Homogeneous Catalysis

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Synthesis of Peptides and Pyrazines from β-Amino Alcohols through Extrusion of H_2 Catalyzed by Ruthenium Pincer Complexes: Ligand-Controlled Selectivity**

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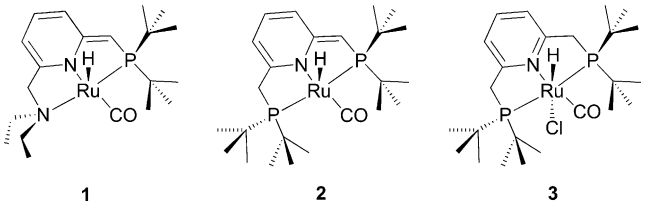
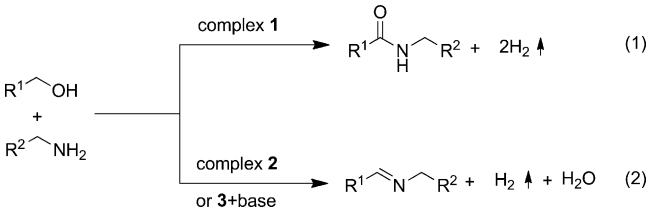
Peptides constitute one of the most important families of compounds in chemistry and biology. Short peptides have found intriguing biological and synthetic applications. For example, the conformational rigidity of cyclic peptides makes them attractive for drug discovery and biomedical research.[1] Several cyclic peptides that show intriguing biological activity are found in nature.[2] Cyclic peptides have been discovered that are novel antibiotics,[3] enzyme inhibitors,[4] and receptor antagonists. Among them are the smallest cyclopeptides, 2,5-diketopiperazines derivatives, which are commonly found as natural products.[5] These compounds exhibit high-affinity binding to a large variety of receptors and show a broad range of biological acitivities,[6] including antimicrobial, antitumoral, antiviral, and neuroprotective effects. 2,5-diketopiperazine derivatives are synthesized in solution or on the solid phase from commercially available and appropriately protected chiral α-amino acids in processes that are usually not atom-economical and generate considerable amounts of waste. Large libraries of cyclic peptides are accessible through solid-phase split-and-pool synthesis,[7] and various methods were developed for their syntheses.[8] Very recently, the synthesis of diketopiperazines from amino acids under microwave irradiation was reported.[9] Green, atom-economical methods for the generation of peptides are highly desirable.

We have developed several reactions catalyzed by PNN and PNP Ru^{II} pincer complexes based on pyridine,[10,11] bipyridine,[12,13] and acridine[14] and have discovered a new mode of metal–ligand cooperation[15] based on ligand aromatization–dearomatization.[16] For example, the PNN Ru^{II} pincer complex **1** (Scheme 1) catalyzes the direct synthesis of amides from alcohols and amines with liberation of H_2[17] (Scheme 2, Eq. (1)). Several reports on amide formation by dehydrogenative coupling of amines with alcohols appeared later.[18] Unlike complex **1**, the analogous PNP complex **2** (or complex **3** in the presence of an equivalent of base) catalyzes the coupling of amines with alcohols to form imines rather than amides with liberation of H_2 and H_2O (Scheme 2, Eq. (2)).[19]



1 2 3

Scheme 1. PNN- and PNP-type pincer ruthenium complexes.



Scheme 2. Reactions of alcohols with amines catalyzed by complexes **1**–**3**.

Herein we report a novel method for peptide synthesis, which involves dehydrogenative coupling of β-amino alcohols with extrusion of H_2 catalyzed by complex **1**. This environmentally benign and atom-economical reaction proceeds under neutral reaction conditions without the use of toxic reagents, activators, condensing agents, or other additives. With the analogous PNP complex **2**, a strikingly different reaction takes place, which leads to pyrazines with extrusion of H_2 and H_2O.

Initially, we were interested to see whether coupling of β-amino alcohols with amines can be accomplished and whether racemization would be involved. Reaction of (*S*)-2-amino-3-phenylpropan-1-ol (**4**), benzylamine, and 1 mol% of the catalyst **1** in toluene at reflux for six hours led to (*S*)-2-amino-*N*-benzyl-3-phenylpropanamide **5** in 58% yield[20a] after column chromatography (Scheme 3). The specific rotation of amide **5** obtained from the catalysis is essentially the same as reported[20b] (+16.0°). The neutral reaction conditions likely help to prevent racemization.

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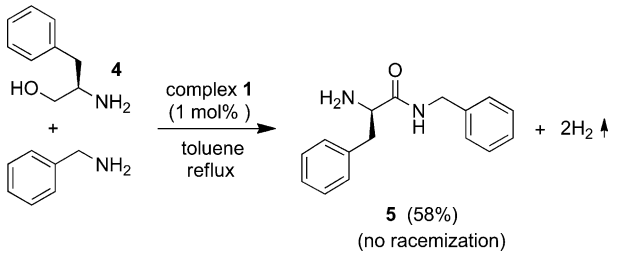
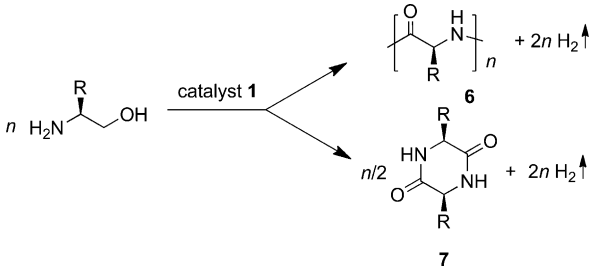


Scheme 3. Amidation of (*S*)-2-amino-3-phenylpropan-1-ol (**4**) with benzylamine catalyzed by **1**.

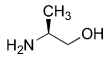
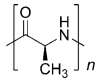
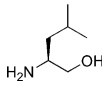
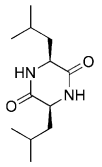
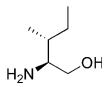
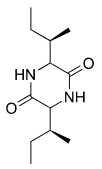
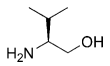
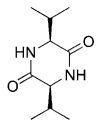
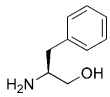
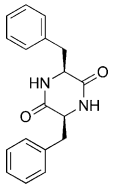
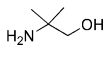
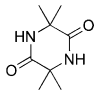
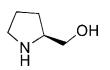
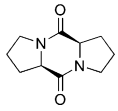


Scheme 4. Peptide formation by dehydrogenative coupling of β-amino alcohols.

Next, we explored the self-reactions of β-amino alcohols. In principle, dehydrogenative coupling of β-amino alcohols can lead to formation of both cyclic and linear peptides (Scheme 4). Heating a 1,4-dioxane solution containing (*S*)-(+)-2-amino-1-propanol (2 mmol) and **1** (1 mol%) to reflux for 19 h in argon atmosphere resulted in 90% conversion of the amino alcohol, as determined by GC–MS. Solvent evaporation, dilution of the residue with CH_2Cl_2, separation of an insoluble solid by filtration, and drying under vacuum gave 72% poly(alanine) **6** (R = Me in Scheme 4) containing a minor quantity of the cyclic dimer 3,6-dimethylpiperazine-2,5-dione **7a**[21] (R = Me in Scheme 4, Table 1, entry 1). The products were characterized by NMR spectroscopy and mass spectrometry. The characteristic peak at 174.9 ppm in the $^{13}C\{^1H\}$ NMR spectrum of **6** indicates the presence of a carbonyl group. The specific rotation of the product in acetic acid was −105°. The ESI mass spectrum revealed the formation of a linear polypeptide sequence. The peak with the highest mass-to-charge ratio found by MALDI-TOF spectrometry was at *m*/*z* 1644, which corresponds to 23 monomer units (see the Supporting Information).

Interestingly, larger substituents in α-position to the amine group lead to the formation of the corresponding cyclic dipeptides as the only products under the same reaction conditions. Thus, a 1,4-dioxane solution of (*S*)-2-amino-4-methylpentan-1-ol heated to reflux with complex **1** (1 mol%) led to isolation of the cyclic dipeptide 3*S*,6*S*-3,6-diisobutylpiperazine-2,5-dione (**7b**) in 64% yield after workup (Table 1, entry 2).[22] The product structure was confirmed by NMR spectroscopy and mass spectrometry (see the Supporting Information). The optical rotation ($[\alpha]_D^{20} = -47°$) was very close to the reported value (−43°), thus indicating

Table 1: Synthesis of cyclic dipeptides from β-amino alcohols catalyzed by complex **1**.[a]

Entry	β-Amino alcohol	Peptide		Yield[b] [%]
1			**6**	72[c]
2			**7b**	64
3			**7c**	72
4			**7d**	78
5			**7e**	72
6			**7f**	92
7			**7g**	99

[a] Complex **1** (0.02 mmol), amino alcohol (2 mmol), and 1,4-dioxane (2 mL) were heated to reflux in argon (oil bath temperature of 135 °C) for 19 h. [b] Yield of isolated product. [c] Including a minor amount of the dipeptide **7a**.

that no racemization had taken place.[23] A lower yield of **7b** (52%) was obtained in toluene as a solvent. Similarly, the use of benzene as a solvent resulted in 48% yield after 26 h. The melting point of the cyclic dipeptide **7b** was 272 °C, as reported.[23]

In contrast to traditional peptide syntheses, which include both solid- and solution-phase methods and produce waste, during this reaction only H_2 is formed as a by-product. Activated esters or carboxylic acids or the use of microwave conditions are not required.

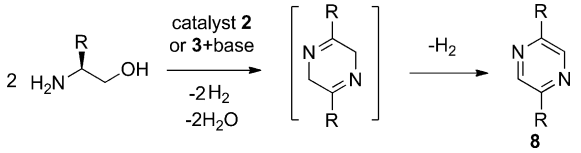
To explore the synthetic utility of this reaction, various β-amino alcohols were studied. A 1,4-dioxane solution containing (2*S*,3*S*)-2-amino-3-methylpentan-1-ol (2 mmol) and catalyst **1** (0.02 mmol) was heated to reflux for 19 h and then cooled to room temperature; subsequently the solid product precipitated, was filtered off, and was dried under vacuum to give pure 3-(*sec*-butyl)-6-(*sec*-butyl)piperazine-2,5-dione **7c** in 72% yield (Table 1, entry 3). The structure was confirmed by NMR spectroscopy and mass spectrometry. Under the same conditions, (*S*)-2-amino-3-methylbutan-1-ol yielded an

insoluble solid, which precipitated from the reaction mixture and was isolated by filtration and dried under vacuum to give 78% of (3*S*,6*S*)-3,6-diisopropylpiperazine-2,5-dione **7d** (Table 1, entry 4). The optical rotation of the pure product (−52°) was essentially the same as reported[24] (−54.8°). Thus, under the described experimental conditions, no racemization took place.

The reaction of (*S*)-2-amino-3-phenylpropan-1-ol and **1** in 1,4-dioxane at reflux led to 90% conversion and isolation of the corresponding (3*S*,6*S*)-3,6-dibenzylpiperazine-2,5-dione[24] **7e** in 72% yield without racemization (Table 1, entry 5 and the Supporting Information). The reaction of 2-amino-2-methylpropan-1-ol under the same conditions gave 100% conversion with isolation of the corresponding cyclic dipeptide 3,3,6,6-tetramethylpiperazine-2,5-dione **7f** in 92% yield (Table 1, entry 6).

Tricyclic ring systems represent an important structural motif in many naturally existing alkaloids. Such a ring system was readily achieved when (*S*)-pyrrolidin-2-yl-methanol was employed in the new cyclopeptidation reaction. Thus, heating a 1,4-dioxane solution of (*S*)-pyrrolidin-2-yl-methanol at reflux in the presence of catalyst **1** led to 100% conversion of the starting material as determined by GC–MS. After solvent evaporation and subsequent hexane addition to the crude solid, the solid was isolated by filtration and washed with hexane to give optically pure (5a*S*,10a*S*)-octahydrodipyrrolo[1,2-a:1′,2′-d]pyrazine-5,10-dione[23] **7g** in 99% yield (Table 1, entry 7).

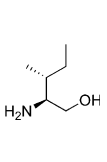
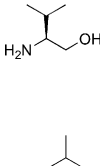
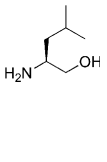
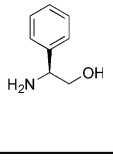
Pyrazines are biologically important organic compounds and their synthesis[25] is of industrial significance. Interestingly, when Ru^{II} PNP complex **2** or **3** in the presence of an equivalent amount of base was used as catalyst, an entirely different reaction took place, which led to pyrazine derivatives of β-amino alcohols rather than to diketopiperazines (Scheme 5). Thus, a toluene solution of isoleucinol with



Scheme 5. Synthesis of pyrazines from β-amino alcohols.

complex **2** (1 mol%) was heated to vigorous reflux in argon for 24 h, while the reaction progress was monitored by GC–MS, which showed complete conversion of isoleucinol. The solvent was evaporated under vacuum and the residue was purified by silica-gel column chromatography to afford 2,6-diisobutylpyrazine **8a** in 53% yield (Table 2, entry 1). In refluxing 1,4-dioxane, 40% conversion of the starting material was observed, yielding 15% of the product **8a** after 24 h. The ^{1}H NMR spectrum exhibits the characteristic aromatic CH signals at 8.27 ppm, and GC–MS confirms the expected molecular weight. The same reaction conducted in open air atmosphere in the presence of complex **2** resulted in isolation of **8a** in 48% yield. The reaction of isoleucinol in air using complex **3** in the presence of one equivalent of base (relative to Ru) under the same reaction conditions resulted in isolation of **8a** in 50% yield. The similar yields of **8a** obtained after reaction in argon and in air indicate that air does not play a role as oxidant in the dehydrogenation of the presumed intermediate 1,4-dihydropyrazine to form the pyrazine. Significantly, no cyclic dipeptide was obtained under these conditions. Similar results were obtained with other amino alcohols. Thus, toluene solutions of (*S*)-2-amino-3-methylbutan-1-ol, (*S*)-2-amino-4-methylpentan-1-ol, and (*S*)-2-amino-2-phenylethanol were heated at vigorous reflux (bath temperature 165°C) for 24 h while the reaction progress was monitored by GC–MS. After complete disappearance of the amino alcohol, the crude product was purified by column chromatography to give the corresponding pyrazine products **8b–d**[26,27] (Table 2).

Table 2: Synthesis of pyrazines from β-amino alcohols catalyzed by complex **2**.[a]

Entry	β-Amino alcohols	Pyrazines	Yield[b] [%]
1		**8a**	53 (48)[c]
2		**8b**	35
3[d]		**8c**	38
4		**8d**	45

[a] Complex **2** (0.02 mmol), an amino alcohol (2 mmol), and toluene (2 mL) were heated at vigorous reflux (oil bath temperature 165°C for 24 h). [b] Yield of isolated product. [c] Reaction performed in air (see the Supporting Information for details). [d] Heated in absence of solvent (oil bath temperature at 165°C).

Although mechanistic studies have not been carried out, we believe that first, O–H activation of the alcohol by complexes **1** or **2** results in aromatization of the pincer complex. Then H_2 liberation leads to the formation of a coordinated aldehyde complex. A sequence involving nucleophilic attack by the amine group of a second amino alcohol molecule on the aldehyde, which is coordinated to the PNN complex **1**, would eventually result in a peptide. In the case of the bulky PNP complex **2**, which lacks a hemilabile amine "arm", dissociation of the aldehyde and attack on it by the amino alcohol take place in solution, resulting in an imine (by water liberation from a hemiaminal), eventually leading to a

pyrazine after aromatization of a presumed 1,4-dihydropyrazine intermediate.

In summary, a new method for peptide-bond formation, in particular selective formation of cyclic dipeptides, and of poly(alanine), was developed using dehydrogenative self-coupling of β-amino alcohols. The reactions are catalyzed by the dearomatized PNN complex **1** and lead to a variety of biologically important cyclic dipeptides. In striking contrast, the closely related dearomatized PNP complex **2** selectively catalyzes the dehydrogenative coupling of β-amino alcohols to form pyrazines. These unprecedented reactions proceed under neutral reaction conditions and generate no waste, thereby representing a clear departure from traditional synthetic methodology.

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