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General Synthesis of Amino Acid Salts from Amino Alcohols and Basic Water Liberating H_2

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Supporting Information

ABSTRACT: An atom-economical and environmentally friendly method to transform amino alcohols to amino acid salts using just basic water, without the need of pre-protection or added oxidant, catalyzed by a ruthenium pincer complex, is developed. Water is the solvent, the source of the oxygen atom of the carboxylic acid group, and the actual oxidant, with liberation of dihydrogen. Many important and useful natural and unnatural amino acid salts can be produced in excellent yields by applying this new method.

Amino acids and their derivatives fulfill key roles in biology and chemistry, and there are many chemical and enzymatic methods for their preparation.[1,2] Traditional chemical procedures involve protection and deprotection steps, since unprotected amine groups can undergo side reactions. Among these methods, transformation of amino alcohols to amino acids is one of the most direct approaches. However, the corresponding methods mainly depend on stoichiometric use of strong and/or toxic oxidants, such as $KMnO_4$,[3a,b] pyridinium dichromate,[3c] Jones reagent,[3d] and 1-hydroxy-1,2-benziodoxol-3(1*H*)-one-1-oxide (IBX).[3e] In addition, some oxidative reactions promoted by catalysts and stoichiometric oxidants were developed for the synthesis of protected amino acids from protected amino alcohols, including systems based on CrO_3/H_5IO_6,[4a] $RuCl_3/NaIO_4$,[4b] TEMPO/$NaClO_2$,[4c] TEMPO/trichloroisocyanuric acid,[4d] and others. However, besides the disadvantages of stoichiometric oxidants which generate copious waste, none of the methods mentioned above was used to transform non-protected amino alcohols to non-protected amino acids; hence, step and atom economies in transforming amino alcohols to amino acids based on these processes are very low. A heterogeneous copper system was reported in a patent to catalyze transformation of amino alcohols to amino acids in water with very low turnover numbers (<6) under nitrogen pressure at 160 °C.[5] To our knowledge, efficient and environmentally benign methods to transform amino alcohols to amino acids are unknown.

We have developed several efficient and environmentally friendly acceptorless dehydrogenative coupling reactions based on ruthenium pincer catalysts, such as those shown in Figure 1.[6,7] In these reactions, an aldehyde intermediate is attacked by a nucleophile, such as an alcohol or an amine, leading to a hemiacetal or hemiaminal, which upon dehydrogenation forms an ester or an amide, respectively (Scheme 1a,b).[7] With water as the nucleophile, carboxylic acids can be produced (Scheme 1c). In this reaction, water is the source of the oxygen atom, and it can be viewed as an unusual oxidant, enabled by hydrogen liberation under thermal conditions. This new type of conversion presents the possibility of a more environmentally friendly and sustainable "oxidation by water" reaction,[8−10] as compared to traditional methods.

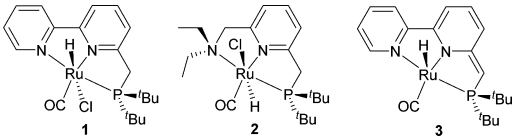
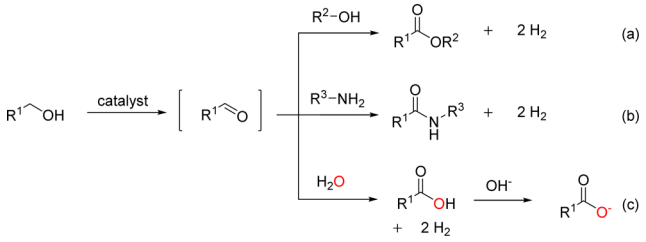


Figure 1. Structures of PNN ruthenium pincer complexes **1**−**3**.

Scheme 1. Synthesis of Esters, Amides, and Carboxylic Acids through Acceptorless Dehydrogenative Coupling Reactions



As recently reported, the Ru complex **1** catalyzes the transformation of primary alcohols to the corresponding carboxylic acid salts in basic water, with no added oxidant.[8−11] Both aliphatic alcohols and benzyl alcohols react smoothly, in good to excellent yields, at low catalyst loading of 0.2 mol%, with H_2 as the only byproduct. However, in the case of 4-aminobutan-1-ol, the product was γ-butyrolactam, not 4-aminobutanoic acid (Scheme 2, eq 1).[8] Apparently, the four-carbon amino alcohol undergoes intramolecular dehydrogenative amidation in preference to reaction with water. We have also reported that employing pre-catalyst **2** and catalytic base, β-amino alcohols underwent bimolecular reactions to form cyclic dipeptides (diketopiperazines) (Scheme 2, eq 2), or oligopeptides (Scheme 2, eq 3).[7e] Hence, it was of interest to explore the challenging prospect of shifting the reaction toward the production of α- and β-amino acids, which are among the most important amino acids (Scheme 2, eq 4). Reported herein is an efficient catalytic method for the direct, one-step transformation of β-, γ-, and long-chain amino alcohols to the

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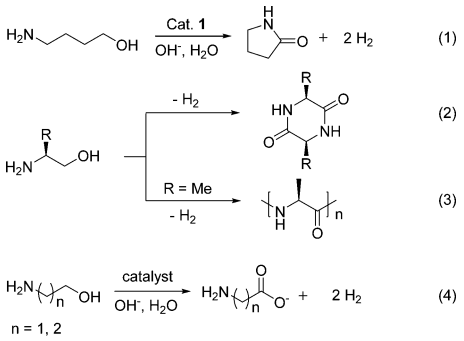
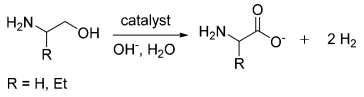
Scheme 2. Acceptorless Dehydrogenation Reactions of Amino Alcohols; Equation 4 Shows Targeted Amino Acid Synthesis



corresponding amino acid salts, using only basic water, not requiring pre-protection or added oxidant.

First, 2-aminoethanol was chosen to test the feasibility of the reaction. Refluxing a water:dioxane (1:1 v/v ratio) solution containing 0.1 mol% complex **1**, 10 mmol of NaOH, and 5 mmol of 2-aminoethanol for 24 h under an argon atmosphere resulted in a quantitative yield of the glycine sodium salt, as determined by ^{1}H NMR spectroscopy; 233 mL of H_2 was collected, amounting to 98% yield based on full conversion of 2-aminoethanol (Table 1, entry 1). Applying catalyst **2** under similar conditions resulted in formation of the glycine salt and H_2 in lower yields of 73% and 74%, respectively (entry 2). Using a *catalytic* amount of KO^{t}Bu (1.2 equiv relative to the catalyst) for generation of the actual catalyst **3** *in situ*, no product was observed (entry 3). Apparently, at least a stoichiometric amount of base is required; otherwise, the generated acid deactivates the catalyst.[8] The outcome of the reaction was influenced by the amount of NaOH; 70% yield of the glycine salt was produced when 1.1 equiv of NaOH was applied (entry 4). Glycine is an important genetic code amino acid and widely used as an additive in foods, a buffering agent in cosmetics, and an important chemical feedstock.[1c,12] Disappointingly, when 2-amino-1-butanol was used, only 46% yield of the corresponding amino acid salt was formed under the conditions of entry 4 (entry 5). Use of catalyst **2** led to an even lower yield of 29% (entry 6). Further optimization revealed that better results can be obtained using H_2O as solvent in the absence of dioxane, leading to 70% yield of α-aminobutyric acid salt (entry 7). Changing the base from NaOH to KOH resulted in a still better yield of 77% (entry 8). The concentration of base strongly influenced the reaction. Thus, doubling the volume of H_2O resulted in a yield drop of α-aminobutyric acid salt to 26% (entry 9). Increasing the catalyst loading to 0.2 mol % under the conditions of entry 8 resulted in a higher yield of 89% (entry 10). Based on the results of entries 9 and 10, 0.2 mol% catalyst **1** was applied in basic H_2O with higher KOH concentration, resulting in excellent yields of α-aminobutyric acid salt (entries 11, 12). α-Aminobutyric acid is a key intermediate in biosynthesis of ophthalmic acid.[13]

Table 1. Optimization Studies for Transformation of Amino Alcohols to Amino Acid Salts[a]



entry	cat. (mol%)	R	base (mmol)	conv[b] (%)	yield[b] (%)
1	**1** (0.1)	H	NaOH (10)	100	>99[c]
2	**2** (0.1)	H	NaOH (10)	73	73[d]
3[e]	**1** (0.1)	H	_	0	0
4	**1** (0.1)	H	NaOH (5.5)	70	70
5	**1** (0.1)	Et	NaOH (5.5)	46	46
6	**2** (0.1)	Et	NaOH (5.5)	31	29
7[f]	**1** (0.1)	Et	NaOH (5.5)	70	70
8[f]	**1** (0.1)	Et	KOH (5.5)	79	77
9[g]	**1** (0.1)	Et	KOH (5.5)	26	26
10[f]	**1** (0.2)	Et	KOH (5.5)	90	89
11[h]	**1** (0.2)	Et	KOH (5.5)	96	94
12[f]	**1** (0.2)	Et	KOH (7.5)	98	95

[a]Conditions: catalyst (as specified), 2-aminoethanol or 2-aminobutan-1-ol (5 mmol), base (as specified), water (0.5 mL), and dioxane (0.5 mL) were refluxed at 125 °C (oil bath temperature) in an open system under argon for 24 h. [b]Conversions and yields determined by NMR. [c]233 mL of H_2 (20 °C, 1 atm) was collected, amounting to 98% yield based on full conversion of 2-aminoethanol. [d]175 mL of H_2 (20 °C, 1 atm) was collected, amounting to 74% yield based on full conversion of 2-aminoethanol. [e]0.12 mol% of KO^{t}Bu was used. [f]0.5 mL of water was used as solvent. [g]1 mL of water was used as solvent. [h]0.3 mL of water was used as solvent.

Employing the optimized reaction conditions, we explored the substrate scope. Interestingly, 2-(2-hydroxyethylamino)-acetic acid salt was produced selectively and quantitatively using diethanolamine, applying water/dioxane (1:1 v/v ratio) as the solvent (Table 2, entry 1). The reason for the observed mono-oxidation rather than formation of the dicarboxylic acid salt is not clear. However, using *N*,*N*′-bis(2-hydroxyethyl)ethylene-diamine, the diacetic acid salt was formed in excellent yield (entry 2). Reaction of 2-aminopropanol catalyzed by **1** (0.1 mol %) resulted quantitavely in the alanine salt in water/dioxane (entry 3). L-Alanine is second only to leucine as the building block of proteins[14a] and is used in radiotherapy.[14b] Reaction of *N*-methylethanolamine resulted in quantitative yields of sarcosine salts using either a mixture of water/dioxane or water only as solvent (entry 4). Sarcosine is ubiquitous in biological materials, is used in manufacturing of biodegradable surfactants, and has been investigated in treatment of mental illness.[15] Under the same conditions, *N*,*N*-dimethylethanol-amine was transformed to the corresponding dimethylglycine salts in 95% and 93% yields, respectively (entry 5). The reaction efficiency was not influenced by steric hindrance of substituted amine groups; both *N*-isopropylethanolamine and *N*-*tert*-butylethanolamine produced the corresponding amino acid salts in excellent yields (entries 6 and 7), and in the case of *N*-*tert*-butylethanolamine, quantitative yield was obtained with 0.5 mol% catalyst. However, with 2-amino-3-methyl-1-butanol, only 25% yield of valine salt was formed, using 0.2 mol% catalyst **1** in ca. 18 M KOH aqueous solution. Increasing the catalyst loading to 1 mol% and using water/dioxane (1:1 v/v ratio) as the solvent resulted in 94% yield of the valine salt (entry 8). The same reaction conditions also worked very well for leucinol (entry 9) and 2-amino-2-methyl-1-propanol (entry 10). Similar reaction conditions but lower catalyst loading (0.5 mol%) also led to an excellent yield of the proline salt when prolinol was applied (entry 11). When 2-amino-3-phenyl-1-propanol and 2-amino-2-phenyl-1-ethanol were tested, the phenylalanine salt and 2-phenylglycine salt were both produced in quantitative yields (entries 12 and 13). Phenylalanine is a natural amino acid and performs as a precursor for many essential bioactive compounds; it is also used in food and

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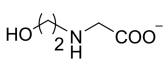
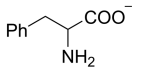
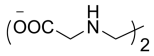
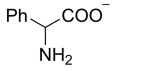
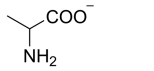
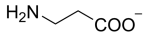
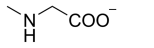
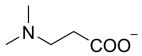
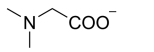
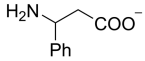
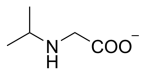
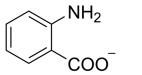
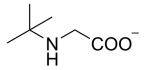
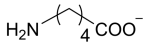
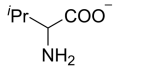
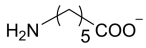
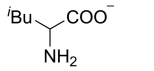
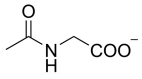
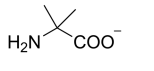
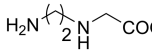
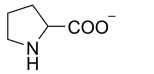
Table 2. Substrate Scope of the Transformation of Amino Alcohols to Amino Acid Salts

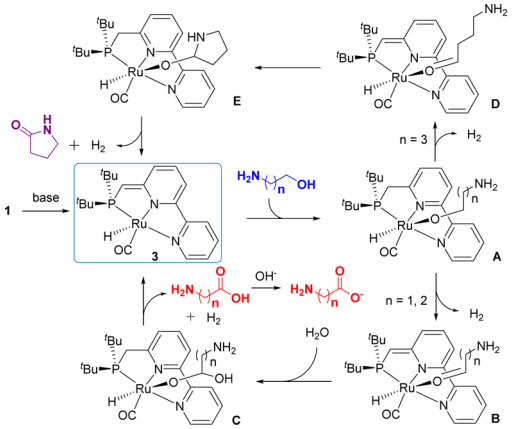
entry	product and yield (%)	entry	product and yield (%)
1	 > 99[a]	12	 > 99[b]
2	 96[b]	13	 > 99[g]
3	 > 99[c] (71)	14	 94[c]
4	 > 99[c] > 99[d]	15	 96[b]
5	 95[c] 93[d]	16	 72[h]
6	 93[c] (87)	17	 94[b]
7	 > 99[b] 95[c]	18	 > 99[c] (71)
8	 25[d] 94[e]	19	 > 99[a] (82)
9	 95[e] (92)	20	 95[f] (94)
10	 94[e] (91)	21	 > 99[a]
11	 > 99[f]		

[a]0.2 mol% **1**, 2.5 mmol of reactant, 10 mmol of NaOH, 0.5 mL of H_2O, and 0.5 mL of dioxane. [b]0.5 mol% **1**, 2 mmol of reactant, 7.5 mmol of KOH, and 0.5 mL of H_2O. [c]0.1 mol% **1**, 5 mmol of reactant, 10 mmol of NaOH, 0.5 mL of H_2O, and 0.5 mL of dioxane. [d]0.2 mol% **1**, 5 mmol of reactant, 5.5 mmol of KOH, and 0.3 mL of H_2O. [e]1 mol % **1**, 1 mmol of reactant, 10 mmol of NaOH, 0.5 mL of H_2O, and 0.5 mL of dioxane. [f]0.5 mol% **1**, 1 mmol of reactant, 10 mmol of NaOH, 0.5 mL of H_2O, and 0.5 mL of dioxane. [g]1 mol% **1**, 1 mmol of reactant, 7.5 mmol of KOH, 0.5 mL of H_2O. [h]0.5 mol% **1**, 1 mmol of reactant, 7.5 mmol of KOH, 0.5 mL of H_2O. Conditions: reflux at 125 °C (oil bath temperature) under argon for 24 h. Yields determined by NMR. Yields in parentheses are isolated yields of corresponding amino acids.

drinks.[16] Significantly, γ-amino alcohols were also good substrates for the reaction. Thus, 3-aminopropanol reacted smoothly under the same conditions as 2-aminopropanol and offered the β-alanine salt in 94% yield (entry 14). β-Alanine is the rate-limiting precursor of the antioxidant carnosine, which acts as an antiglycating agent.[17] Applying *N*,*N*-dimethyl-3-aminopropanol as substrate yielded 96% of the corresponding amino acid salt (entry 15). 3-Amino-3-phenyl-1-propanol gave 72% yield of 3-amino-3-phenyl-1-propanic acid salt, catalyzed by 0.5 mol% **1** (entry 16). 2-Aminobenzyl alcohol was converted under similar conditions to anthranilic acid salt in 94% yield (entry 17). Amino alcohols with longer chains also led to the corresponding amino acid salts in excellent yields (entries 18 and 19). Interestingly, the 2-acetamid group of 2-acetamidoethanol was tolerated under the basic conditions, and 93% yield of 2-acetamido-acetic acid salt was obtained (entry 20). The reaction was effective also with a substrate bearing two amino groups (entry 21). However, the sulfur-bearing methioninol did not yield the product, likely because of catalyst poisoning.

Based on our former research on transformation of primary alcohols to carboxylic acids[8] and the results presented above, a possible mechanism for the oxidation of amino alcohols to amino acid by water is shown in Scheme 3. Deprotonation of **1**

Scheme 3. Proposed Mechanism for the Catalytic Transformation of Amino Alcohols to Amino Acids or Lactams



leads to the actual dearomatized catalyst **3**. Addition of the amino alcohol to **3** can lead to the aromatized intermediate **A**. H_2 elimination (involving the hydride ligand and the "arm") can generate a dearomatized intermediate, followed by β-H elimination to form the dearomatized species **B**, bearing a coordinated aldehyde. Water addition to the formyl group of **B** can provide the aromatized intermediate **C**, which eliminates the product amino acid and dihydrogen and regenerates catalyst **3**.[18] The amino acid is then converted to the salt. In the case of $n = 3$, such as with 4-aminobutan-1-ol, the longer alkyl amino group condenses with the formyl group of the dearomatized intermediate **D**, generating a five-membered cyclic hemiaminal and forming the aromatized intermediate **E**, which upon dehydrogenation produces γ-butyrolactam.

In conclusion, a highly efficient and simple method for the production of amino acid salts directly from amino alcohols at low catalyst loadings by dehydrogenation in basic water was developed. No added oxidant is required, and no protection groups are needed. Excellent yields of amino acid salts were generally obtained. Though at this stage optically pure amino acids cannot be provided due to the basic environment, many other important and useful natural and unnatural amino acid salts can be produced by this new method. In industry and laboratory, many α-amino acids, such as glycine and alanine, are usually produced through Strecker amino acid synthesis,[19] for which highly toxic KCN or NaCN is needed. Importantly, our method is atom-economical and environmentally friendly, as opposed to traditional methods, the only byproduct being H_2, valuable by itself.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b03488.

Experimental and spectroscopic details (PDF)

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Notes

The authors declare no competing financial interest.

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(18) See Supporting Information for a $H_2{}^{18}O$ labeling experiment. ^{18}O-labeled products were observed as the major products. Combined with the H_2 collection results (Table 1, entries 1 and 2), it is clear that H_2O, and not O_2 or other oxygen sources, is the origin of oxygen atom of the generated carboxylic acid group. See also ref 8.

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