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Synthesis of α-Hydroxy Carboxylic Acids *via* a Nickel(II)-Catalyzed Hydrogen Transfer Process

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Abstract: A new catalytic system for β-alkylation of lactic acid with primary alcohols has been developed. In the presence of nickel(II) acetate tetrahydrate [$Ni(OAc)_2(H_2O)_4$] and base, lactic acid reacts with primary alcohols to afford the corresponding coupled α-hydroxy carboxylic acids in good to excellent yields *via* a hydrogen transfer process without any hydrogen acceptor or hydrogen donor.

Keywords: hydrogen transfer process; α-hydroxy carboxylic acids; lactic acid; nickel-catalyzed reaction; primary alcohols

α-Hydroxy carboxylic acids are broadly used in the cosmetics and pharmaceutical industries.[1] The main method for the synthesis of this type of compounds is *via* the cyanation of aldehyde followed by hydrolysis as shown in the literature.[2] However, the aldehydes used are usually low in stability and sodium cyanide is highly toxic.

Catalytic β-alkylation of secondary alcohols with primary alcohols is a convenient way to make higher alcohols. Only few examples of this type of catalytic reactions are reported in the literature.[3,4] Most of the homogeneous catalysts used for these reactions are Ru complexes[4] and Ir complexes under nitrogen conditions.[5] The base-mediated β-alkylation of alcohols under aerobic conditions without transition metal catalysts was also reported by Crabtree.[6] In addition, although that many secondary alcohols were employed for the β-alkylation catalyzed by these complexes, no α-hydroxy carboxylic acids as the substrates has been investigated.

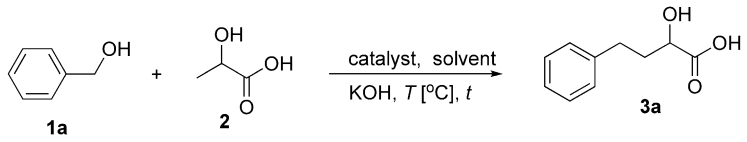
Direct condensation of simple lactic acid with primary alcohols catalyzed by an air-stable metal complex for the synthesis of α-hydroxy carboxylic acids could be an environmentally more friendly route than the one using aldehydes and sodium cyanide as the reagents.

Our continued interest in nickel-catalyzed reactions recently[7] prompted us to explore the possibility of using low-cost nickel complexes as the catalysts for hydrogen transfer process reactions. We found that the air stable $Ni(OAc)_2(H_2O)_4$ complex can catalyze the β-alkylation lactic acid with primary alcohols to give the corresponding products in good yields.

This nickel-catalyzed β-alkylation of lactic acid depends greatly on the reaction conditions. To optimize the conditions, we examined the effect of solvent, base, and ligand on the reaction yield (Table 1). Benzyl alcohol (**1a**) and lactic acid were used as the substrates in these studies. The catalytic reaction did not proceed or proceeded very slowly at 120 °C (entries 1–5). When a mixture of **1a** (3.0 mmol) and lactic acid (3.60 mmol) was heated in the presence of $Ni(OAc)_2(H_2O)_4$ (5 mol%) and KOH (5.40 mmol) at 155 °C under nitrogen for 3 h, 2-hydroxy-4-phenylbutanoic acid (**3a**) was obtained in excellent yield (entry 10). Product **3a** is an important building block for the production of a large variety of angiotensin-converting enzyme (ACE) inhibitors.[8] Under similar reaction conditions, the addition of a phosphine ligand such as dppm, dppe or PPh_3 resulted in 85–92% product yields (Table 1, entries 7–9). $NiCl_2$ or $NiBr_2$ was also effective for the benzylation of lactic acid (entries 17 and 18).

An advantage of this nickel(II)-catalyzed β-alkylation of lactic acid is that the reaction can also successfully proceed under aerobic conditions. As shown in entry 11, when **1a** and **2** were heated in the presence of $Ni(OAc)_2(H_2O)_4$ under an atmosphere pressure of air, the reaction gave **3a** in 87% yield. In a control reaction, benzyl alcohol and 2-hydroxypropionic acid in

Table 1. Optimization of β-alkylation of lactic acid.[a]



1a 2 3a

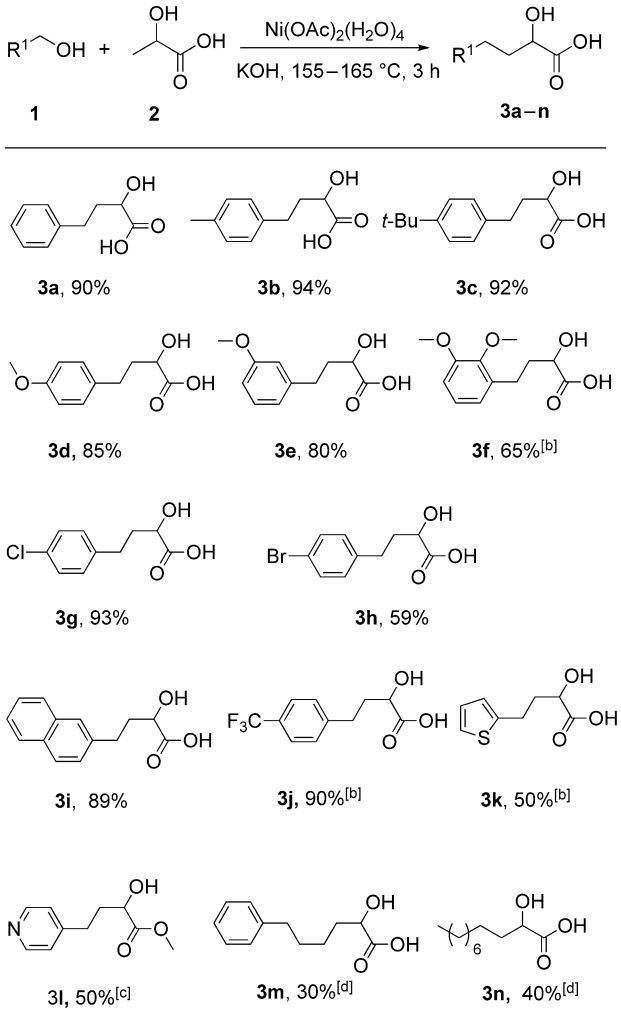
Entry	Catalyst	Ligand	Base	Solvent	T	Yield [%]
1	$Ni(Ni(OAc)_2$	dppm	KOH	*t*-BuOH	100	0
2	$Ni(OAc)_2$	dppm	KOH	H_2O	120	0
3	$Ni(OAc)_2$	dppm	KOH	PhMe	120	0
4	$Ni(OAc)_2$	dppm	KOH	BuOH	120	16
5	$Ni(OAc)_2$	dppm	KOH	ethyl glyme	120	13
6	$Ni(OAc)_2$	dppm	KOH	–	140	20
7[b]	$Ni(OAc)_2$	dppm	KOH	–	155	90
8[b]	$Ni(OAc)_2$	dppe	KOH	–	155	85
9[b]	$Ni(OAc)_2$	Ph_3P	KOH	–	155	92
10[b]	$Ni(OAc)_2$	–	KOH	–	155	90
11[c]	$Ni(OAc)_2$	–	KOH	–	155	87
12[c]	$Ni(OAc)_2$	–	KOH	–	180	85
13[c]	–	–	KOH	–	165	6
14[c]	$Ni(OAc)_2$	–	K_2CO_3	–	155	8
15[c]	$Ni(OAc)_2$	–	K_3PO_4	–	155	12
16[c]	$Ni(OAc)_2$	–	DBU	–	155	0
17[c]	$NiCl_2$	–	KOH	–	155	90
18[c]	$NiBr_2$	–	KOH	–	155	85

[a] Unless otherwise mentioned, the reaction was carried out with **1a** (3.0 mmol), **2a** (3.60 mmol), $Ni(OAc)_2(H_2O)_4$ (0.150 mmol, 5 mol%), KOH (5.40 mmol), and N_2 for 30 h in a sealed tube. Yields were determined by ^1H NMR.
[b] Heated under a nitrogen atmosphere (one atm at room temperature) at 155 °C for 3 h.
[c] Heated under aerobic conditions at 155 °C for 3 h; then at 180 °C for 0.5 h.

the presence of KOH but without $Ni(OAc)_2(H_2O)_4$ were heated at 165 °C for 3 h under aerobic conditions, to afford **3a** in only 6% yield (entry 13). The result indicates that a nickel catalyst is essential to achieve high yield of product **3a** even when the reaction was carried out under aerobic conditions (one atm at room temperature).[6] In the absence of a base, the catalytic reaction did not proceed. Various bases were tested for the catalytic reaction. Among them, KOH gave the highest yield of product **3a** (entries 10–16). Other bases such as K_3PO_4, K_2CO_3 and DBU were less effective, giving **3a** in very low yield. The choice of temperature is also vital to the catalytic reaction (entries 5–9). When the temperature was below 140 °C (entries 1–6), product **3a** was detected in 0–20% yields. However, when the temperature was raised to 155 °C, the β-alkylation of lactic acid could be carried out in the absence of solvents and the reaction gave **3a** in 90% yield. It is critical to keep the temperature higher than 155 °C, because the mixture is turned into a cream; the potassium lactate generated appears to be melted and the mixing of reaction components is better above this temperature. When the temperature was raised to 180 °C, β-alkylation of lactic acid was completed within 30 min in the presence of $Ni(OAc)_2(H_2O)_4$ under aerobic conditions.

Encouraged by this result, we decided to try out the reaction of various primary alcohols with lactic acid. The results are shown in Table 2. 4-Methyl- and 4-*tert*-butylbenzyl alcohols reacted similarly to afford the corresponding α-hydroxy carboxylic acids **3b** and **3c** in excellent yields. Treatment of lactic acid with various methoxy-substituted benzyl alcohols led to the formation of products **3d–3f** in 65–85% yields. These products are important building blocks for preventives and remedies for diabetes pharmaceuticals.[9] 4-Chloro- and 4-bromobenzyl alcohols were examined for their reactivity with lactic acid under similar reaction conditions and gave the expected products **3g** and **3h** in 93 and 59% yields, respectively. These two products are known to be intermediates for several important pharmaceuticals.[9a,10] Substituted benzyl alcohols with electron-donating 2,3-dimethoxy and electron-withdrawing trifluoromethyl groups and thienylmethyl alcohol also reacted smoothly with lactic acid to afford products **3f**, **3j** and **3k**, respectively, in 50–90% yield. However, a much higher reaction temperature of 175–180 °C in the presence of less basic K_3PO_4 was required for the reactions. It is noteworthy that 2-hydroxy-4-(4-(trifluoromethyl)phenyl)butanoic acid (**3j**), a soluble epoxide hydrolase inhibitor,[11] was obtained in 90% yield. The present catalytic reaction was also successfully applied to aliphatic alcohols,

Table 2. Nickel-catalyzed alkylation of lactic acid with primary alcohols.[a]



[a] *Reaction conditions:* primary alcohol (3.0 mmol), lactic acid (3.60 mmol), $Ni(OAc)_2(H_2O)_4$ (0.150 mmol), KOH (5.40 mmol), 155–165 °C, 3 h, under aerobic conditions. Isolated yield based on the primary alcohol used.

[b] Primary alcohol (3.0 mmol), lactic acid (3.60 mmol), $Ni(OAc)_2(H_2O)_4$ (0.150 mmol), K_3PO_4 (14.4 mmol), 175-180 °C, 3 h, under aerobic conditions. Isolated yield based on primary alcohol.

[c] 1) Reaction conditions as in footnote[a]; 2) methanol (20.0 mL), H_2SO_4 (3.0 mL), reflux 3 h.

albeit in lower yields. Thus, 3-phenylpropanol and 1-octanol reacted with lactic acid to afford the corresponding α-hydroxy carboxylic acid **3m** and **3n** in 30 and 40% yields, respectively.

Our catalytic system is also effective for the alkylation of 2-alkanols with benzyl alcohol giving the corresponding β-alkylated products (**3o–3q**) in 75–85% yields under nitrogen atmosphere (Scheme 1). In a control reaction, benzyl alcohol and 1-phenylethanol in toluene in the presence of KOH, but without $Ni(OAc)_2(H_2O)_4$ and dppm, were heated at 115 °C for 30 h and the corresponding alkylation product **3o** was obtained in merely 12% yield.

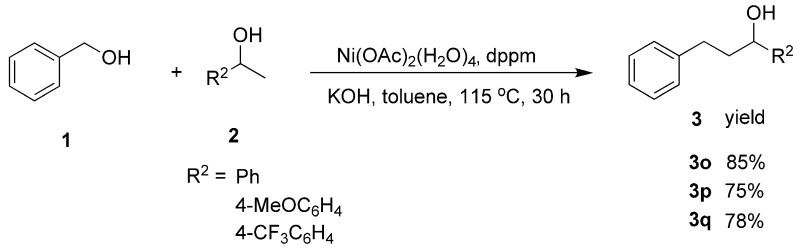
A possible mechanism for this Ni(II) complex-catalyzed β-alkylation of lactic acid with primary alcohols is described in Scheme 2. The initial key step involves the β-hydrogen elimination of alkoxide–NiX to give aldehyde, potassium pyruvate and a hydridonikel species. The cross-aldol reaction of the aldehyde with potassium pyruvate generated affords the α,β-unsaturated ketone intermediate. Successive transfer hydrogenation of C=C and C=O double bonds of the α,β-unsaturated ketone by the hydridonikel species generated in the first step leads to the final product. In this catalytic reaction, the addition of a hydrogen donor or acceptor is not necessary, unlike the $RuCl_2(PPh_3)_3$ catalytic system, making our system a more atom economical process.

In summary, we have shown a new efficient system for the β-alkylation of lactic acid with primary alcohols catalyzed by air-stable Ni(II) complexes. Many biologically active α-hydroxy carboxylic acids can be synthesized in high yields using this nickel system as the catalyst.

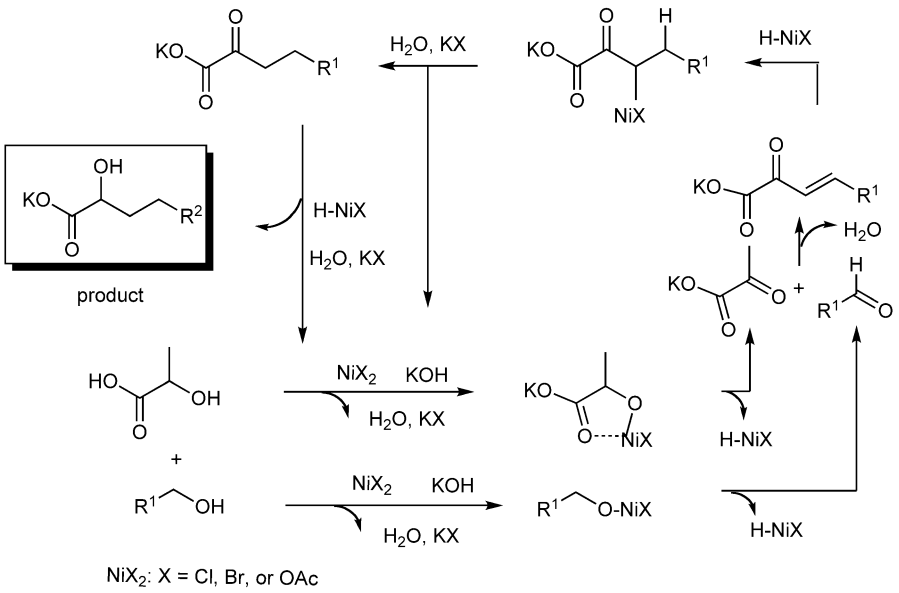
Experimental Section

Typical Procedure for the Synthesis of 3a–3n

To an ice-cooled solution of KOH (5.40 mmol) in H_2O (6.0 mL) and toluene (10.0 mL) in a 25-mL round-bottom flask equipped with a Dean–Stark apparatus, lactic acid (3.60 mmol) was added slowly. The reaction mixture was



Scheme 1. Nickel-catalyzed β-alkylation of secondary alcohols with benzyl alcohols. *Reaction conditions:* **1** (1.2 mmol), **2** (1.0 mmol), dppm (0.050 mmol), $Ni(OAc)_2(H_2O)_4$ (0.050 mmol), KOH (3.0 mmol), toluene (3.0 mL), in a sealed tube, 115 °C, N_2 1 atm (ambient room pressure), 30 h. Isolated yield based on **2**.



Scheme 2. A possible catalytic reaction pathway.

stirred for 50–70 min in a 135 °C silicon oil bath to remove the water in the mixture. Primary alcohol (3.0 mmol) and $Ni(OAc)_2(H_2O)_4$ (0.150 mmol) were then added into the flask. The reaction mixture was stirred at 155–165 C for 3 h and subsequently water (50.0 mL) was added. The solution was extracted with toluene (2×20.0 mL). The water phase was acidified with concentrated HCl to pH < 3.0, then extracted with EtOAc (3×30.0 mL) and combined with the organic solution. The organic layer was washed with brine (2× 10.0 mL), dried with sodium sulfate, and filtered. The filtrate was evaporated under vacuum. The crude product was purified on a silica gel column using hexane-ethyl acetate (1/5–1/1 v/v) as eluent to give the corresponding pure product **3a–3n**.

Supporting Information

Experimental details and copies of NMR spectra of all compounds are available as Supporting Information.

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