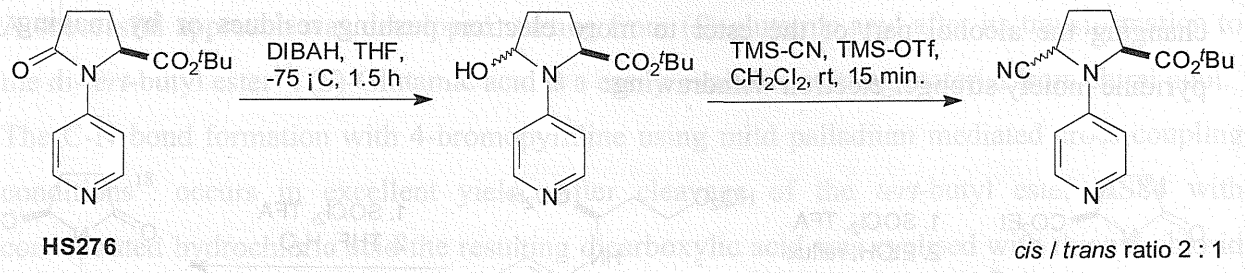

Scheme 9: Preparation of the ethyl and *tert*-butyl ester.

At first it was tried to increase the selectivity by changing the alcohol part of the ester. The ethyl ester **HS177** gives under the described condition practical the same product mixture like methyl ester **HS87**.




Scheme 10: DIBAH reduction of **HS117**.

The corresponding *tert*-butylester **HS276** is selectively reduced only on the amide moiety. However further transformation to the aminonitril showed that the *tert*-butyl group did not has any influence on the ration of epimer formation (1:2, *trans* is minor). Taking in account that the additional steps for preparation of the *tert*-butylester **HS276** lowers the overall yield, it seem that this rout is not much more applicable.



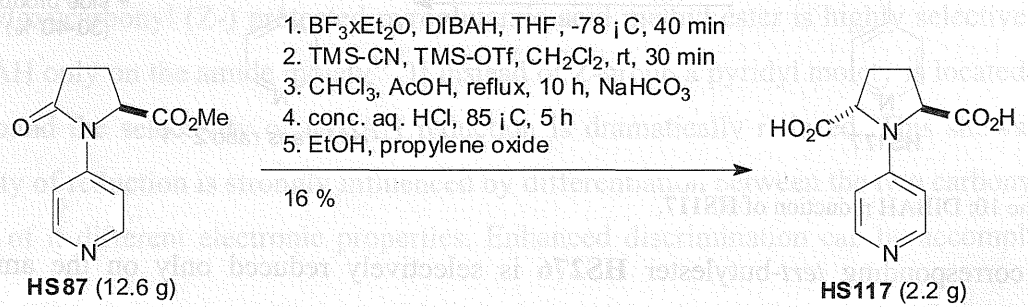

Scheme 11: DIBAH reduction of **HS276** and aminonitrile formation.

According to earlier results it was found that PPY derivatives forms a very stable complex with boron trifluoride which should strongly increase the electron withdrawing properties of the pyridine moiety. If **HS87** is treated before DIBAH reduction with one equivalent boron trifluoride diethyl ether complex the following reduction occurs significant faster and with high selectivity. If the substrate was treated before reduction with a alternative lewis acid like aluminium chloride the reaction proceeds unaffected in terms of conversion and selectivity.

After aqueous work up around 60 % of the product still appears as boron complex which can be easily assigned by proton NMR (broad signals of pyridine protons). Complete cleavage can be accomplished under basic ($CHCl_3$, $NEt_3$, reflux) or acidic conditions (HOAc, $CHCl_3$, reflux).

The obtained hemiaminal can be easily transformed to the aminonitrile by reaction with TMS-CN under TMS-triflate catalysis[20].

For large quantity the obtained crude material after DIBAH reduction was directly further transformed to the amino nitrile, followed by cleavage of the boron complex by refluxing with acetic acid in chloroform.




Scheme 12: Optimized synthetic sequence of for synthesis of **HS117** from **HS87**.

[20] DeGoey, D.A.; Chen, H.; Flosi, W.J.; Grampovnik, D.J.; Yeung, C.M.; Klein, L.L.; Kempf, D.J. *J. Org. Chem.* **2002**, 67, 5445.

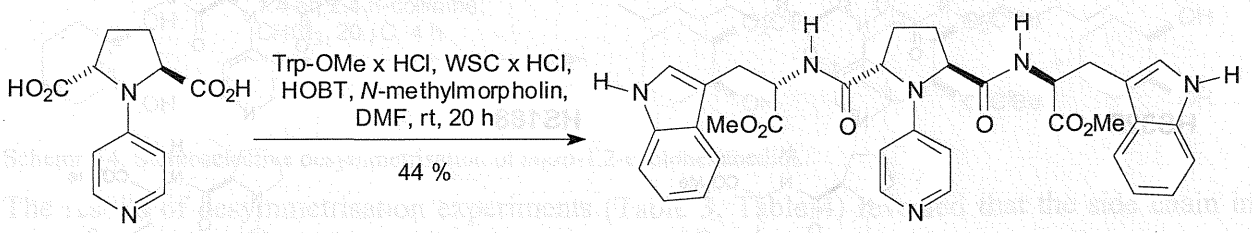
The obtained mixture of epimers **HS113I**, **HS113II** could be separate by flash chromatography. After saponification of the nitril moiety to the dicarboxylic acid the separation of the amino acid hydrochloride from the formed ammonium chloride is not simple. It was found that the amino acid hydrochloride is much more soluble in ethanol than ammonium chloride. After a first separation from inorganic salt by different solubility, the obtained solution was treated with propylene oxide to precipitate the free amino acid **HS117** in pure form.

After this optimisation the remaining limiting factor for overall yield is the stereochemical yield (30 %) of *trans*-amino nitril **HS113I** because of epimer formation.

Every transformations keep the stereochemical integrity of C-2 initially provided from (*S*)-glutamic acid and furnished the dicarboxylic acid with 98 %ee. The described synthetic route was scaled up to a preparative scope and the key intermediate **HS117** could be obtained in gram quantity.

## 2.2 Synthesis of Catalysts

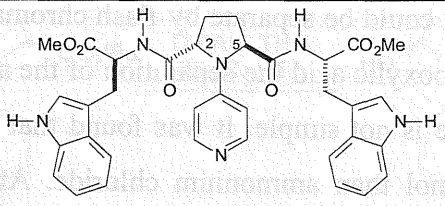
For preparation of catalysts the carboxylic acid **HS117** was condensed with the corresponding amine or alcohol after its activation with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and addition of 1-hydroxy benzotriazol (HOBT).



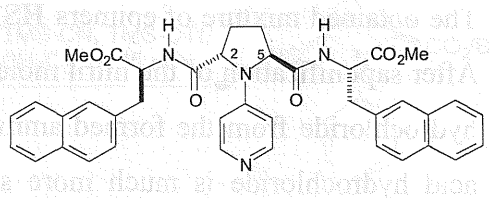

**HS177** **HS179**

Scheme 13: Example for synthesis of a $C_2$-symmetric catalyst.

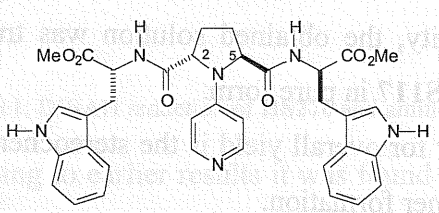
As solvent usually dichloromethane was used. In some cases DMF was necessary to proceed successful coupling reaction. After aqueous work up the obtained crude material was analysed by proton NMR. In any case no remarkable indication for racemization could be found. Than the crude products were purified according to appearance by flash chromatography, preparative TLC (chloroform / methanol) or recrystallization. In some cases (**HS356**, **HS187**) the products are extremely insoluble in organic solvents and they could be isolated just by filtration and washing.



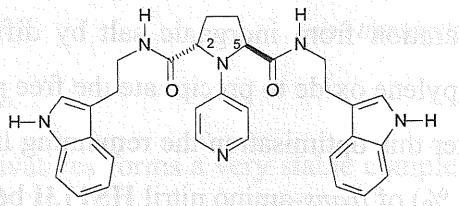

HS179



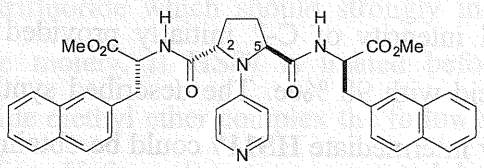

HS187



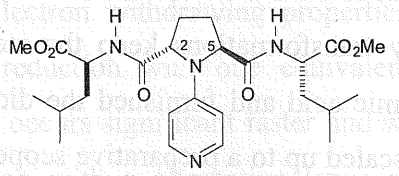

HS197



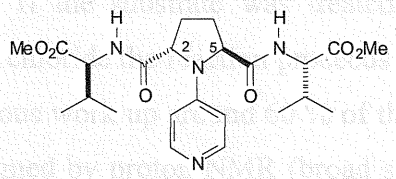

HS201



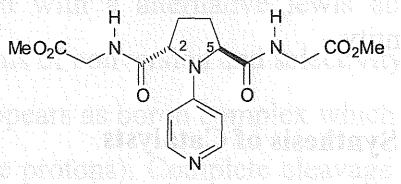

HS202



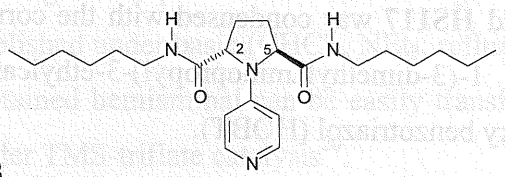

HS220



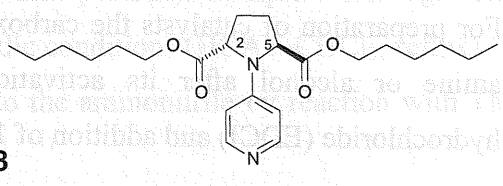

HS265



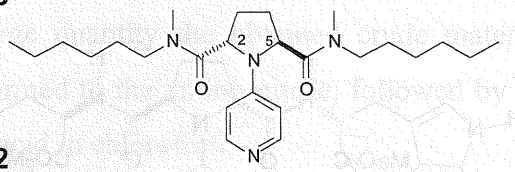

HS213



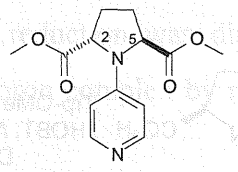
HS308



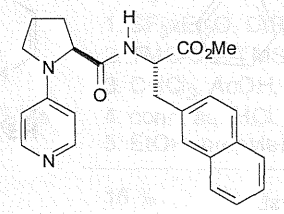
HS318



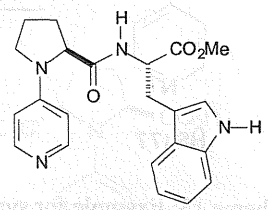
HS322



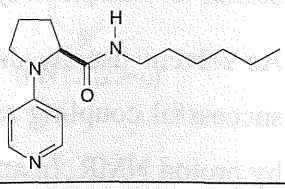
HS188




HS340




10



HS339

Table 2: Synthesized chiral PPY based catalysts.

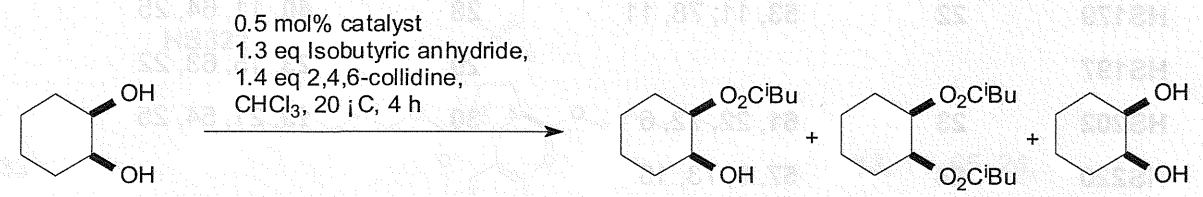
## 2.3 Desymmetrisation of *meso*-Diols

### 2.3.1 Influence of Side Chain and Substrate

To prove the hypothesis that the achieved stereoselectivity depends from a facial shielding effect of the side chain, a number of different side chains were introduced. Especially it was assumed that aromatic side chains and the acylpyridinium intermediate are interacting, because of π,π-interactions, which leads to a special shaped geometry of the catalyst. For the introduced side chains in particular the following characteristics can be distinguished:

- aromatic side chain (**HS201**)
- aromatic side chain with chiral carbon (**HS179**, **HS187**, **HS197**, **HS202**)
- alkyl side chain (**HS213**)
- alkyl side chain with chiral carbon (**HS220**, **HS265**)
- *n*-alkyl side chain (**HS308**)

For desymmetrisation experiments the corresponding *meso*-diol were acylated under standard conditions (Scheme 14) and the ratio of products and the enantiomeric excess of the monoacylated product were determined.




Scheme 14: Stereoselective desymmetrisation of *meso*-1,2-cyclohexanediol.

The results of desymmetrisation experiments (Table 3, Table 4) revealed that the side chain in general has a minor influence on the observed stereoselectivity. For *meso*-1,2-cyclohexanediol (entry **2-10**) nearly any catalysts shows a selectivity between 70-80 %ee. Aromatic (entry **2**, **3**, **4**, **5**, **6**) as well as alkyl side chains (entry **7**, **8**, **9**) leads to comparable results. Even more a additional chiral carbon in the side chain did not have a remarkable effect on stereoselectivity. Surprisingly a *n*-hexyl side chain shows also for different substrates one of the best stereoselectivity (entry **10**, **20**, **26**). This makes clear, that in case of aromatic side chains, π,π-interactions if existing they are not essential for stereoselectivity and that they having no direct influence on stereoselectivity.

| Catalyst | Entry | *meso*-1,2-Cyclohexanediol | Entry | *meso*-1,3-Cyclohexanediol |
|---|---|---|---|---|
| **PPY** | **1** | **0**, 3, 75, 22 | **11** | **0**, 4, 35, 39 |
| **HS179** | **2** | **73**, 0, 85, 15 | **12** | **37**, 6, 62, 32 |
| **HS197** | **3** | **54**, 12, 70, 18 | **13** | **0**, 8, 59, 33 |
| **HS201** | **4** | **72**, 10, 74, 16 | **14** | **38**, 10, 69, 21 |
| **HS187** | **5** | **74**, 5, 70, 25 | **15** | **27**, 9, 48, 43 |
| **HS202** | **6** | **83**, 9,77, 14 | **16** | **20**, 21, 49, 30 |
| **HS220** | **7** | **81**, 5, 75, 20 | **17** | **19**, 6, 62, 33 |
| **HS265** | **8** | **54**, 6, 76, 18 | | |
| **HS213** | **9** | **71**, 9, 72, 19 | **19** | **26**, 28, 60, 12 |
| **HS308** | **10** | **87**, 3, 75, 23 | **20** | **31**, 7, 69, 24 |

Table 3: Desymmetrisation of *meso*-1,2-cyclohexanediol and *meso*-1,3-cyclohexanediol as function of different side chains (data are reported as %ee of monoacylated compound, %starting material, %monoacylated, %diacylated, 20 ¡C, $CHCl_3$).

| Catalyst | Entry | *meso*-2,3-Butanediol | Entry | *meso*-Hydrobenzoin |
|---|---|---|---|---|
| **PPY** | **21** | **0**, 5, 75, 20 | **27** | **0**, 14, 54, 32 |
| **HS179** | **22** | **53**, 11, 78, 11 | **28** | **40**, 11, 64, 25 |
| **HS197** | | | **29** | **23**, 15, 63, 22 |
| **HS202** | **23** | **61**, 22, 72, 6 | **30** | **19**, 21, 54, 25 |
| **HS220** | **24** | **57**, 9, 73, 18 | | |
| **HS213** | **25** | **62**, 7, 77, 16 | | |
| **HS308** | **26** | **66**, 9, 78, 13 | | |

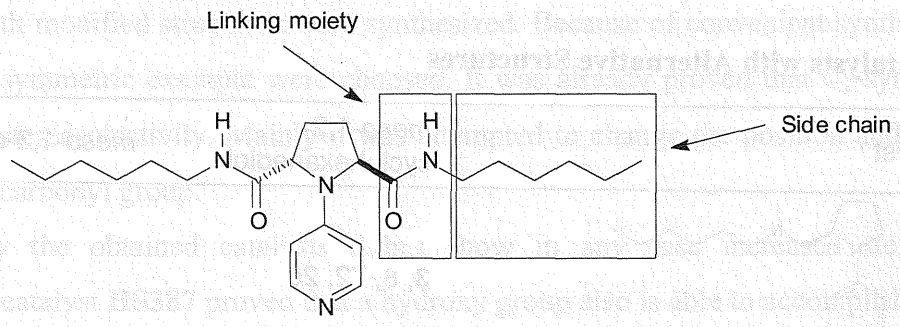
Table 4: Desymmetrisation of *meso*-2,3-butanediol and *meso*-hydrobenzoin as function of different side chains (data are reported as %ee of monoacylated compound, %starting material, %monoacylated, %diacylated, 20 ¡C, $CHCl_3$).

However different *meso*-diols shows very different stereoselectivity. The obtained results are in between excellent and poor stereoselectivity. It can be assumed that this is an strong evidence that the substrate plays also an important role in the mechanism of stereoselection.

### 2.3.2 Influence of the Linking Moiety

Typically side chains were linked *via* amide bond obtained from coupling with primary amines. As alternative structures it was tried to introduce side chains by ester or amides formed with

secondary amines (Table 5). In every cases catalysts with dramatic decreased stereoselectivity were obtained.




Scheme 15: Linking moiety and side chain of catalyst **HS308**.

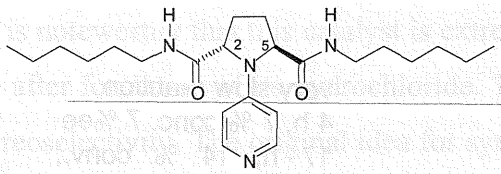
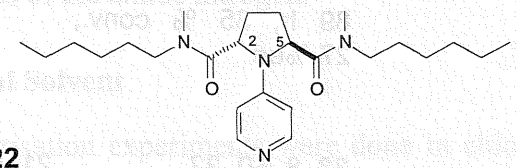
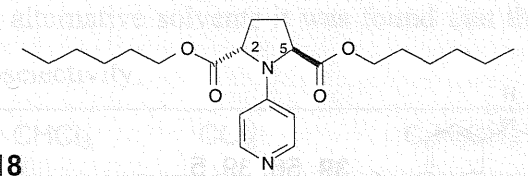
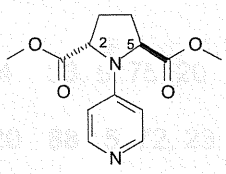
| Entry | Catalyst | *meso*-1,2-Cyclohexanediol |
|---|---|---|
| **31** |  **HS308** | **87**, 3, 75, 23 |
| **32** |  **HS322** | **13**, 6, 79, 15, |
| **33** |  **HS318** | **13**, 11, 65, 24, |
| **34** |  **HS188** | **10**, 9, 67, 24, |

Table 5: Influence of the linking moiety on stereoselectivity of *meso*-diol desymmetrisation (data are reported as %ee of monoacylated compound, %starting material, %monoacylated, %diacylated, 20 ¡C, $CHCl_3$).

This type of strong influence also was also recently described for another PPY analogues[21,1a]. According to this interesting effect it can be assumed that the linking moiety, which is directly

[21] Jarvo, E.R.; Copeland, G.T.; Papaioannou, N.; Bonitatebus, P.J.; Miller, S.J. *J. Am. Chem. Soc.* **1999**, *121*, 11638.

attached to the pyrrolidine ring of the PPY core, plays a essential role for stereoselectivity (Scheme 15).

### 2.3.3 Catalysts with Alternative Structures

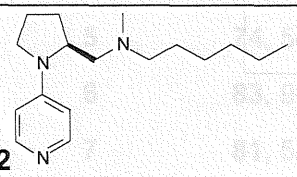
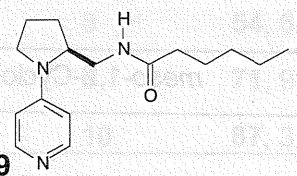
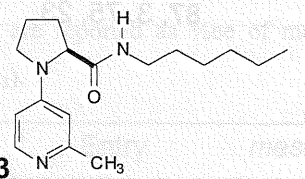
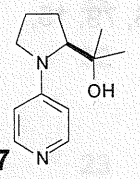
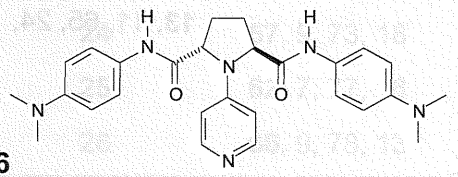
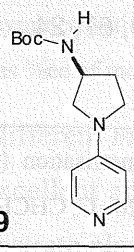
| Catalyst | *meso*-1,2-cyclohexanediol | *meso*-1,3-cyclohexanediol |
|---|---|---|
|  **HS362** | **3**, 8, 72, 20 | |
|  **HS379** | **23**, 6, 68, 26 | **12**, 16, 42, 42 |
|  **HS393** | very slow reaction<br>4 h, 7 % conc. 7 %ee<br>17 h, 14 % conv., 30 %ee<br>89 h, 35 % conv., 27 %ee | |
|  **HS387** | **38**, 8, 60, 32 | **21**, 9, 43, 48 |
|  **HS356** | **39**, 56, 39, 5 | |
|  **HS239** | **0**, 4, 70, 26 | **0**, 9, 44, 47 |

Table 6: Desymmetrisation experiments using PPY based catalysts with alternative structure (data are reported as %ee of monoacylated compound, %starting material, %monoacylated, %diacylated, 20 ¡C, $CHCl_3$, 5 mol% catalyst).

In order to experiments which shows the importance of the amide moiety for stereoselectivity it was tried to get more informations about this process. For this purpose several examples of PPY analogues with modified structures were synthesized. Because of convenient synthetic approach only non $C_2$-symmetric example were choosed. It was already proved that $C_2$-symmetry is not essential for stereoselectivity. Mainly it was attempted to change the position and properties of nitrogen and carbonyl group.

Unfortunately the obtained catalysts didn t show in any case increased stereoselectivity. Interestingly catalyst **HS387** proved that a hydroxy group also is able to accomplish considerable stereoselectivity. However it is essential that this hydroxy group can not be acylated under desymmetrisation conditions. This shows ones more that H-bonding between catalyst and substrate is crucial for stereoselective desymmetrisation with this type of PPY catalysts. In case of catalyst **HS356** it is noteworthy that this catalyst is extremely insoluble in any solvent, except in water and DMSO after formation of its hydrochloride. This may be is mainly responsible for the observed low stereoselectivity. The original idea for synthesis of **HS356** was to moderate the electronic properties of the amide nitrogen.

### 2.3.4 Influence of Solvent

Usually desymmetrisation experiments were done in chloroform as solvent. After the reaction were conducted in alternative solvents it was found that the nature of solvent also has a strong influence on stereoselectivity.

| catalyst | $CHCl_3$ | $CCl_4$ | $C_6H_5CH_3$ | THF | $CH_3CN$ |
|---|---|---|---|---|---|
| *meso*-1,2-Cyclohexanediol | | | | | |
| **HS202** | **83**, 9,77, 14 | **93**, 5, 75, 20 | **91**, 6, 75, 19 | **51**, 15, 57, 28 | **34**, 8, 69, 23 |
| **HS220** | **81**, 5, 75, 20 | **88** , 5, 72, 23 | **76**, 7, 70, 23 | | |
| **HS308** | **87**, 3, 75, 23 | **86**, 7, 70, 23 | **84**, 10, 73, 17 | | |
| *meso*-1,3-Cyclohexanediol | | | | | |
| **HS308** | **31**, 7, 69, 24 | | | **6**, 9, 46, 45 | |

Table 7: Influence of solvent on stereoselectivity of desymmetrisation (data are reported as %ee of monoacylated compound, %starting material, %monoacylated, %diacylated, at 20 ¡C).

As general trend it was found that desymmetrisation in less polar solvents proceeds with significant higher stereoselectivity, while polar solvents strongly causes decreasing of stereoselectivity. Some catalysts and some diols shows in less polar solvents low solubility. Because of this results it can be supposed that H-bonding plays an important role. There fore solvents with strengthening of intermolecular H-bonding enhances stereoselectivity.

### 2.3.5 Influence of Temperature

In order to improve the stereoselectivity of *meso*-diol desymmetrisation, further experiments were conducted at lower temperature. In many cases desymmetrisation at low temperature occurs with strong enhanced stereo- and chemical selectivity. However, especially reactions which occurs at 20°¡C already with high selectivity shows less influence of lower temperature on stereoselectivity. This conditions are limited by solubility problems of substrate and catalyst at low temperature. Also in some cases the conversion rate decreased dramatically. The solubility problems of the catalyst can be overcome by introduction of a *n*-hexyl side chain (catalyst **HS308**) which enables sufficient solubility.

| catalyst | Diol | 20 ¡C | -40 ¡C | -60 ¡C |
|---|---|---|---|---|
| | *meso*-1,2-Cyclohexanediol | | | |
| **HS220** | | **81**, 5, 75, 20 | **87**, 9, 85, 6 | |
| **HS308** | | **87**, 3, 75, 23 | **88**, 4, 92, 5 | |
| **HS188** | | **10**, 9, 67, 24 | **30**, 39, 55, 6 | |
| | *meso*-2,3-butanediol | | | |
| **HS220** | | **57**, 9, 73, 18 | **85**, 14, 82, 4 | **92**, 39, 61, <1 |
| **HS308** | | **66**, 9, 78, 13 | | **87**, 21, 72, 7 |
| | *meso*-Hydrobenzoin | | | |
| **HS179** | | **40**, 11, 64, 25 | **61**, 39, 55, 6, | |

Table 8: Influence of temperature on desymmetrisation reaction (data are reported as %ee of monoacylated compound, %starting material, %monoacylated, %diacylated, $CHCl_3$, 5 mol% catalyst).

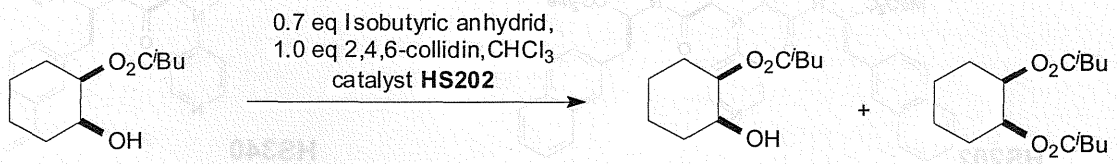
### 2.3.6 Influence of Stoechiometric Factors

For characterisation of the general catalytical properties the desymmetrisation reaction was also investigated as function of the amount of catalyst. Usually experiments were run with the average concentration for catalysts in organic synthesis of 5 mol%. The concentration of the catalyst was than successive reduced. It was found that also at a ten times lower concentration (0.5 mol%) the catalyst reached full stereoselectivity. At one hundred times lower concentration (0.05 mol%) the catalyst is still highly active, but the reaction time becomes noticeable slowly and the monoacylated compound were obtained in 15 % lower enantiomeric excess.

| time (h) | amount of catalyst | | |
|---|---|---|---|
| | 5 mol% | 0.5 mol% | 0.05 mol% |
| 2 | | | **65**, 68,30, 2 |
| 4 | **87**, 3, 75, 23 | | |
| 6 | | | **75**, 53, 43, 4 |
| 8 | | **83**, 6, 74, 20 | |
| 24 | **90**, 4, 79, 17 | **90**, 3, 76, 20 | **74**, 24, 66, 10 |
| 48 | | | **77**, 16, 75, 9 |
| 96 | | | **75**, 9, 77, 14 |

Table 9: Desymmetrisation of *meso*-1,2-cyclohexanediol with different amount of catalyst, $CHCl_3$, 20 ¡C, 1.3 eq isobutyric anhydride, 1.4 eq 2,4,6-collidine, catalyst **HS308** (data are reported as %ee of monoacylated product, %starting material, %monoacylated, %diacylated).

During desymmetrisation reaction also further diacylation of already formed mono acylated product takes place. Diacylation of *cis*-1,2-cyclohexanediol isobutyrate proceeds with a selectivity factor of S = 8.




racemic

conversion 53 % (23 h)
recovered substrate 67 % ee (S = 8)

Scheme 16: Kinetic resolution of *rac-cis*-1,2-cyclohexanediol isobutyrate.

Because of this, simultaneously increasing of enantiopurity of monoacylated product occurs through chiral resolution. The conversion rate of diacylation (18 % after 2 h, 53 % after 23 h) is much more lower than monoacylation. Diacylation can be forced by addition of excess anhydride combined with prolonged reaction time. Under this conditions the starting material can be fully consumed and the monoacylated product can be obtained in excellent enantiopurity.

| equivalents of isobutyric anhydride | | |
|---|---|---|
| 1.0 eqv | 1.3 eqv | 1.6 eqv |
| **81**, 9, 84, 7 | **90**, 4, 79, 17 | **>98**, 0, 59, 41 |

Table 10: Desymmetrisation of *meso*-1,2-cyclohexanediol as function of the amount of isobutyric anhydride, 1.7 eq 2,4,6-collidine, 5mol% catalyst **HS308**, $CHCl_3$, 24 h, 20 ¡C (data are reported as %ee of monoacylated product, %starting material, %monoacylated, %diacylated).

### 2.3.7 Influence of $C_2$-Symmetry

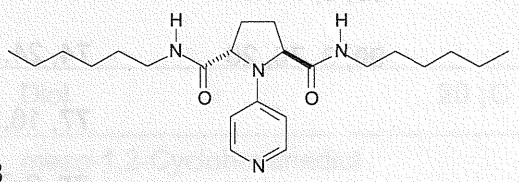
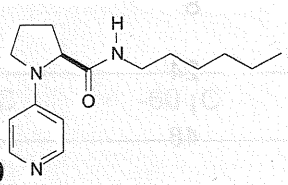
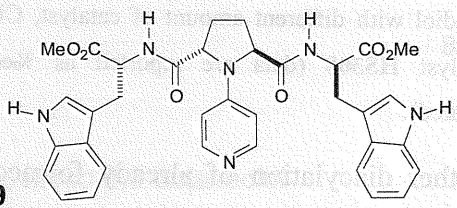
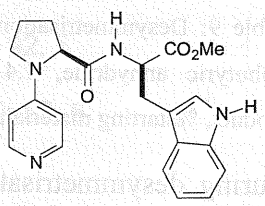
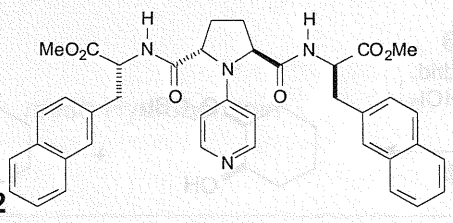
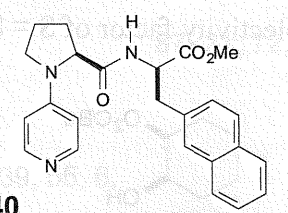
| $C_2$-symmetric | non $C_2$-symmetric |
|---|---|
|  **HS308** **87**, 3, 75, 23 |  **HS309** **76**, 4, 70, 26 |
|  **HS179** **73**, 0, 85, 15 |  **10** **56**, 1, 78, 21 |
|  **HS202** **83**, 9,77, 14 |  **HS340** **41**, 5, 61, 34 |

Table 11: Comparison of the catalytical properties of $C_2$-symmetric and non $C_2$-symmetric catalysts (data are reported as %ee of monoacylated product, %starting material, %monoacylated, %diacylated, 20 ¡C, $CHCl_3$, 4 h).

On three examples each of $C_2$-symmetric and non $C_2$-symmetric catalysts the influence of $C_2$-symmetry was studied. According to this results it is doubtless that $C_2$ symmetry leads to clearly increased stereoselectivity for the here examined desymmetrisation of *meso*-1,2-cyclohexanediol. As it is expected the interaction of side chain (linking moiety) and substrate is a crucial point. In case of the $C_2$-symmetric catalyst, both sides of the molecule became equal and can participate in the same manner.

### 2.3.8 Stability of Monoacylation Products

After stereoselective acylation of *meso*-2,3-butanediol, the enantiomeric purity of the monoacylation product was determined directly from the reaction mixture. Than the monoacylation product was isolated by preparative TLC and the enantiomeric purity was determined again. The isolated product was leaved as chloroform solution at ambient temperature and the enantiomeric purity was observed over a period of time. The results shows clearly a slowly decreasing of enantiomeric purity, probably because of a intramolecular acyl transfer process.

In case of *cis*-1,2-cyclohexanediol isobutyrate the enantiomeric purity did not change after storing the neat substance for one month at ambient temperature.

| time | 4 h (reaction mixture) | 24 h (after PTLC) | 48 h | 96 h | 168 h |
|---|---|---|---|---|---|
| %ee | 88 | 84 | 80 | 75 | 71 |

Table 12: Stability of *cis*-2,3 butanediol isobutyrate in Chloroform at ambient temperature.

# 3 Summary

A new class of $C_2$-symmetric PPY type catalysts based on *trans*-*N*-(4-pyridino)-pyrrolidin-2,5-dicarboxylic acid (**HS117**) has been developed. For the PPY core **HS117** a preparative synthetic approach starting from L-glutamic acid was established. From **HS117** a number of catalysts were obtained by attaching of various side chains. For extensive characterisation of the catalytic properties, the catalysts were used for desymmetrisation of different *meso*-diols.

According to the obtained results it is supposed that the stereoselective acylation occur through a new principle, based on complex formation between catalyst and substrate because of H-bonding. In opposite to stereoselective catalysis based on sterical repulsion, an acceleration of the preferred acylation takes place. As result the new type of catalyst shows unchanged high catalytic activity even at low concentration up to 0.5mol%.

As conditions for high stereoselectivity the catalyst requires a amide moiety closed to the pyrrolidine ring of PPY. Alternatively also a hydroxy group which can not be acylated because of sterical shielding achieves good stereoselectivity. Since the substrate also is directly involved in the process of stereoselection, it needs closed to the acylated hydroxy group another moiety which is able to interact by H-bonding. So fare with simple secondary alcohols stereoselective acylation can not be achieved. Further the solvent plays an important role. In general in less polar solvents like tetrachloromethan, chloroform, toluene high stereoselectivity is achieved, whereas in polar solvents like acetonitrile or tetrahydrofurane lack of stereoselectivity was observed.

As shown the $C_2$-symmetry of the catalyst is not essential for stereoselectivity but leads to a strong increasing of stereoselectivity.

For some examples of *meso*-diols the described catalytic principle achieves acylative desymmetrisation in high up to excellent stereoselectivity.

| Diol | %ee | % yield | |
|---|---|---|---|
| *meso*-1,2-Cyclohexanediol | 98 | 59 | Table 10 |
| *meso*-1,3-Cyclohexanediol | 38 | 69 | Table 3 |
| *meso*-2,3-Butanediol | 92 | 61 | Table 8 |
| *meso*-Hydrobenzoin | 61 | 55 | Table 8 |

# 4 Experimental Section

**General.** Melting points (uncorrected) were obtained on a Yanagimoto micro-point apparatus. Analytical thin layer chromatography (TLC) was performed using commercial glass plates bearing 0.25 mm layer of Merck Kiesel-Gel 60 $F_{254}$. For preparative TLC plates with 0.5 mm layer were used. Flash column chromatography was carried out with Silica Gel 60N (40-100 µm) from Kanto Chemical Co., Inc. If not mentioned others NMR spectra were obtained with a Varian Gemini 200 ($^1$H 199.977 MHz, $^{13}$C 50.289 MHz). In some cases also a JEOL LNM-AL 300 and a JEOL JMN-GX 400 spectrometer were used. $^1$H data are reported as: chemical shift (ppm) downfield from tetramethylsilane, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration. $^{13}$C chemical shifts are reported downfield from tetramethylsilane. Specific rotation were measured with a Horiba SEPA-200 automatic digital polarimeter. MS spectra were recorded with a JEOL JMS-DX300 mass spectrometer. Infrared spectra were obtained on a JASCO FT / IR-300. GC was performed on a γ-DEX 225 cappillary column (30 m × 0.25 mm × 0.25 µm). HPLC was performed on a Chiralcel OJ column (4.6 mm × 25 cm) with hexane and 5 % isopropanol at 0.5 ml × min.$^{-1}$ flow rate. As dry solvents guaranteed solvents (<50 ppm water content) were used.

**(*S*)-*N*-Pyridyl glutamic acid di-*tert*-butyl ester (HS84):** Preparation of free 4-bromopyridine: To a solution of $NaHCO_3$ (8.0 g) in water (150 mL) 4-bromopyridine hydrochloride (18.0 g) was added portion wise with stirring. After complete dissolving 4-bromopyridne was separated as lower phase. After drying over $Na_2SO_4$ free 4-bromopyridine was obtained as colourless liquid (at room temperature rapid decomposition to yellow and finaly red solid). This predried material (10.0 g) was diluted with toluene (50 mL) and stirred again with $Na_2SO_4$. After filtration this solution was used for palladium coupling. Coupling reaction: $Pd(OAc)_2$ (650 mg, 2.9 mmol) *rac*-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (BINAP) (3.6 g, 5.8 mmol) and $Cs_2CO_3$ (21.0 g, 63.6 mmol) were suspended in toluene (300 mL) and a mixture of 4-bromopyridine (10.0 g, 63.6 mmol, in 50 mL toluene ) and L-glutamic acid di-*tert*-butylester (15.0 g, 57.8 mmol) were added. After bubbling with argon (10 min) the mixture was stirred at 90-100 ¡C for 20 h. After cooling to rt EtOAc (700 mL) was added followed by washing with $NaHCO_3$ solution and brine (150 mL each). Drying over $MgSO_4$ and evaporation furnished **HS84** as sticky red brown oil (24.0 g). For the further described transformations this crude product was used. Pure **HS84** was obtained by

further chromatographic purification (EtOAc/MeOH/1/1) as colourless sticky oil in 92 % yield: $^1$H NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.43 (s, 9H), 2.01-2.10 (m, 2H), 2.30-2.38 (m, 2H), 4.08 (m, H), 5.13 (d, 8.0, H), 6.43 (dd, 5.0, 1.6, 2H), 8.16 (dd, 5.0, 1.6, 2H); $^{13}$C NMR ($CDCl_3$) δ 27.52, 28.12, 28.20, 31.47, 55.27, 80.93, 82.57, 108.08, 149.97, 152.52, 171.66, 172.15; IR (film) 1715, 1605, 1522 $cm^{-1}$; $[\alpha]^D$ -20 (c 1, $CHCl_3$); EI-MS m/z (%) 336 (13, $M^+$), 280 (16), 263 (9), 224 (38), 207 (61), 179 (100), 161 (82), 133 (36), 105 (13), 78 (9); HRMS calculated for $C_{18}H_{28}N_2O_4$ 336.2049, found 336.2034.

**(*S*)-*N*-(4-Pyridyl)-2-methoxycarbonyl-5-oxo pyrrolidine (HS87):** Crude **HS84** (24.0 g) was dissolved in concd aq HCl (100 mL) and kept at rt for 2 h. After dilution with water (100 mL) removing of precipitated BINAP by filtration and evaporation a sticky clear red brown oil (15.8 g) remains. After dissolving in trifluoro acetic acid (10 mL) $SOCl_2$ (40 mL) was carefully added. After stirring for 20 h at rt excessive thionyl chloride was removed in vacuum and the obtained solid residue was dissolved in MeOH (500 mL) and heated to refluxed for 2-3 h ($^1$H-NMR reaction control in $D_2O$). Evaporation furnished a dark oil (18.0 g) which was dissolved in water (250 mL). Solid materials were removed by filtration over celite and than $NaHCO_3$ (20.0 g) were added. Extraction with EtOAc (5×100 mL) drying over $Na_2SO_4$ and evaporation gave a green oil (11.3 g). Purification by flash chromatography (EtOAc/MeOH/5/1) gave **HS87** as slightly brownish slowly crystallising oil (8.8 g, 69 %): $^1$H NMR ($CDCl_3$) δ 2.11-2.25 (m, H), 2.39-3.72 (m, 3H), 3.73 (s, 3H), 4.72 (dd, 9.0, 2.4, H), 7.45 (dd, 4.9, 1.6, 2H), 8.47 (dd, 4.9, 1.6, 2H); $^{13}$C NMR ($CDCl_3$) δ 23.04, 31.26, 53.12, 60.02, 113.14, 145.17, 150.68, 171.61, 174.86; IR (film) 3000, 1722, 1712, 1590, 1500, 1380 $cm^{-1}$; $[\alpha]^D$ -48 (c 1, $CHCl_3$); mp 60-65 ¡C; EI-MS m/z (%) 220 (25, $M^+$), 161 (100), 133 (14), 105 (8), 78 (11); EA calc (found) C 59.99 (59.70), H 5.49 (5.58), N 12.72 (12.57).

**(*trans*)-/ (*cis*)-4-(*N*-5-Cyano-2-methoxycarbonylpyrrolidino)pyridine (HS113I, HS113II):** **HS87** (12.6 g, 57.6 mmol) was dissolved in THF (250 ml) after cooling to –75 ¡C $BF_3$ $Et_2O$ complex (7.2 ml, 57.6 mmol) was added follow by DIBAH (118 ml, 0.95 mol/L, hexane solution), after stirring for 40 min the reaction mixture was poured into sodium potassium tartrate solution (126 g in 370 ml water) and stirred for 2 h. Separation and extraction with EtOAc (4×100 ml) gave after drying over $Na_2SO_4$ and evaporation the crude material (12.9 g). These product was dissolved in $CH_2Cl_2$ (400 ml) and TMS-CN (18.6 ml, 139 mmol) and TMS-

OTf (16.4 ml, 91 mmol) were added successive under cooling with ice water. After removing of the cooling bath the mixture was stirred for 30 min at rt and than poured into $NaHCO_3$ solution and stirred for 30 min (Caution high concentration of hydrogen cyanide!). After separation, extraction with EtOAc (4×100 ml) and drying over $Na_2SO_4$ followed by evaporation, the remaining residue was dissolved in $CHCl_3$ (250 ml) and after addition of AcOH (25 ml) refluxed for 12 h. The reaction mixture was carefully poured into $NaHCO_3$ solution (50 g in 300 ml water). After separation, extraction with EtOAc (4×100 ml), drying over $Na_2SO_4$ and evaporation the crude material (9.6 g) was obtained. The epimer mixture was separated by flash chromatography (ether/methanol/6/1) after addition of 2-mercaptopyridine (2.0 g) and furnished the *trans*-epimer **HS113I** (2.9 g, 22 %) and *cis*-epimer **HS113II** (4.6 g, 35 %) as yellowish oily liquids: **HS113I** (2*S*,5*S*) $^1$H NMR ($CDCl_3$) δ 2.25-2.62 (m, 4H), 3.76 (s, 3H), 4.45 (m, H), 4.68 (m, H), 6.50 (dd, 4.8, 1.7, 2H), 8.37 (dd, 4.8, 1.7, 2H); $^{13}$C NMR ($CDCl_3$) δ 29.53, 29.65, 48.77, 52.91, 59.93, 108.19, 117.96, 148.90, 150.43, 172.15; IR (film) 1740, 1595, 1510, 1380 cm$^{-1}$; $[\alpha]^D$ -235 (c 1, $CHCl_3$); EI-MS m/z (%) 231 (35, $M^+$), 172 (100), 145 (61), 105 (10); HRMS calculated for $C_{12}H_{13}N_3O_2$ 231.10077, found 231.1006. **HS113II** (2*S*,5*R*) $^1$H NMR ($CDCl_3$) δ 2.30-2.60 (m, 4H), 3.73 (s, 3H), 4.37 (m, H), 4.55 (m, H), 6.47 (dd, 4.9, 1.8, 2H), 8.30 (dd, 4.9, 1.6, 2H); $^{13}$C NMR ($CDCl_3$) δ 29.15, 30.00, 48.54, 52.66, 60.43, 107.70, 117.40, 148.87, 150.14, 171.81; IR (film) 1740, 1600, 1510, 1380 cm$^{-1}$; $[\alpha]^D$ +79 (c 1, $CHCl_3$); EI-MS m/z (%) 231 (20, $M^+$), 172 (100), 145 (25); HRMS calculated for $C_{12}H_{13}N_3O_2$ 231.10077, found 231.1010.

**(2*S*, 5*S*)-*N*-(4-Pyridino)pyrrolidin-2,5-dicarboxylic acid (HS117): HS113I** (2.9 g, 12.5 mmol) was dissolved in concd aq. HCl (18 ml) and after heating to 85 ¡C for 12 h evaporated. The remaining residue was treated with hot ethanol (20 ml) and after cooling and filtration from ammonium chloride treated with propene oxide (0.5 ml). Within 8 h the amino acid precipitates slowly. After collecting of the product and repetition of the procedure the pure product (2.2 g, 75 %) was obtained as crystalline white powder: $^1$H NMR ($D_2O$) δ 2.12-2.28 (m, 4H), 4.50 (d, 7.2, 2H), 6.56 (d, 7.4, 2H), 7.95 (d, 7.4, 2H); $^{13}$C NMR ($D_2O$/DCl) δ 28.09, 61.15, 108.46, 139.07, 155.20, 173.97; IR (KBr) 1730, 1645, 1580, 1540, 1400 cm$^{-1}$; $[\alpha]^D$ -202 (c 1, $H_2O$); mp from 260 ¡C decomposition; HRMS (HCl salt) calcd for $C_{11}H_{13}N_2O_4$ 237.0875, found 237.0877; EA calcd for $C_{11}H_{12}N_2O_4$×_$H_2O$ (found) C 54.87 (54.87), H 5.23 (5.25), N 11.63 (11.64).

**(*cis*)-*N*-(4-Pyridino)pyrrolidin-2,5-dicarboxylic acid hydrochloride (HS115): HS113b** (3.19 g, 13.8 mmol) were dissolved in concd aq HCl (15 mL) and heated to 85 ¡C for 5 h. After cooling to rt the product precipitates. Collection by filtration and washing with acetone gave **HS115** (2.6 g, 70 %) as colourless needles. $^{1}$H NMR ($D_2O$) δ 2.15-2.50 (m, 4H), 4.65 (m, partially overlapping with water signal), 6.74 (d, 6.5, 2H), 8.03 (d, 6.5, 2H); $^{13}$C NMR ($D_2O$) δ 28.48, 62.01, 108.44, 138.90, 155.62, 174.08; IR (KBr) 1740, 1640, 1595, 1540 cm$^{-1}$; mp 225-235 ¡C; FAB-MS m/z 237 ($M^+$); EA calcd for $C_{11}H_{12}N_2O_4$ (found) C 48.45 (48.28), H 4.81 (4.92), N 10.27 (10.33).

**HS177:** From 0.6 g of starting material 71 mg ester was obtained after preparative TLC (ethyl acetate/methanol/5/1) as colourless oil; $^{1}$H NMR ($CHCl_3$) δ 1.25 (t, J 7.4 Hz, 3H), 2.22-2.82 (m, 4H), 4.24 (q, J = 7.0 Hz, 2H), 4.74 (dd, J 9.0, 2.6 Hz, 1H), 7.52 (dd, J 5.0, 1.6 Hz, 2H), 8.54 (dd, J 5.0, 1.8 Hz, 2H).

**HS188: HS117** (30 mg, 0.11 mmol) was dissolved in MeOH (3.0 mL) and $SOCl_2$ (0.5 mL) was added drop wise at –30 ¡C. After refluxing for 1 h and evaporation the residue was dissolved in MeOH (1.0 mL) and $NEt_3$ (0.25 mL) was added. This mixture was evaporated and the residue extracted with $Et_2O$. Evaporation of the ether solution followed by preparative TLC ($CHCl_3$/MeOH/10/1) gave **HS188** (20 mg, 69 %) as colourless crystals: $^{1}$H NMR ($CDCl_3$) δ 2.16 (m, 2H), 2.52 (m, 2H), 3.75 (s, 6H), 4.51 (d, 8.0, 2H), 6.31 (dd, 4.8, 1.6, 2H), 8.25 (dd, 4.8, 1.8, 2H); $^{13}$C NMR ($CDCl_3$) δ 29.05, 52.65, 60.63, 107.75, 150.05, 150.28, 173.08; mp 128-130 ¡C; IR (KBr) 1740, 1600, 1515, 1395 [cm$^{-1}$]; $[\alpha]^D$ -143 (c 1, $CHCl_3$); HRMS calcd for $C_{13}H_{16}N_2O_4$ 264.111, found 264.1107; 98 % ee (HPLC, Chiralcell OD, hexane/2-propanol/diethylamin/80/20/0.1).

**HS239:** yield 50 %, $^{1}$H NMR ($CDCl_3$, 200 MHz) δ 1.46 (s, 9H), 2.00 (m, H), 2.30 (m, H), 3.20 (m, H), 3.21 (m, 2H), 3.60 (m, H), 4.40 (m, H), 5.03 (m, H), 6.39 (dd, 5.2, 1.6, 2H), 8.16 (dd, 5.2, 1.6, 2H).

**HS273:** yield 64 %, mp 210-215 ¡C (fused capillary), $[\alpha]^D$ –38.3 (c 1, $H_2O$); $^{1}$H NMR ($D_2O$) δ 2.20-2.74 (m, 4H), 5.03 (d, 8.8 Hz, H), 8.02 (d, 6.2 Hz, 2H), 8.50 (d, 6.4 Hz, 2H); HRMS (HCl salt) calcd for $C_{10}H_{10}N_2O_3$ 206.06914, found 206.0682.

**HS276: HS273** (0.3 g, 1.2 mmol) was suspended in dioxane (8 ml) after drop wise addition of concd sulphuric acid (1 ml) under ice water cooling isobutene (1 ml) was condensed into the

suspension followed by stirring at rt for 48 h. For workup the reaction mixture was poured into $NaHCO_3$ solution (30 ml). Extraction with ethyl acetate (4×10 ml), drying over $Na_2SO_4$ and evaporation followed by preparative TLC (ethyl acetate/methanol/5/1) gave 126 mg (41 %) of the pure compound as white crystalline solid; mp 110-115 ¡C; $[\alpha]^D$ –39.9 (c 1, $CHCl_3$); $^1H$ NMR ($CHCl_3$) δ 1.42 (s, 9 H), 2.18-2.89 (m, 4H), 4.62 (dd, J 8.8, 2.8 Hz, 1H), 7.52 (dd, J 4.8, 1.8 Hz, 2H), 8.54 (dd, J 4.8, 1.6 Hz, 2H); $^{13}C$ NMR ($CHCl_3$) δ 22.94, 27.94, 31.35, 61.04, 83.29, 113.28, 145.39, 150.67, 170.20, 174.90; IR (KBr) 3437, 2979, 1736, 1702 $cm^{-1}$.

**HS356:** $^1H$ NMR ($D_2O$/DCl, 300 MHz) δ 2.34 (m, 2H), 2.52 (m, 2H), 3.15 (s, 12H), 4.95 (d, 7.8, 2H), 6.79 (d, 7.8, 2H), 7.53 (m, 8H), 8.08 (d, 7.5, 2H).

**HS362:** $^1H$ NMR ($CDCl_3$, 200 MHz) δ 0.90 (t, 6.8, 3H), 1.29-1.38 (m, 8H), 1.90-2.50 (m, 11H), 3.16 (m, H), 3.40 (m, H), 3.86 (m, H), 6.42 (dd, 5.1, 1.6, 2H), 8.18 (dd, 5.1, 1.4, 2H); HRMS calculated for $C_{17}H_{29}N_3$ 275.236148, found 275.2369.

**HS379:** $^1H$ NMR ($CDCl_3$, 200 MHz) δ 0.89 (t, 7.2, 3H), 1.23-1.34 (m, 4H), 1.57-1.68 (m, 2H), 1.96-2.06 (m, 4H), 2.19 (t, 8.4, 2H), 2.95-3.20 (m, 2H), 3.40-3.60 (m, 2H), 3.98 (m, H), 6.48 (m, H), 6.63 (d, 6.0, 2H), 8.19 (d, 5.6, 2H); HRMS calculated for $C_{16}H_{25}N_3O$ 275.199763, found 275.1989.

**HS387:** Obtained after palladium coupling with (*S*)-dimethyl prolidin-2-yl methanol[22]; mp 165-167 ¡C; $^1H$ NMR ($CDCl_3$, 200 MHz) δ 1.21 (s, 3H), 1.28 (s, 3H), 1.80-2.20 (m, 4H), 3.30 (m, H), 3.55 (m, H), 3.91 (m, H), 6.68 (d, 5.2, 2H), 8.16 (d, 6.0, 2H); HRMS calculated for $C_{12}H_{18}N_2O$ 206.141913, found 206.1423.

**HS393:** PPY Core obtained after palladium coupling with 4-bromo-2-picoline[23]; mp 52-54 ¡C; $^1H$ NMR ($CDCl_3$, 200 MHz) δ 0.85 (m, 3H), 1.22 (m, 6H), 1.40 (m, 2H), 2.04 (m, 2H), 2.26 (m, 2H), 2.43 (s, 3H), 3.16-3.30 (m, 3H), 3.62 (m, H), 4.07 (m, H), 6.31 (m, 3H), 8.14 (d, 5.0, H); HRMS calculated for $C_{17}H_{27}N_3O$ 289.215413, found 289.215.

**General procedure for preparation of catalysts:** To the corresponding amino compound or alcohol (1.6 mmol) and **HS117** (130 mg, 0.55 mmol) dissolved in DMF or suspended in $CH_2Cl_2$ (10 mL) *N*-methylmorpholine (148 µl, 1.6 mmol) was added followed by 1-ethyl-3-(3-

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[22] Sibi, M.P.; Zhang, R.; Manyem, S. *J. Am. Chem. Soc.* **2003**, *125*, 9306.

[23] Ashimori, A.; Ono, T., Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446.

dimethylaminopropyl)carbodiimid hydrochlorid (EDCI) (312 mg, 1.6 mmol) and 1-hydroxybenzotriazol (HOBT) (222 mg, 1,6 mmol ). After stirring for 24 h the mixture was evaporated and after dissolving in EtOAc (200 mL) washed with $NaHCO_3$ solution and brine (10 ml). Drying over $Na_2SO_4$ and evaporation followed by chromatographic purification or re recrystallization gave the pure compound.

**HS179.** From (*S*)-tryptophane methyl ester hydrochloride in DMF as crystalline powder: yield 48 % (from methanol); $^1$H NMR (DMSO) δ 1.73 (m, 2H), 2.20 (m, 2H), 3.05 (dd, 14.6, 10.6, H), 3.24 (dd, 14.6, 4.2, H), 4.22 (d, 7.8, H), 4.53 (m, H), 5.78 (d, 6.0, H), 6.96-7.13 (m, 2H), 7.21 (s, H), 7.38 (d, 8.0, H), 7.55 (d, 7.2, H), 7.74 (d, 5.0, H), 8.68 (d, 8.4, H); $^{13}$C NMR (DMSO) δ 24.34, 26.62, 49.60, 50.36, 58.63, 104.93, 107.26, 108.99, 115.55, 115.99, 118.54, 121.27, 124.53, 133.67, 146.23, 147.45, 169.39, 169.74; IR (KBr) 3255, 1755, 1735, 1655, 1600 cm$^{-1}$; $[\alpha]^D$ –25.5 (c 0.5, DMSO); mp 223-225 ¡C; HRMS calcd for $C_{11}H_{13}N_2O_4$ 237.0875, found 237.0877; EA calcd for $C_{11}H_{13}N_2O_4$ (found) C 66.03 (65.91), H 5.70 (5.79), N 13.20 (13.00).

**HS187.** From (*S*)-Naphtylalanine methyl ester hydrochloride in DMF as white powder: yield 41 % (from isopropanole); $^1$H NMR (DMSO) δ 1.55 (m, 2H), 2.09 (m, 2H), 3.05 (dd, 13.0, 13.0, 2H), 3.34 (dd, 13.0, 4.0, 2H), 3,62 (s, 6H), 4.10 (d, 7.2, 2H), 4.60 (m, 2H), 5.53 (d, 6.2, 2H), 7.10 (d, 5.8, 2H), 7.41-7.55 (m, 6H), 7.76-7.94 (m, 8H), 8.66 (d, 8.4, 2H); $^{13}$C NMR (DMSO) δ 29.64, 37.14, 52.85, 53.69, 61.90, 107.99, 126.36, 126.83, 128.09, 128.27, 128.41 (two carbon atoms are overlapped), 132.60, 133.59, 135.88, 149.17, 150.36, 172.41, 172.52; IR (KBr) ν 3255, 1750, 1650, 1600 cm$^{-1}$; $[\alpha]^D$ 39 (c 0.25, MeOH); mp 225-228 ¡C; HRMS calcd for $C_{39}H_{39}O_6N_4$ 659.28696, found 659.2859.

**HS197.** From (*R*)-tryptophane methyl ester hydrochloride in DMF after flash chromatography (ethyl acetate/methanol/5/1) as crystalline powder: yield 34 %; $^1$H NMR ($CD_3OD$) δ 1.53 (m, 2H), 2.03 (m, 2H), 3.12 (dd, 14.9, 9.4, 2H), 3.31 (dd, 14.9, 4.4, 2H, overlapping with solvent), 3.71 (s, 6H), 4.29 (d, 7.8, 2H), 4.75 (dd, 9.2, 4.8, 2H), 6.28 (d, 6.8, 2H), 6.90-7.13 (m, 8H), 7.33 (d, 8.0, 2H), 7.45 (d, 7.4, 2H), 7.93 (d, 6.8, 2H); $^{13}$C NMR ($CD_3OD$) δ 26.21, 28.43, 50.99, 52.50, 61.61, 107.91, 108.69, 110.46, 117.23, 117.96, 120.62, 122.42, 126.58, 136.06, 144.93, 151.68, 171.73, 172.00; IR (KBr) ν 3380, 3260, 1740, 1665, 1600 cm$^{-1}$; $[\alpha]^D$ –58.2 (c 0.5, DMSO); mp 176-178 ¡C; HRMS calcd for $C_{35}H_{36}O_6N_4$ 636.26963, found 637.2748.

**HS201.** From tryptamin hydrochloride in DMF after flash column (ethyl acetate/methanol/5/1) as crystalline powder: yield 40 %; $^{1}$H NMR ($CD_3OD$) δ 1.81 (m, 2H), 2.22 (m, 2H), 2.91 (dd, 7.6, 7.6, 4H), 3.49 (dd, 7.0, 7.0, 4H), 4.31 (d, 7.6, 2H), 6.16 (d, 6.6, 2H), 6.94-7.12 (m, 6H), 7.32 (m, 2H), 7.52 (m, 2H), 7.85 (d, 6.6, 2H); $^{13}$C NMR ($CD_3OD$) δ 24.14, 28.67, 39.23, 61.75, 107.62, 110.41, 110.95, 117.36, 117.76, 120.48, 121.66, 126.87, 136.17, 147.30, 150.66, 171.41; IR (KBr) ν , 3240, 1640, 1600, 1518 cm$^{-1}$; $[\alpha]^D$ –36.1 (c 0.5, MeOH); mp 140-145 ¡C; HRMS calcd for $C_{31}H_{32}O_2N_6$ 520.258675, found 521.2657.

**HS202.** From (*R*)-naphtylalanine methyl ester hydrochloride in DMF after flash chromatography (ethyl acetate/methanol/4/1) as amorphous powder: yield 53 %; $^{1}$H NMR ($CD_3OD$) δ 1.36 (m, 2 H), 1.87 (m, 2 H), 3.05 (dd, 13.9, 10.8, 2 H), 3.41 dd, 13.9, 4.4, 2H), 3.74 (s, 6H), 4.26 (d, 7.6, 2H), 4.83 (dd, 10.8, 4.6, 2H), 6.18 (d, 6.6, 2H), 7.25 (dd, 8.4, 1.6, 2H), 7.43-7.54 (m, 6H), 7.68-7.83 (m, 8H); $^{13}$C NMR ($CD_3OD$) δ 28.38, 36.21, 51.12, 52.58, 61.37, 107.71, 124.88, 125.34, 126.23, 126.63, 126.72, 126.79, 127.21, 131.89, 132.82, 133.79, 146.70, 150.74, 171.26, 172.41; IR (KBr) ν 3240, 1740, 1657, 1600 cm$^{-1}$; $[\alpha]^D$ -89.6 (c 0.5, MeOH); mp 191-193 ¡C; HRMS calcd for $C_{39}H_{38}O_6N_4$ 658.279135, found 659.2859.

**HS213.** From glycin methyl ester hydrochloride in DMF after preparative TLC (ethylacetate/methanol/2/1) as crystalline white powder: yield 16 %; $^{1}$H NMR ($CD_3OD$) δ 2.18 (m, 2H), 2.55 (m, 2H), 3.73 (s, 6H), 3.96 (d, 6.2, 4H), 4.59 (d, 8.2, 2H), 6.56 (d, 6.4, 2H), 8.14 (d, 6.4, 2H); $^{13}$C NMR ($CD_3OD$) δ 28.65, 39.93, 50.74, 61.71, 108.15, 147.22, 150.83, 169.49, 173.37; IR (KBr) 3245, 1742, 1642, 1600, 1542, 1519 cm$^{-1}$; $[\alpha]^D$ -75.7 (c 0.25, MeOH); mp 222-225 ¡C; HRMS calcd for $C_{17}H_{23}O_6N_4$ 379.161760, found 379.1598.

**HS220.** From (*S*)-leucine methyl ester hydrochloride in $CH_2Cl_2$ after preparative TLC (ethylacetate/methanol/5/1) as white crystalline powder: yield 71 %; $^{1}$H NMR ($CD_3OD$) δ 0.93 (d, 5.8, 6H), 1.02 (d, 6.2, 6H), 1.70 (m, 5H), 2.16 (m, 2H), 2.50 (m, 2H), 3.70 (s, 6H), 4.50 (m, 2H), 4.58 (d, 7.6, 2H), 6.46 (d, 5.5, 2H), 8.10 (d, 5.5, 2H); $^{13}$C NMR ($CD_3OD$) δ 19.64, 21.55, 24.37, 28.61, 39.10, 50.23, 50.83, 61.39, 107.69, 147.10, 151.03, 172.24, 172.93; IR (KBr) 2880, 1745, 1660, 1600, 1545, 1518 cm$^{-1}$; $[\alpha]^D$ –132.7 (c 0.5, MeOH); mp 187-189 ¡C; HRMS calcd for $C_{25}H_{38}O_6N_4$ 490.27914, found 490.2796.

**HS265.** From (*S*)-valine methyl ester hydrochloride in $CH_2Cl_2$ after preparative TLC (ethyl acetate/methanol/3/1) as white crystalline powder: yield 29 %; $^{1}$H NMR ($CD_3OD$) δ 0.99 (d, 3.2,

6H), 1.03 (d, 3.2, 6H), 2.12-2.28 (m, 4H), 2.53 (m, 2H), 3.73 (s, 6H), 4.37 (d, 5.6, 2H), 4.66 (d, 7.6, 2H), 6.47 (d, 6.4, 2H), 8.09 (d, 6.4, 2H); $^{13}$C NMR ($CD_3OD$) δ 16.67, 17.82, 28.74, 29.71, 50.65, 57.42, 61.15, 107.55, 147.28, 150.96, 171.28, 173.08; IR (KBr) 3255, 2880, 1740, 1655, 1600 cm$^{-1}$; $[\alpha]^D$ –116.6 (c 0.5, MeOH); mp 203-205 ¡C; HRMS calcd for $C_{23}H_{34}O_6N_4$ 462.24784, found 462.2490.

**HS308.** From *n*-hexylamine in $CH_2Cl_2$ without addition of *N*-methylmorpholine after preparative TLC ($CHCl_3$/MeOH/5/1) and recrystallisation from EtOAc as white crystalline powder: yield 54 %; $^1$H NMR ($CDCl_3$) δ 0.85 (t, 6.8, 6H), 1.22 (m, 12H), 1.41 (m, 4H), 2.18 (m, 2H), 2.44 (m, 2H), 3.20 (m, 4H), 4.42 (d, 7.6, 2H), 6.37 (dd, 5.0, 1.6, 2H), 6.46 (m, 2H), 8.13 (dd, 5.0, 1.4, 2H); $^{13}$C NMR ($CDCl_3$) δ 14.12, 22.69, 26.72, 29.62, 30.05, 31.56, 39.70, 62.41, 108.31, 148.99, 150.52, 172.26; IR (KBr) 3288, 2928, 1651, 1596, 1552, 1510 cm$^{-1}$; $[\alpha]^D$ –86 (c 0.5, $CHCl_3$); mp 222-223 ¡C; HRMS calcd for $C_{23}H_{38}O_2N_4$ 402.29948, found 402.2974.

**HS318.** From *n*-hexanol in $CH_2Cl_2$ whithout addition of *N*-methylmorpholine after preparative TLC ($Et_2O$/MeOH/10/1) as colourless oil: yield 38 %; $^1$H NMR ($CDCl_3$) δ 0.88 (t, 6.6, 6H), 1.27 (m, 12 H), 1.60 (m, 4H), 2.17 (m, 2H), 2.52 (m, 2H), 4.13 (m, 4H), 4.48 (d, 8.2, 2H), 6.33 (dd, 4.8, 1.6, 2H), 8.24 (dd, 4.8, 1.4, 2H); $^{13}$C NMR ($CDCl_3$) δ 14.10, 22.62, 25.61, 28.65, 29.11, 31.42, 60.88, 65.71, 107.77, 150.03, 150.36, 172.74; IR (film) 2956, 2858, 1743, 1595, 1510 cm$^{-1}$; $[\alpha]^D$ –77(c 0.25, $CHCl_3$); HRMS calcd for $C_{23}H_{36}O_4N_2$ 404.26751, found 404.2673.

**HS322.** From *N*-methyl hexylamine in $CH_2Cl_2$ without addition of *N*-methylmorpholine after preparative TLC ($CHCl_3$/MeOH/5/1) as colourless soft solid: yield 42 %; $^1$H NMR (400 MHz, $CHCl_3$, mixture of isomers) δ 0.87 (t, 6.8), 0.93 (t, 7.0), 1.28 (m), 1.37 (m), 1.56 (m), 1.73 (m), 1.95 (m, 2H), 2.58 (m, 2H), 2.98 (s), 3.15 (s), 3.31 (m), 3.49 (m), 4.83 (m, 2H), 6.09 (m, 2H), 8.16 (m, 2H); $^1$H NMR (DMSO, 400 MHz, 150 ¡C) δ 0.90 (t, 6.8, 6H), 1.33 (m, 12H), 1.58 (m, 4H), 1.90 (m, 2H), 2.42 (m, 2H), 3.04 (m, 6H), 3.38 (t, 6.8, 4H), 4.81 (d, 7.8, 2H), 6.12 (d, 6.2, 2H), 8.02 (d, 6.2, 2H); IR (KBr) 2931, 1650, 1603, 1513 cm$^{-1}$; $[\alpha]^D$ –28 (c 0.5, $CHCl_3$); HRMS calcd for $C_{25}H_{42}O_2N_4$ 430.33077, found 430.3311.

**HS339.** To *n*-hexylamine (87 µl, 0.66 mmol) and *N*-(4-pyridyl)-L-proline hydrochloride (100 mg, 0.44 mmol) dissolved in $CH_2Cl_2$ (10 mL) *N*-methylmorpholine (48 µl, 0.44 mmol) was added followed by EDCI (125 mg, 0.66 mmol) and HOBT (89 mg, 0.66 mmol ). After stirring for 24 h the mixture was evaporated and after dissolving in EtOAc (200 mL) washed with $NaHCO_3$

solution and brine (10 ml each). Drying over $Na_2SO_4$ and evaporation followed by preparative TLC ($CHCl_3$/MeOH/5/1) gave **HS339** as colourless needles: yield 34 % (41 mg); $^1$H NMR ($CDCl_3$) δ 0.85 (t, 6.4; 3H), 1.23 (m, 6H), 1.42 (t, 6.6, 2H), 2.06 (m, 2H), 2.28 (m, 2H), 3.17-3.37 (m, 3H), 3.64 (m, H), 4.10 (dd, 5.4, 5.4, H), 6.24 (m, H), 6.46 (d, 5.9, 2H), 8.27 (d, 5.9, 2H); $^{13}$C NMR ($CDCl_3$) δ 14.10, 22.64, 24.01, 26.56, 29.65, 31.42, 31.47, 39.52, 48.86, 63.48, 108.17, 150.03, 152.05, 171.97; IR (KBr) 3299, 2928, 1650, 16021551, 1518 cm$^{-1}$; $[\alpha]^D$ –110 (c 0.5, $CHCl_3$); mp 45 ¡C; HRMS calcd for $C_{16}H_{25}ON_3$ 275.19976, found 275.1999.

**HS340.** (*R*)-Naphtylalanin methyl ester hydrochloride (212 mg, 0.8 mmol) and *N*-(4-pyridyl)-L-proline hydrochloride (122 mg, 0.53 mmol) were dissolved in $CH_2Cl_2$ (12 mL) and N-methylmorpholine (146 µl, 1.6 mmol) was added followed by EDCI (150 mg, 0.8 mmol) and HOBT (109 mg, 0.8 mmol ). After stirring for 24 h the mixture was evaporated and after dissolving in EtOAc (200 mL) washed with $NaHCO_3$ solution and brine (10 ml each). Drying over $Na_2SO_4$ and evaporation followed by preparative TLC (MeOH) gave **HS340** as amorphous solid: yield 83 % (197 mg); $^1$H NMR ($CDCl_3$) δ 1.98 (m, 2H), 2.22 (m, 2H), 3.18 (m, 3H), 3.44 (m, H), 3.75 (s, 3H), 4.03 (dd, 7.8, 3.4, H), 5.02 (m, H), 6.28 (dd, 6.4, 1.4, 2H), 6.59 (d, 8.8, H), 6.98 (dd, 8.2, 1.6, H), 7.27 (s, H), 7.43-7.50 (m, 4H), 7.77 (m, H), 8.14 (d, 6.4, 2H); $^{13}$C NMR (100 MHz) δ 23.52, 31.28, 37.73, 48.51, 52.19, 52.41, 63.03, 107.94, 125.85, 126.21, 126.77, 127.56, 127.58, 127.79, 128.37, 132.37, 132.64, 133.20, 149.96, 151.74, 171.68, 172.07; IR (KBr) 2950, 1743, 1670, 1599, 1517 cm$^{-1}$; $[\alpha]^D$ –121 (c 0.5, $CHCl_3$); mp 68-70 ¡C; HRMS calcd for $C_{24}H_{25}O_3N_3$ 403.18959, found 403.1903.

**Procedure for desymmetrisation.** The corresponding diol (0.1 mmol) and the catalyst (0.005 mmol) was suspended in $CHCl_3$ (0.5 ml) or an alternative solvent and 2,4,6-collidine (0.14 mmol, 18.5 µl) followed by isobutyric anhydride (0.13 mmol, 21.5 µl) was successive added. After shaking for 4 h at 20 ¡C the mixture was poured into EtOAc (70 ml) and washed successive with 1°M aq HCl (4 ml) $NaHCO_3$ solution (4 ml) and brine (4 ml). After drying over $Na_2SO_4$ and evaporation the obtained residue was dissolved in $C_6D_6$ (0.7 ml) and the product ration was determined by NMR ($^1$H, 300 MHz). The ratio of enantiomers was determined directly by GC or HPLC.

**Monoacylated (*cis*)-diols. (*cis*)-2,3-Butanediol isobutyrate.** $^1$H NMR ($CDCl_3$) δ 1.19 (m, 12H), 2.57 (m, H), 3.88 (m, H), 4.86 (m, H); IR (film) 3425, 2890, 2870, 2840, 1725 $cm^{-1}$; HRMS calcd for $C_8H_{15}O_3$ 159.10212, found 159.1027; $[\alpha]^D$ 64 (c 0.25, $CHCl_3$), 83 %ee.

**(*cis*)-2,3-Butanediol diisobutyrate.** $^1$H NMR ($CDCl_3$) δ 1.11-1.16 (m, 12H), 1.18 (d, 5.4, 6H), 2.50 (m, 2H), 4.95 (m, 2H); IR (film) 2890, 2870, 2840, 1730 $cm^{-1}$; HRMS calcd for $C_{12}H_{22}O_4$ 230.15181, found 230.1521.

**(*cis*)-Hydrobenzoin isobutyrate.** $^1$H NMR ($CDCl_3$) δ 1.03 (t, 7.2, 6H), 2.14 (d, 3.6, H), 2.48 (sept, 7.0, H), 4.96 (dd, 6.6, 3.6, H), 5.89 (d, 6.4, H), 7.30-7.35 (m, 10H); IR (KBr) 3470, 2885, 2870, 2835, 1715 $cm^{-1}$; mp 98 ¡C; HRMS calcd for $C_{18}H_{20}O_3$ 284.14125, found 284.1407; $[\alpha]^D$ –6.9 (c 0.5, $CHCl_3$) 59 %ee (HPLC).

**(*cis*)-Hydrobenzoine diisobutyrate.** $^1$H NMR ($CDCl_3$) δ 1.04 (t, 6.8, 12H), 2.49 (sept, 6.8, 2H), 6.07 (s, 2H), 7.24-7.31 (m, 10H); IR (KBr) 2885, 2865, 2840, 1725 $cm^{-1}$; mp 110 ¡C; HRMS calcd for $C_{22}H_{26}O_4$ 354.18311, found 354.1820.

**(*cis*)-1,2-Cyclohexanediol isobutyrate.** $[\alpha]^D$ –4.3 (c 0.5, $CHCl_3$), 92 %ee (GC);

**(*cis*)-1,2-Cyclohexanediol diisobutyrate.** $^1$H NMR ($CDCl_3$) δ 1.29 (dd, 7.0, 1.4, 12H), 1.44-1.85 (m, 8H), 2.53 (sept, 6.8, 2H), 5.02 (d, 8.4, 2H); IR (film) 2885, 2875, 2840, 1735 $cm^{-1}$; HRMS calcd for $C_{14}H_{24}O_4$ 256.16746, found 256.1665.

**(*cis*)-1,3-Cyclohexanediol isobutyrate.** $^1$H NMR ($CDCl_3$) δ 1.16 (d, 7.2, 6H), 1.24-1.50 (m, 4H), 1.81-1.87 (m, 3H), 2.18-2.24 (m, H), 2.52 (sept, 6.8, H), 3.72 (m, H), 4.76 (m, H); IR (film) 3400, 2880, 2875, 2835, 1718, 1730 $cm^{-1}$; HRMS calcd for $C_{10}H_{18}O_3$ 186.12559, found 186.1248.

**(*cis*)-1,3-Cyclohexanediol diisobutyrate.** $^1$H NMR ($CDCl_3$) δ 1.15 (d, 7.2, 12H), 1.17-1.54 (m, 4H), 1.81-1.96 (m, 3H), 2.50 (sept, 6.8, 2H), 2.17-2.28 (m, H), 4.75 (m, 2H); IR (film) 2885, 2875, 2840, 1725 $cm^{-1}$; HRMS calcd for $C_{14}H_{24}O_4$ 256.16746, found 256.1677.

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工業所有権の出願・取得状況

１、光学活性アミノ酸誘導体およびその製造法・特願２００２－１８６５９７

２、光学活性アミノ酸誘導体及びその製法・特願２００２－２３８３９１

３、光学活性含窒素環状化合物及びその製造法・特願２００３－２０５４４３

４、光学活性含窒素環状化合物及びその製造方法・特願 ２００３－３１９６３３

５、ピリジルピロリジンジカルボン酸およびアミド誘導体・特願２００３－３６８２３９

６、光学活性複素環化合物及びその製造方法・特許公開２００４－１９７６２１

７、光学活性アミノ酸ヒドロキシエステル誘導体及びその製造方法・特許公開２００４－０７５６０９

８、ヒドロキシプロリン誘導体・特許公開２００４－２３８２９２

９、ピリジルプロリン誘導体・特許公開２００４－１０７２９７