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[A0036]

Synthesis of Enantiomerically Pure Pipecolic Acid Derivatives via Combination of Biocatalysis and Transition Metal Catalysis

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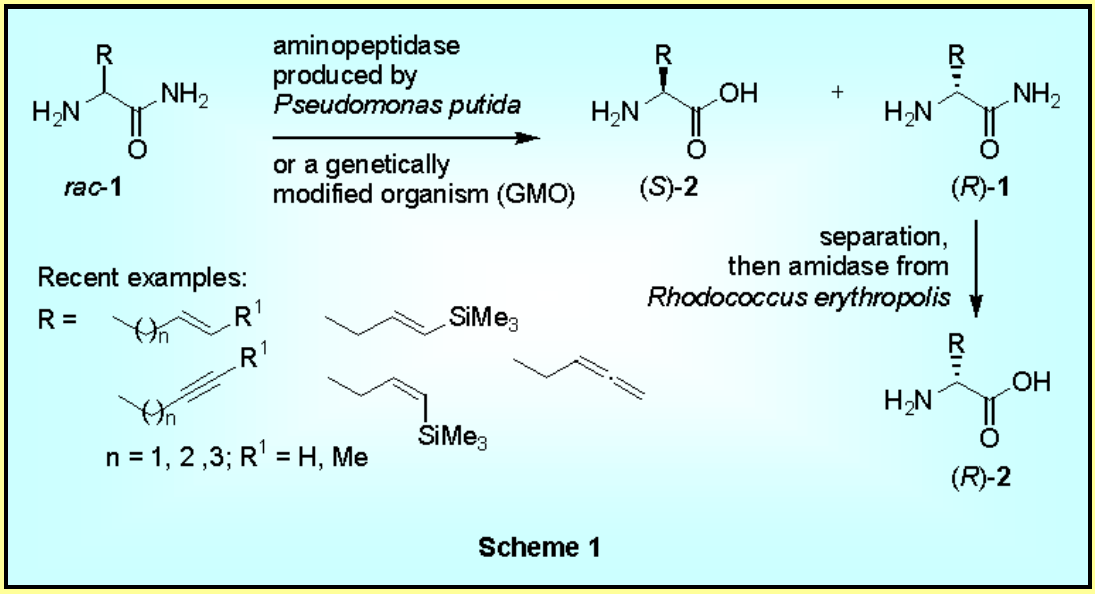
Introduction

The combination of biocatalysis and transition metal catalysis provides a powerful and versatile pathway for the synthesis of multifunctional building blocks. In this approach, the biocatalyst is used to generate enantiomerically pure starting materials, while transition metals are used in a catalytic fashion for further synthetic elaboration.

Biocatalytic Production of Non-Proteinogenic Amino Acids

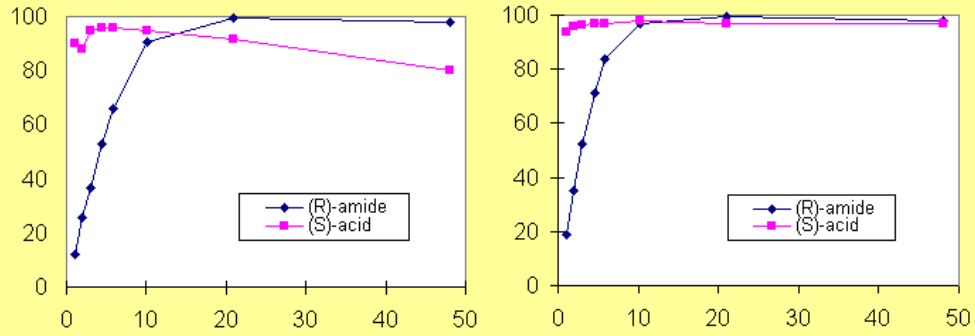
Racemic amino acid amides can be conveniently resolved into the corresponding (*S*)-amino acids and (*R*)-amino acid amides by an enantioselective aminopeptidase produced by *Pseudomonas putida* ATCC 12633. The enzyme is highly selective for a wide range of R-groups and virtually independent of functionalities in this side chain (Scheme 1).



Scheme 1

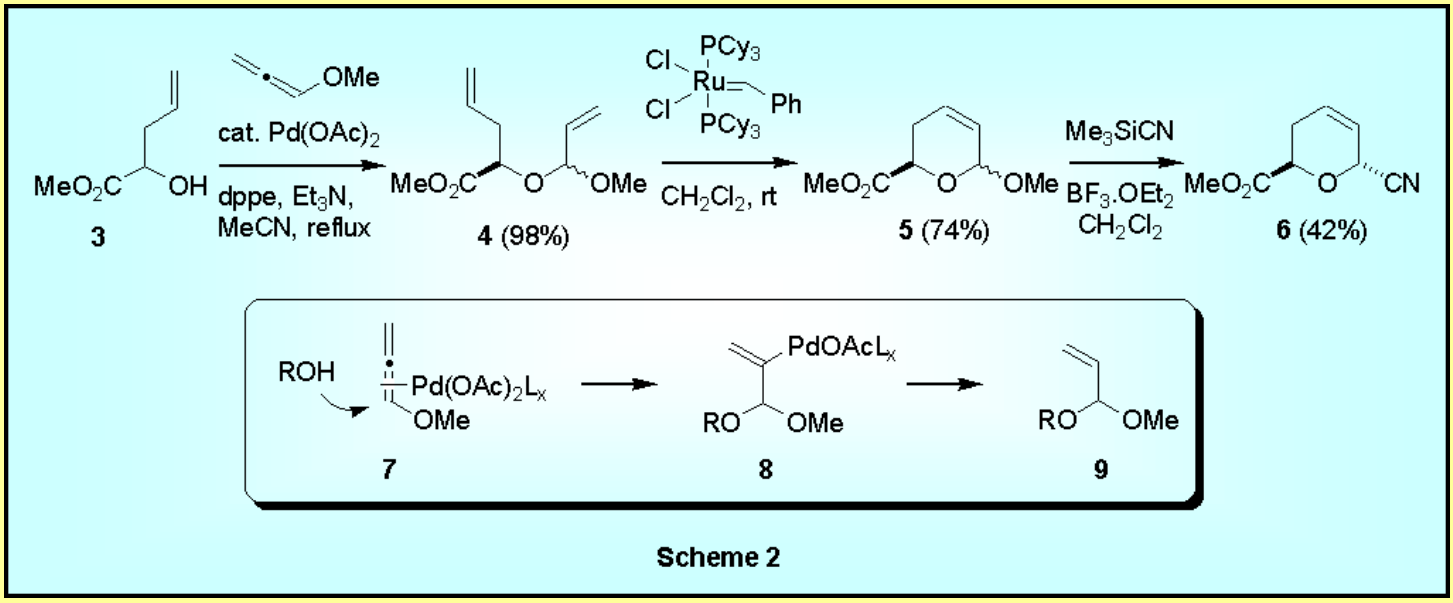
However, the enzymatic resolution gave anomalous results for methionine resembling amino acids due to the presence of a *methionine racemase* in the whole cells

produced by the *Pseudomonas putida* strain (Fig. 1, exemplified for homopropargylglycine (HPG)). Therefore, a recombinant enzyme system was developed, which appeared a reliable alternative leading to both (*S*)-amino acids and (*R*)-amino amides in >99% ee (Fig. 2, shown for HPG).[1] Fig. 1: Resolution of HPG with *Pseudomonas putida* Fig. 2: Resolution of HPG with a recombinant organism



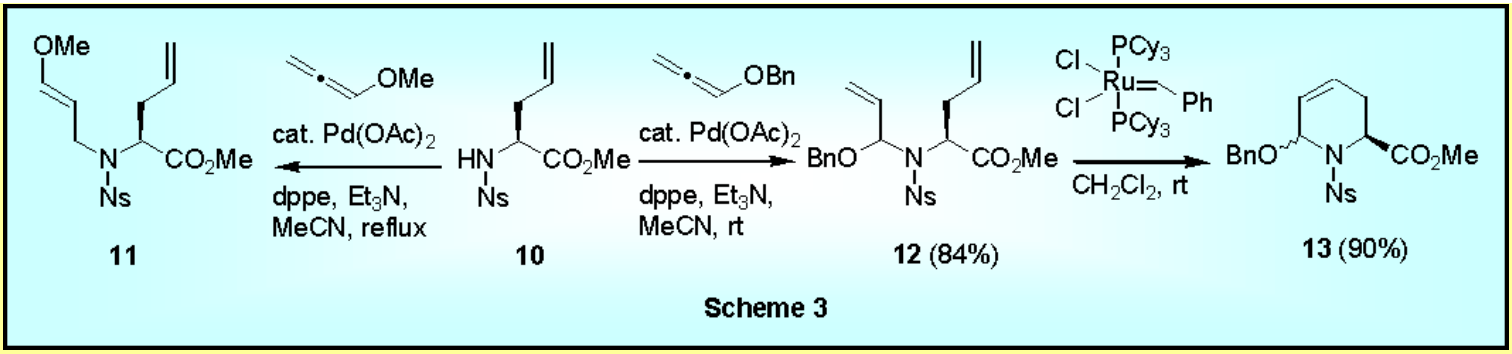
A Novel Route to Modified Pipecolic Acids

Recently, we developed a novel route for the synthesis of 2,6-disubstituted dihydropyran systems such as **6**.[2] A key step in this pathway was the novel Pd-catalyzed formation of allylic acetals using an alkoxyallene as one of the reaction partners (Scheme 2). Further elaboration via the cyclic acetals **5** via the corresponding oxycarbenium ion provided the target compounds **6**. The mechanism presumably proceeds as indicated in the same Scheme. Electrophilic activation of the most electron rich double bond (*viz*. **7**), followed by attack of the alcohol and subsequent protonolysis of the resulting vinylpalladium species **8** gives the acetal **9**.



Scheme 2

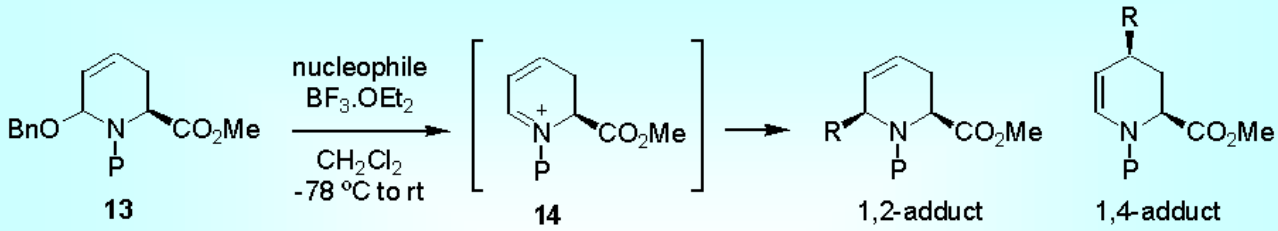
Pipecolic acid (hexahydropyridine-2-carboxylic acid) derivatives are used to introduce conformational restriction in peptides, but may also be used as a starting point for the construction of (libraries of) biologically active compounds and/or natural products. Inspired by the efficient Pd-catalyzed formation of acetals starting from alcohols and by previous RCM-mediated cyclization reactions of allylglycine derivatives,[3] we set out to explore a similar route to form the corresponding *N,O*-acetals, which – if an enantiopure allylglycine deivative (*viz*. **10**, Scheme 3) is used as the starting material - eventually should give rise to unsaturated 2,6-disubstituted pipecolic acid derivatives. Initial results with methoxy-allene were unsatisfactory, leading to the undesired regioisomer **11**. However, by using benzyloxy-allene the reaction proceeded smoothly at room temperature to provide the linear allylic *N,O*-acetal **12**. Subjection to standard RCM-conditions then gave the cyclic counterparts **13**.

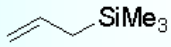
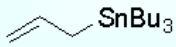
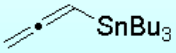
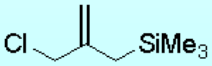
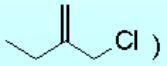


Scheme 3

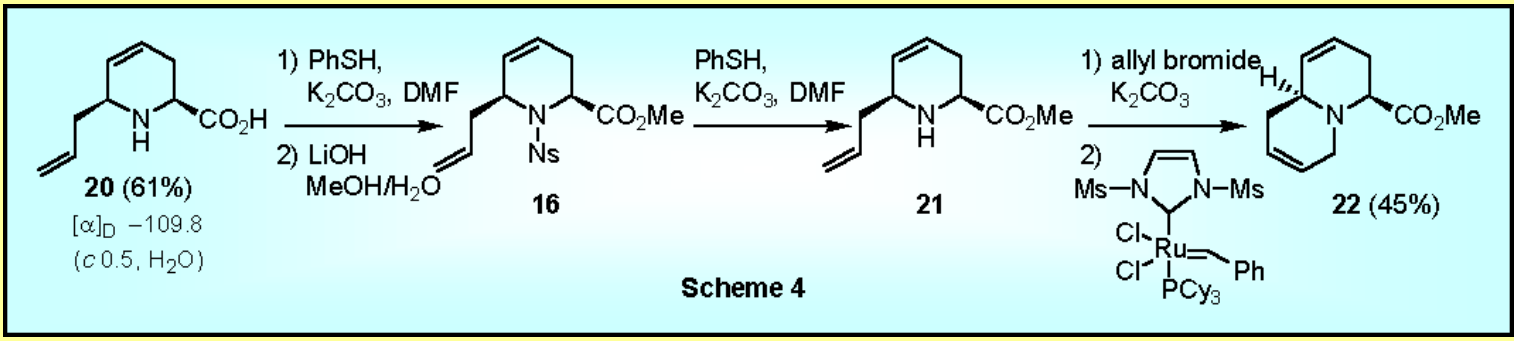
Treatment of the cyclic *N,O*-acetals with al Lewis acid in the presence of several nucleophiles led to the corresponding functionalized pipecolic acid derivatives **15**-**19**. In general, a highly diastereoselective CC-bond forming reaction took place via the intermediate *N*-sulfonyliminium ion **14**, although in some cases a small amount of the regioisomeric 1,4-adduct was formed.

Table 1



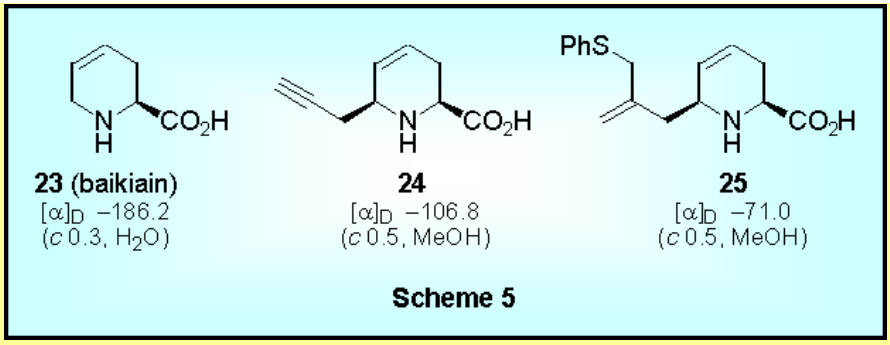
Entry	Nucleophile	Product	Ratio (1,2:1,4)	Yield (%)
1	Et_3SiH	**15** (R = H)	100:0	88
2		**16** (R = Allyl)	75:25	79
3		**16** (R = Allyl)	98:2	94
4	$Me_3Si{-}C{\equiv}N$	**17** (R = CN)	100:0	89
5		**18** (R = Propargyl)	100:0	75
6		**19** (R = )	80:20	67

Deprotection of the protected pipecolic acid **16** proceeded readily via PhSH-mediated cleavage of the sulfonamide bond, followed by hydrolysis of the ester to give the amino acid **20** (Scheme 4). Alternatively, desulfonylation followed by allylation and subsequent ring closure via RCM gave the bicyclic amino acid derivative **22** in 45% yield. The latter sequence has not been optimized yet and is currently under investigation.



Scheme 4

In a similar fashion, deprotection of additional cyclization products led to the enantiomerically pure pipecolic acid derivatives **23**-**25** including the naturally occurring amino acid baikiain (Scheme 5).



Scheme 5

Concluding Remarks

We have developed an efficient enantiomerically pure synthesis of 2,6-disubstituted unsaturated pipecolic acid derivatives, consisting of several transition metal-mediated transformations. At present, we are exploring the possibilities to use these building blocks as starting point for natural product synthesis and the generation of libraries of potentially biologically active compounds.

Acknowledgements

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References

1. T Sonke, B Kaptein, WHJ Boesten, QB Broxterman, J Kamphuis, F Formaggio, C Toniolo, FPJT Rutjes, HE Schoemaker in *Stereoselective Biocatalysis*, RN Patel, Ed, Marcel Dekker: New York, 2000, pp. 23-58.

2.FPJT Rutjes, TM Kooistra, H Hiemstra, HE Schoemaker, *Synlett* **1998**, 192.

3.FPJT Rutjes, HE Schoemaker *Tetrahedron Lett*. **1997**, *38*, 677.

4.KCMF Tjen, SS Kinderman, HE Schoemaker, H Hiemstra, FPJT Rutjes *Chem. Commun.* **2000**, 699.
