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Preparation and properties of chiral 4-pyrrolidinopyridine (PPY) analogues with dual functional side chains

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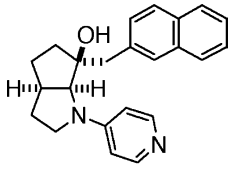
Abstract—Chiral 4-pyrrolidinopyridine analogues **8**–**13** with two distinct functional side chains at C(2) and C(4) of the pyrrolidine ring were prepared from 4-hydroxy-L-proline. We examined desymmetrization of *meso*-1,3-cyclohexanediol through enantioselective acylation using these catalysts and found that introduction of a C(4)-side chain was effective for improving both the chemo- and enantioselectivity of acylation.

Nonenzymatic kinetic resolution of racemic alcohols via enantioselective acylation is a recent focus of synthetic attention.[1–3] We developed chiral 4-pyrrolidinopyridine (PPY) analogue **1** which could effectively catalyze acylative kinetic resolution of racemic diol and amino alcohol derivatives with high enantioselectivity.[3] A unique feature of **1** is that chiral elements are not present in the catalytically active pyridine ring. Recently, we reported that chiral PPY analogue **2** could also promote the acylative kinetic resolution of *racemic*-**3** with a selectivity factor (*s*) of 8.1.[4,5] The structure of the peptide side chain at C(2) in **2** was found to be closely related to the enantioselectivity of the acylative catalysis.[4,6] We report here the preparation and properties of a new class of chiral PPY analogues **8**–**13** with dual functional side chains at C(2) and C(4) on the pyrrolidine ring (Scheme 1). Our hypothesis involves the expectation that a peptide side chain at C(4) might participate in substrate-recognition through hydrogen-bonding interaction with a substrate.[7] Combinatorial introduction of functional side chains at C(2) and C(4) is possible and may make it possible to search for a catalyst that is most suitable for the reaction of interest.

Side-chain structures at C(4) of **8**–**13** were selected based on the expected function of a 1,4-disubstituted imidazole subunit in **8** and **9** as a general base,[8] a tryptophan residue in **10** as a hydrogen-bond donor and for π–π interaction, and a protected proline subunit in **11**–**13** as a hydrogen-bond acceptor. Compound **4**,[9] which is readily prepared from commercially available *trans*-4-hydroxy-L-proline, was selected as a starting material for the preparation of chiral nucleophilic catalysts **8**–**13**. Hydrogenolysis of **4** followed by condensation with 4-bromopyridine gave *trans*-2,4-disubstituted pyrrolidinopyridine (**5**) in 50% yield. The key intermediate **6** for **8**–**13** was obtained in 87% yield by treatment of **5** with iodotrimethylsilane[10] followed by 4 M HCl in ethyl acetate. Condensation of **6** with L-tryptophan methyl ester was performed without protecting the 4-hydroxyl group by treatment with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBT) in the presence of *N*-methylmorpholine (NMM) to give **7** in 85% yield. A second amino acid residue was easily introduced at C(4) by the EDCI/HOBT method to give the desired catalysts **8**–**13** in yields of 64–100%. In contrast to a recent report on the preparation of *N*-pyridinyl prolines,[5b] no



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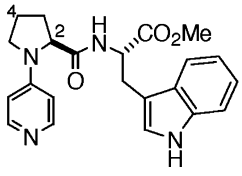

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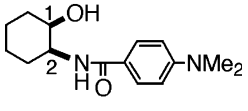

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Keywords: pyrrolidinopyridine; nucleophilic catalyst; desymmetrization; chemoselectivity; combinatorial chemistry.
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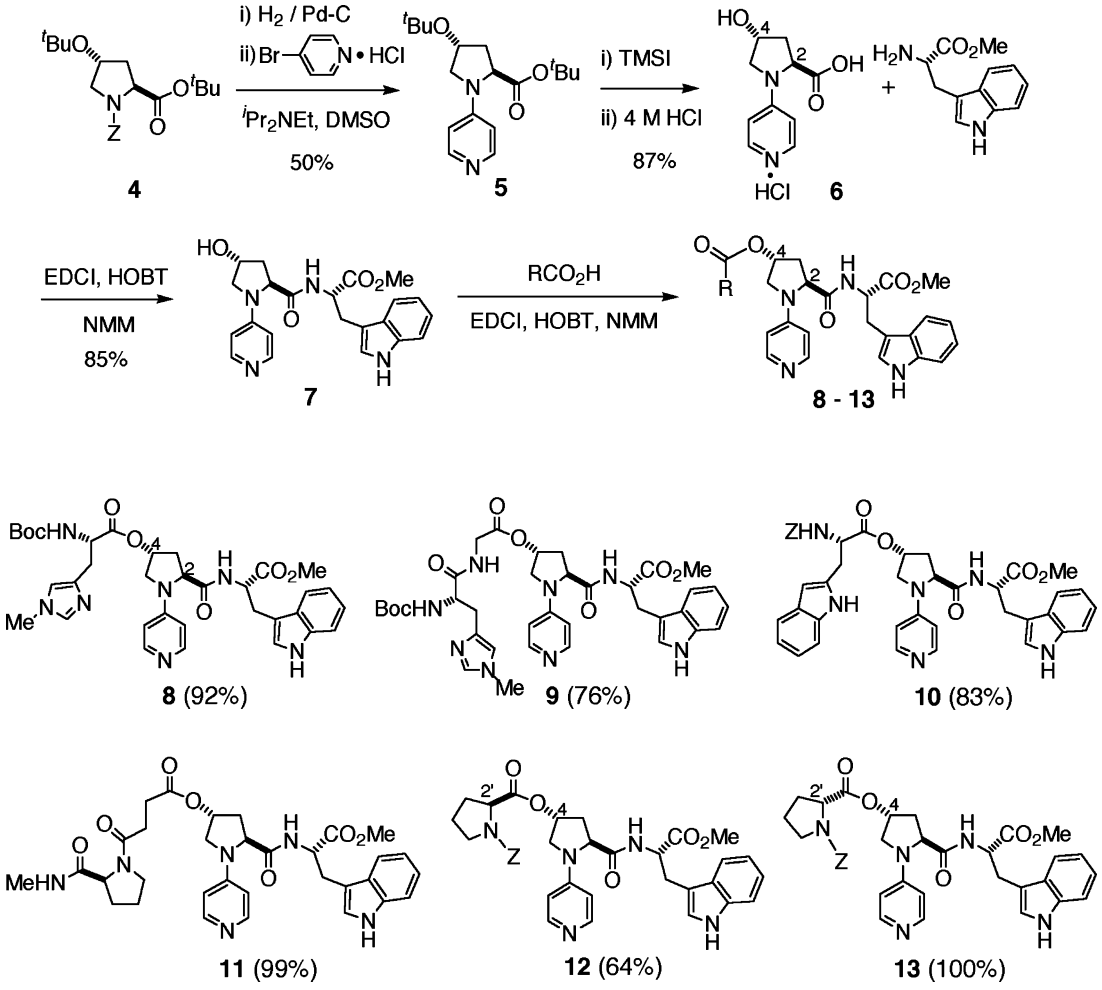


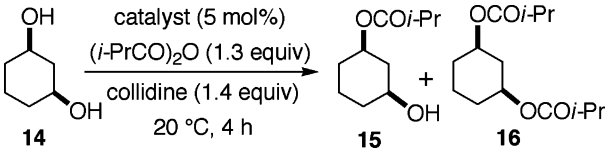
Scheme 1.

epimerization at C(2) was observed throughout the transformation. All of these molecules displayed catalytic activity for the acylation of alcohols.[11,12]

We examined enantioselective desymmetrization of *meso*-1,3-cyclohexanediol (**14**) (Table 1). Treatment of **14** with 1.3 mole equivalents of isobutyric anhydride in the presence of 5 mol% of catalyst **1** and 1.4 mole equivalents of 2,4,6-collidine in toluene at 20°C for 4 h gave monoester **15** in 27% yield (32% ee), diester **16** in 48% yield, and 6% recovery of **14** (entry 3). The predominant formation of **16** over **15** could be ascribed to the fact that **14** is less soluble than **15** in toluene, and the reaction mixture was suspended at an early stage of the reaction. The corresponding reaction in a chloroform solution, however, gave a similar ratio of **15** to **16** (entry 4). The observed chemoselectivity seems intrinsic to the acylation of **14**, since the ratio of **15** to **16** obtained by acylation with PPY was comparable to that obtained with **1** (entries 1–4). Similar chemo- and enantioselectivity was observed in acylation of **14** with catalyst **2** (entries 3 versus 5). On the other hand, monoester **15** was the major product of the acylation with catalysts **8**–**11** (entries 7–12). Among them, catalyst **10** gave the most improved chemoselectivity (60%, entry 12) and enantioselectivity (52% ee, entry 11) for acylation. Thus, the introduction of an ester side chain at C(4) in the nucleophilic catalyst improved both the chemo- and enantioselectivity of the acylation (entries 5, 6 versus 11, 12). To the best of our knowledge, this is the first example of nonenzymatic enantioselective acylation of **14**.[13–15]

The asymmetric desymmetrization of *meso*-1,2-diol **17** was also examined with catalysts **2** and **8**–**13** (Table 2). Acylation of **17** with isobutyric anhydride in the presence of catalyst **2** in toluene gave mono-ester (1*R*, 2*S*)-**18** in 60% ee and in 59% yield (entry 1). Only slight differences were observed in the chemo- and enantioselectivity of acylation with changes in the structure of catalysts **8**–**13** (entries 2–9). The highest chemoselectivity (77%, entry 7) and enantioselectivity (65% ee, entry 9) for mono-acylation were achieved with catalysts **11** and **13**, respectively. The difference in chirality at C(2′) in the C(4)-side chains of **12** and **13** did not affect the selectivity of acylation (entry 8 versus 9). The enantiomeric purity of **18** is the result of enantioselective acylation of **17** followed by kinetic resolution of **18**. The ee of **18** was increased with an increase in diester-formation (entry 5 versus 6). This indicates that the minor enantiomer **18** formed by enantioselective mono-acylation of **17** is consumed faster than the major enantiomer in the following kinetic resolution. In fact,

Table 1. Enantioselective desymmetrization of *meso*-1,3-diol **14**

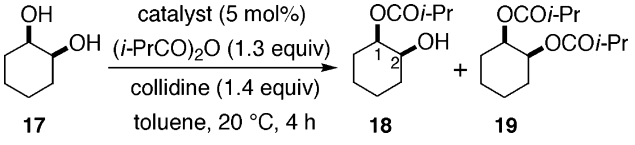


14 **15** **16**

Entry	Catalyst	Solvent	**15**:**16**:**14** (%)[a]	Ee of **15** (%)[b]
1	PPY[c]	Toluene	19:48:5	–
2	PPY[c]	$CHCl_3$	35:39:4	–
3	**1**	Toluene	27:48:6	32
4	**1**	$CHCl_3$	32:46:2	34
5	**2**	Toluene	30:43:12	28
6	**2**	$CHCl_3$	44:29:8	23
7	**8**	Toluene	37:35:9	33
8	**8**	$CHCl_3$	49:31:7	20
9	**9**	Toluene	43:28:12	44
10	**9**	$CHCl_3$	53:22:9	32
11	**10**	Toluene	48:32:9	52
12	**10**	$CHCl_3$	60:28:5	41
13	**11**	Toluene	45:36:19	39
14	**11**	$CHCl_3$	44:9:37	24

[a] Yields determined by ^1H NMR with dibenzyl ether as an internal standard.
[b] Determined by GC analysis with a chiral stationary phase, beta-DEX™ 225.
[c] 4-Pyrrolidinopyridine.

Table 2. Enantioselective desymmetrization of *meso*-1,2-diol **17**



17 **18** **19**

Entry	Catalyst	**18**:**19**:**17** (%)[a]	Ee of **18** (%)[b,c]
1	**2**	59:26:11	60
2	**8**	52:26:6	43
3	**9**	65:22:7	58
4	**10**	72:19:3	54
5	**11**	61:27:7	59
6[d]	**11**	59:13:21	50
7[e]	**11**	77:18:5	51
8	**12**	64:28:6	63
9	**13**	61:27:6	65

[a] Yield determined by ^1H NMR with dibenzyl ether as an internal standard.
[b] Determined by GC analysis with a chiral stationary phase, gamma-DEX™ 225.
[c] (1*R*,2*S*)-Isomer was obtained in each entry.
[d] 0.9 Equiv. of isobutyric anhydride was used.
[e] Run in $CHCl_3$.

kinetic resolution of *racemic*-**18** by acylation with isobutyric anhydride in the presence of **12** gave (1*R*, 2*S*)-**18** in 54% ee at 68% conversion ($s=2.7$). Thus, the enantiomeric purity of **18** was enhanced by the cooperative effects of consecutive acylation processes,[16] which is often observed in the enzymatic hydrolysis of diesters.[17]

In conclusion, we have developed a new class of chiral PPY analogues with two distinct functional side chains at C(2) and C(4) of the pyrrolidine ring. Introduction of the C(4)-side chain was effective for improving the chemo- and enantioselectivity of acylation. Although these catalysts are not yet practically useful, this approach provides clues to the development of catalysts with the desired substrate-specificity.

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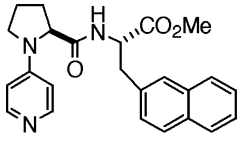
6. For examples, acylative kinetic resolution of *racemic*-**3** catalyzed by **20** and **21** proceeds with selectivity factors of 11 and 1.6, respectively, see Ref. 4.



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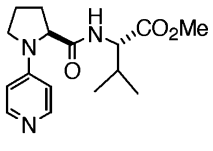

21

7. It has been reported that *N*-methylimidazole analogues with peptide side chains effectively promote asymmetric acylation and phosphorylation of alcohols, see: (a) Jarvo, E. R.; Copeland, G. T.; Papaioannou, N.; Bonitatebus, P. J., Jr.; Miller, S. J. *J. Am. Chem. Soc*. **1999**, *121*, 11638; (b) Sculimbrene, B. R.; Morgan, A. J.; Miller, S. J. *J. Am. Soc. Chem*. **2002**, *124*, 11653.

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12. Selected data: **7**: Colorless prisms (MeOH/Et_2O), mp 217–220°C. $[\alpha]_D^{20}$ −62 (*c* 1.0, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 7.81 (d, $J=6.3$ Hz, 2H), 7.56 ($J=8.1$ Hz, 1H), 7.37 (d, $J=8.1$ Hz, 1H), 7.12 (td, $J=8.1$, 1.2 Hz, 1H), 7.10 (s, 1H), 7.04 (td, $J=8.1$, 1.0 Hz, 1H), 6.12 (d, $J=6.3$ Hz, 2H), 4.78 (dd, $J=7.3$, 5.3 Hz, 1H), 4.40 (quintet, $J=5.1$ Hz, 1H), 4.20 (t, $J=6.1$ Hz, 1H), 3.70 (s, 3H), 3.60 (dd, $J=10.0$, 5.1 Hz, 1H), 3.38 (dd, $J=15.4$, 5.3 Hz, 1H), 3.25 ($J=10.0$, 4.4 Hz, 1H), 3.17 (dd, $J=15.4$, 10.0 Hz, 1H), 2.30–2.23 (m, 1H), 2.05–1.98 (m, 1H); IR (KBr) 3294, 1741, 1667, 1601, 1520, 1227, 1005 cm^{-1}; MS *m*/*z* (rel intensity) 408 (M^+, 20), 279 (30), 163 (100); HRMS calcd for $C_{22}H_{24}N_4O_4$, M^+, 408.1798, found *m*/*z* 408.1770. **11**: Colorless prisms (MeOH/Et_2O), mp 128–132°C. $[\alpha]_D^{20}$ −61 (*c* 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14, 9.11 (two s, ratio = 1:5, 1H), 8.13 (d, $J=6.6$ Hz, 2H), 7.46, 7.45 (two d, $J=8.1$ and 8.1 Hz, ratio = 5:1, 1H), 7.36 (d, $J=8.1$ Hz, 1H), 7.17 (td, $J=8.1$, 1.0 Hz, 1H), 7.10 (td, $J=8.1$, 0.7 Hz, 1H), 6.90 (d, $J=2.2$ Hz, 1H), 6.79, 6.71 (two q, $J=4.9$ and 4.9 Hz, ratio = 5:1, 1H), 6.60 (d, $J=8.1$ Hz, 1H), 6.22 (d, $J=6.6$ Hz, 2H), 4.93 (quint, $J=5.1$ Hz, 1H), 4.87–4.80 (m, 1H), 4.50, 4.34 (two dd, $J=8.3$, 2.2 and 8.8, 2.2 Hz, ratio = 5:1, 1H), 4.11 (dd, $J=9.0$, 6.1, 1H), 3.69 (s, 3H), 3.64–3.35 (m, 4H), 3.24–3.18 (m, 2H), 2.84, 2.70 (two d, $J=4.9$ and 4.9 Hz, ratio = 1:5, 3H), 2.67–2.46 (m, 4H), 2.36–2.29 (m, 2H), 2.16–1.88 (m, 4H); IR (KBr) 3286, 1737, 1660, 1601, 1543, 1518, 1440, 1227, 1007 cm^{-1}; MS (FAB) *m*/*z* (rel intensity) 619 (MH$^+$, 3), 335 (4), 181 (6), 169 (100); HRMS calcd for $C_{32}H_{39}N_6O_7$, M^+, 619.2880 (MH$^+$), found *m*/*z* 619.2875.
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15. Typical procedure for enantioselective desymmetrization of **14** (Table 1, entry 11): Isobutyric anhydride (22 μL, 0.13 mmol) was added to a solution of **14** (12 mg, 0.10 mmol), **10** (3.6 mg, 5 μmol), and 2,4,6-collidine (19 μL, 0.14 mmol) in 0.5 mL of toluene at 20°C. The mixture was stirred at 20°C for 4 h. The reaction mixture was diluted with ethyl acetate and washed with 1 M HCl, satd aq. $NaHCO_3$, and brine, dried with Na_2SO_4, filtered and evaporated in vacuo. Yields of **15**, **16**, and **14** were determined to be 48, 32, and 9%, respectively by 300 MHz ^{1}H NMR with dibenzyl ether an internal standard. Enantiomeric purity of **15** was determined to be 52% ee by GLC analysis with beta-DEX™ 225 at 115°C, $t_R=65$, 67 min.
16. Similar cooperative effect, albeit less significant, was observed in the acylation of **14** with **10** in toluene: Kinetic resolution of *racemic*-**15** with **10** in toluene gave recovered **15** in 18% ee at 47% conversion ($s=1.8$) whose absolute configuration was same as that obtained by mono-acylation of **14** with **10**.
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