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Metal–Ligand Cooperation in the Catalytic Dehydrogenative Coupling (DHC) of Polyalcohols to Carboxylic Acid Derivatives

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Abstract: Several polyols, which are easily available from sugars through biochemical conversion or hydrogenolytic cleavage, are directly converted into carboxylic acids and amides. This efficient dehydrogenative coupling process, catalyzed by a rhodium(I) diolefin amido complex, is an attractive approach for the production of organic fine chemicals from renewable resources. This method tolerates the presence of several hydroxy groups and can be extended to the direct synthesis of lactams from the corresponding amino alcohols under mild conditions.

Keywords: biomass · cooperative effects · ligand effects · polyols · rhodium · sustainable chemistry · transfer hydrogenation

Introduction

Many organic fine chemicals, commodity chemicals, and polymer components are currently derived from the partial air oxidation of fossil feedstocks.[1] The rapid increase in the price of limited fossil fuels combined with their long-standing environmental harm have led to heightened interest in alternative renewable resources, which ideally are neutral in carbon dioxide consumption and production.[2] In the past few years, vast efforts have been made in the chemical transformation of biorenewable feedstocks into valuable and fine chemicals and fuels.[3] The more abundant and sustainable alternatives to fossil carbon resources are carbohydrates and their polyol derivatives. The development of highly selective and reactive transition-metal catalysts for the conversion of highly functionalized molecules, which are obtained from sugar-rich crops and biomass fermentation, into fine chemicals remains a challenge.[4]

The inherent advantage of an approach based on a homogeneous catalytic system is better control of the process parameters leading to high selectivity compared to conventional transformations based on fermentation and pyrolysis processes. An ideal homogeneous catalyst needs to be compatible with the common functionalities present in biomass carbohydrates [(poly)hydroxyl, carbonyl, and acetal groups] and should be stable and efficient in an aqueous environment. The design of an active and chemoselective catalytic system for the dehydrogenation of unprotected polyhydroxy compounds like sugars is especially burdened by the multitude of possible interactions of the substrate with the metal center, eventually leading to the inactivation of the catalyst. Relatively few metal-based homogeneous catalytic systems exhibit high chemoselectivities in the oxidation of primary and/or secondary alcohols using hydrogen transfer as a strategy.[5] In sugars, this process typically affects the secondary hydroxy functions and the precursor molecules are transformed into keto-sugars.[6] There is an increasing interest in the selective transformation of glycerol into useful building blocks for the synthesis of fine chemicals based on simple and selective oxidation processes.[7] The direct conversion of an alcohol into a carbonyl compound using a dehydrogenative oxidation reaction in the first step and the immediate, subsequent conversion into another product in a tandem reaction using a single catalyst is an attractive approach for the direct transformation of alcohols into valuable chemicals.[8]

Some homogeneous catalysts based on rhodium[9] and ruthenium[10,11] complexes have demonstrated high efficiency in the direct synthesis of carboxylic acid derivatives from simple primary alcohols. Milstein et al. established a PNN-ruthenium (PNN = 2-di-*tert*-butylphosphinomethyl-6-diethylaminomethylpyridine) assisted dehydrogenative coupling reaction (DHC) of alcohols of the type $R{-}CH_2{-}OH + EH \rightarrow R{-}CO(E) + 2\,H_2$ (E = OR, NHR, R = alkyl, aryl) under acceptorless conditions, in which molecular hydrogen is released as a carrier of chemical energy.[11h–j] This catalyst also allowed the direct conversion of alcohols into amides, which is a new reaction.[11j] Later, catalysts containing ruthenium and a *N*-heterocyclic carbene ligand and showing a high efficiency for the transformation of alcohols into amides were reported.[11k–p] However, only monoalcohols or special diols with a long spacer group of at least six methylene units between the two hydroxy groups can be employed as substrates with these catalysts.[12] Other dihydroxy compounds with shorter spacer groups are not converted, most likely due to poisoning of the ruthenium complex through chelation to the metal center.

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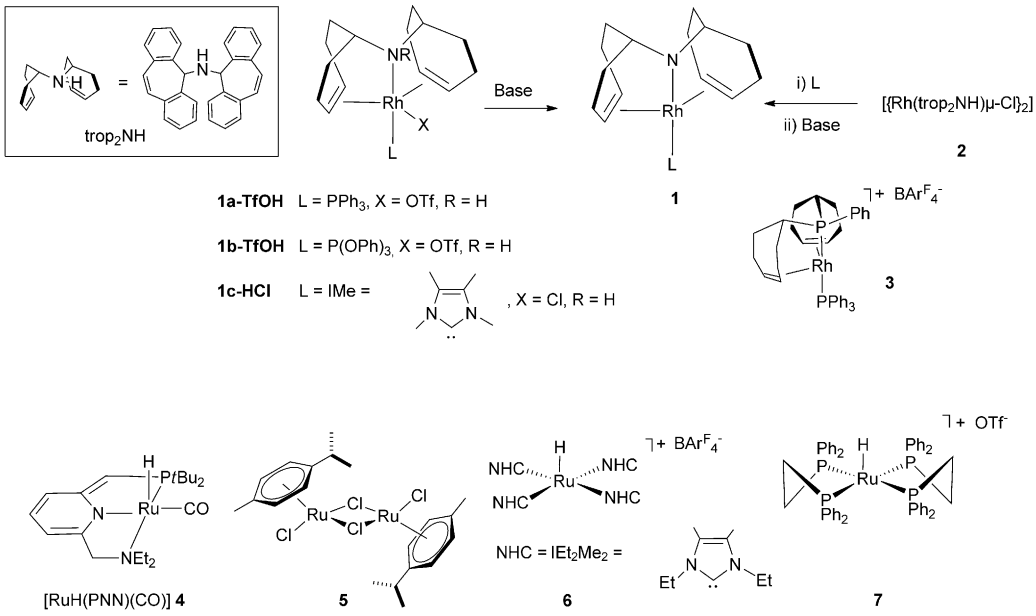
Only recently has the direct synthesis of five and six membered cyclic imides from diols and a primary amine using an in situ generated *N*-heterocyclic carbene (NHC) catalyst been reported.[13] In general, these reactions require elevated temperatures and long reaction times. For the transformation of sensitive substrates it is desirable to find a catalytic system which operates at low temperatures with low catalyst loadings, with high stability and chemoselectivity, which tolerates a wide variety of functional groups by proceeding through simple protocols, and which has an easy workup. We reported the first experiments that allowed the chemoselective, homogeneously catalyzed DHC of simple primary alcohols with water, methanol, or amines to give carboxylic acids, methyl esters, or amides, respectively, under very mild reaction conditions using diolefin rhodium (I) complexes **1a-TfOH** or **1a** (Scheme 1).[9b–d] These reactions require a hydrogen acceptor. Cyclohexanone was found to be especially suitable because it can be quantitatively regenerated from cyclohexanol with hydrogen peroxide, H_2O_2, as an environmentally benign secondary oxidant in a second catalytic reaction. Hence, the overall net reaction reads: $R{-}CH_2{-}OH + EH + 2H_2O_2 \rightarrow R{-}CO(E) + 4H_2O$; E = OH, methoxy (OMe), NHR′ (R′ = Bn). The motivation of the present work is to contribute to the development of an efficient oxidation of primary hydroxyl groups in unprotected polyols that can complement the existing methodologies. Here we report the activity of a series of well defined homogeneous rhodium(I) complexes which gives remarkable results with respect to the chemo and regioselectivity in dehydrodenative catalytic processes.

Results and Discussion

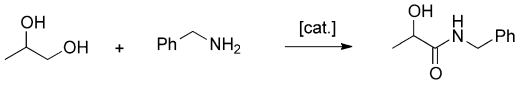
The reaction between 1,2-propanediol and benzylamine was chosen as a model for the optimization of amidation reaction conditions. A screening of catalysts was performed. We used either a series of diolefin amine rhodium(I) complexes, combined with a hydrogen acceptor, or several ruthenium based catalytic systems under acceptorless conditions (Scheme 1 and Table 1). Application of the conditions originally reported by Milstein (**4** as catalyst at $>100\,^{\circ}C$[11j]) only yielded traces of product (entry 1, Table 1). Catalytic systems containing a ruthenium precursor like **5** and a NHC as a potential ligand were found to be active for the amidation of monoalcohols (entry 2, Table 1),[11l] but it only showed moderate activity after 24 h, although the conversion continuously increased with time without an apparent deactivation of the catalyst (up to 46% after 48 h). Well-defined hydridoruthenium complexes supported by four NHC-carbene ligands, $[RuH(IEt_2Me_2)_4][BAr^F{}_4]$ (**6**, IEt_2Me_2 = 1,3-diethyl-4,5-dimethylimidazole-2-ylidene, $Ar^F = C_6H_3(CF_3)_2$),[14] or bearing bidentate phosphane ligands, $[HRu(dppe)_2(OTf)]$ (**7**, dppe = 1,2-bis(diphenylphosphanyl)ethane, OTf = triflate),[15] showed little activity (entries 3 and 4, Table 1). Based on previous findings, we investigated a number of diolefin amide rhodium complexes (**1**–**3**) in the catalytic DHC of polyols.

The active catalyst can be generated from the precursor (**1-TfOH**, **1-HCl** or **2**) by employing a stoichiometric amount of base (potassium *tert*-butoxide (*t*BuOK), lithium bis(trimethylsilyl)amide (LiHMDS), or NaH). A difference in the efficiency of the reaction was not observed if the catalyst **1a** is used directly or if it is generated in situ. Among the solvents tested, the best results were obtained with THF or when carrying out the reaction without a solvent but with



Scheme 1. Selection of complexes for the catalyst screening in the dehydrogenative coupling of polyols; $Ar^F = C_6H_3(CF_3)_2$, IMe = 1,3,4,5-tetramethylimidazole-2-ylidene, NHC = IEt_2Me_2 = 1,3-diethyl-4,5-dimethylimidazole-2-ylidene, OTf = triflate, PNN = 2-di-*tert*-butylphosphinomethyl-6-diethylaminomethylpyridine, $P(OPh)_3$ = triphenylphosphite.

Table 1. Screening with different catalysts and conditions for the amidation of 1,2-propanediol.[a]



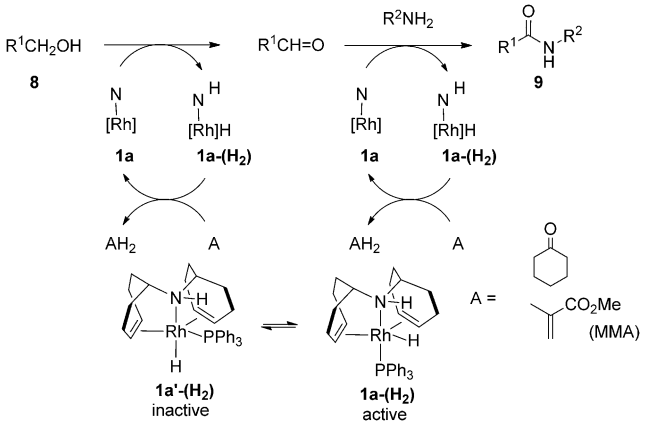
entry	Catalyst [mol %]	Ligand	Additive [mol %]	Conditions	Yield [%][b]
1[c]	[RuH(PNN)(CO)] **4** (0.1)	–	–	reflux, 24 h	0
2[d]	$[RuCl_2(p\text{-cymene})]_2$ **5** (2.5)	I*i*Pr, PCy_3	*t*BuOK (15)	reflux, 48 h	46
3	$[RuH(IEt_2Me_2)_4][BAr^F{}_4]$ **6** (5)	–	*t*BuOK (20)	reflux, 24 h	9
4	$[RuH(dppe)_2(OTf)]$ **7** (5)	–	*t*BuOK (20)	reflux, 24 h	18
5[e]	**1a-TfOH** (0.2)	–	*t*BuOK (0.2)	rt, 4 h	10
6[f]	**1a** (0.2)	–	–	rt, 12 h	46
7[g]	**1a-TfOH** (0.2)	–	*t*BuOK (0.2)	rt, 4 h	90
8[h]	**1a** (0.2)	–	–	rt, 1 h	99
9	**1b-TfOH** (0.2)	–	LiHMDS (0.2)	rt, 12 h	38
10	**1c-HCl** (0.2)	–	LiHMDS (0.2)	rt, 12 h	32
11	**1c-HCl** (0.2)	–	LiHMDS (0.2)	60 °C, 12 h	49
12[i]	**2** (0.1)	I*i*Pr	NaH (1)	rt, 12 h	40
13[i]	**2** (0.1)	I*i*Pr	NaH(1)	60 °C, 12 h	63
14	**3** (0.2)	–	–	rt, 12 h	0

[a] General conditions for entries 1–4: 1,2-propanediol (0.5 mmol) and $BnNH_2$ (0.5 mmol) in toluene were added to the catalyst and heated under an argon atmosphere; General conditions for entries 5–15: To a 1 M solution of 1,2-propanediol (0.5 mmol) in THF (0.5 mL), $BnNH_2$ (1.5 mmol, 3 equiv), MMA (1.5 mmol, 3 equiv), and the catalyst were added and stirred under an argon atmosphere; Cy = cyclohexyl, *i*Pr = isopropyl. [b] Determined by GC. [c] Conditions from reference [11j]. [d] The catalyst was generated in situ using a NHC precursor (1,3-diisopropylimidazolium chloride, 5 mol %), PCy_3, (5 mol %) and *t*BuOK in toluene.[11l] [e] With 3 equiv of cyclohexanone instead MMA. [f] The reaction was carried out with toluene as the solvent. [g] The catalyst was generated in situ by adding a base, and the reaction was carried out with 3 equiv of $BnNH_2$ and 3 equiv MMA in THF. The same conversion was obtained by adding **1a** in its pure form. [h] The reaction was carried out without solvent and with 6 equiv of MMA. [i] The catalyst was generated in situ by adding a NHC precursor (1,3-diisopropylimidazolium chloride, 0.2 mol %) and NaH.

an excess of benzyl amine ($BnNH_2$) and methyl methacrylate (MMA) as a hydrogen acceptor (entries 7 and 8, Table 1). The influence of the ancillary ligand in the axial position on the catalytic activity and the thermal stability of the rhodium complex were evaluated. We found that with triphenylphosphine (PPh_3) ligands a very efficient catalytic system was obtained (entries 7 and 8, Table 1; 90–99 % yield), but triphenylphosphite ($P(OPh)_3$) in **1b-TfOH** lead to a less active catalyst (entry 9, Table 1).

The coordination of a strong σ-donor N-heterocyclic carbene ligand (1,3,4,5-tetramethylimidazole-2-ylidene (IMe)) has a significant effect on the acidity of the NH function in complex **1c-HCl**.[9e] A strong base such as $Li[N(SiMe_3)_2]$ (Me = methyl) is necessary to achieve the clean formation of the corresponding rhodium amide complex. Although the complex is remarkably stable under thermal conditions for prolonged periods of time and neither a dissociation of the NHC from the metal nor isomerization to the inactive species [Rh(ax-H)($trop_2$NH)L] is observed (ax = axial, trop = 5-*H*-dibenzo[*a*,*d*]cycloheptен-5-yl, L = IMe; Scheme 2), only a moderate yield of the amide product was obtained. A reason for this may be the steric encumbrance of the active site in the complex which is caused by the methyl groups at the nitrogen atoms of the ligand (entries 10 and 11, Table 1).

Similarly, a rather low yield (40 %) was obtained by preparing the catalyst in situ by cleavage of the chloro bridge dimer (**2**, Scheme 1) with the NHC precursor 1,3-diisopropylimidazolium chloride, in the presence of NaH (entry 12, Table 1). The yield is improved by heating the reaction mixture for an extended period of time (entry 13, Table 1). Clearly, the isolated rhodium(I) amide [Rh($trop_2$N)(PPh_3)] (**1a**, $trop_2$N = bis(5-*H*-dibenzo-[*a*,*d*]cycloheptен-5-yl)amide), in combination with methyl methacrylate, provides an excellent catalytic system for the highly chemoselective transformation of 1,2-propanediol to a lactic acid amide (entry 8, Table 1). The superior activity of the catalysts for this type of reaction under mild conditions may be the result of the neighboring coexistence of the Lewis basic amido function and the Lewis acidic metal center as a consequence of the butterfly-type structure of **1a**. The amido ligand acts as a cooperative ligand[16] in both subsequent reaction steps: 1) the dehydrogenation of the alcohol to the corresponding aldehyde and 2) the dehydrogenative coupling reaction between the aldehyde and the amine. A simplified catalytic cycle consistent with our observations is outlined in Scheme 2. In the proposed mechanism, the amido complex [Rh($trop_2$N)(PPh_3)] (**1a**) and the amino hydride complex [Rh(eq-H)($trop_2$NH)(PPh_3)] (**1a-H$_2$**, eq = equatorial, $trop_2$NH = bis(5-*H*-dibenzo[*a*,*d*]cycloheptен-5-yl)amine) are formed as key intermediates (for a detailed computational study see reference [9b, c]). Our assumption that the amido complex (**1a**) plays an active role in the catalysis is supported by the fact that neither the N-methyl derivative,

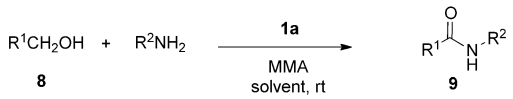


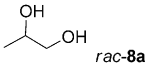
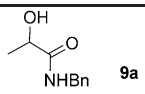
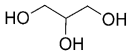
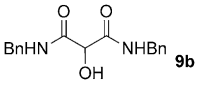
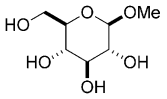
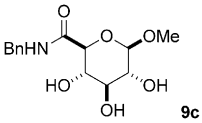
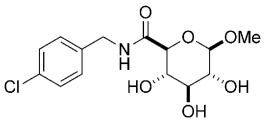
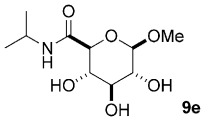
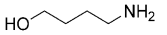
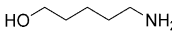
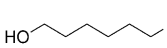
Scheme 2. Simplified catalytic cycle for the dehydrogenative coupling (DHC) of alcohols and amines with complex **1a**; R^1 = alkyl, aryl; R^2 = alkyl.

[Rh(trop$_2$N*Me*)(PPh$_3$)][OTf] (trop$_2$NMe = bis(5-*H*-dibenzo-[*a*,*d*]cyclohepten-5-yl) methylamine),[22] nor the phosphane diolefin (**3**; entry 14, Table 1) promote the conversion of the alcohol under identical conditions. The formation and dehydrogenation of **1a-H$_2$** by a hydrogen acceptor (**A** = MMA) was proven by stoichiometric experiments.[17]

Next, we investigated in more detail the DHC reaction between alcohols and amines to the corresponding amides to determine the scope and limitations of the reaction. Indeed, **1a** is a general catalyst for the dehydrogenative coupling of polyols with primary amines when the reaction is conducted under anhydrous conditions in THF and methyl methacrylate (MMA) is used as the hydrogen acceptor. In the first experiments, benzyl amine (BnNH$_2$) was employed as the coupling partner for the synthesis of a series of amides derived from polyol compounds (Table 2). The transformation of glycerol (**8b**) can be carried out efficiently, obtaining the bis-(amide) **9b** in up to 83% isolated yield when the amount of amine (up to 8 equiv) and hydrogen acceptor (MMA) is increased. Under the same conditions, alcohols with more than three hydroxyl groups are relatively unreactive. We assume that the limited solubility of the molecules with an extended number of hydroxy groups in the organic solvents is responsible for the low yield of products. These shortcomings are largely overcome and the yields are greatly improved when the reactions are carried out in the presence of powdered molecular sieve (4 Å) and by using diluted solutions (0.1 M) of the substrates in dimethoxyethane (DME). Under these modified reaction conditions, only the primary hydroxy function of the monomethylated sugar derivative, 1-methyl-β-D-glucopyranose (**8c**), is converted, allowing the direct and selective amidation to the glucopyranuronamides (**9c**–**9e**). This reaction proceeds more slowly than with simple alcohols but shows a remarkable efficiency with several amines (entries 3–5, Table 2), and, most importantly, all of the stereogenic centers of the sugar molecule are preserved.

Table 2. Scope of rhodium catalyzed DHC of polyols to amides.



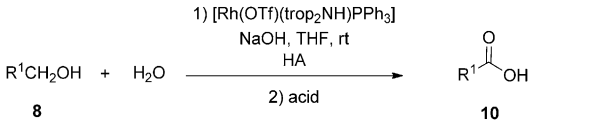
entry	Alcohol	Product	Time at room temperature	Yield [%][a]
1	 *rac*-**8a**	 **9a**	1 h	90[b]
2	 **8b**	 **9b**	2 h	60[c] (83)[d]
3	 **8c**	 **9c**	12 h	85[e]
4	**8c**	 **9d**	12 h	81[e]
5	**8c**	 **9e**	12 h	90[e]
6	 **8d**	 **9f**	12 h	92[f]
7	 **8e**	 **9g**	12 h	96[f]
8	 **8f**	 **9h**	12 h	37[f]

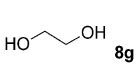
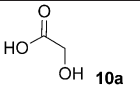
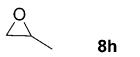
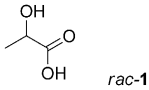
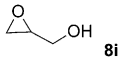
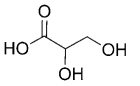
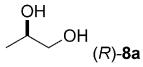
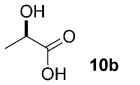
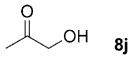
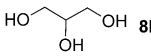
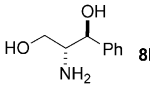
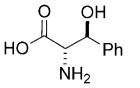
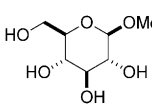
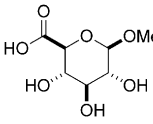
[a] Yield of isolated product. [b] A (neat) mixture of the alcohol (1 equiv), BnNH$_2$ (3 equiv), [Rh(trop$_2$N)(PPh$_3$)] (0.2 mol%), and MMA (6 equiv) were stirred for the indicated time at room temperature. [c] The reaction was performed with 6 equiv of BnNH$_2$, 6 equiv of MMA and without solvent; 10% of N-benzyl-2,3-dihydroxypropanamide was also isolated. [d] With 8 equiv of BnNH$_2$ and 6 equiv of MMA. [e] The reaction was performed with BnNH$_2$ (2 equiv), MMA (3 equiv) and powdered 4 Å MS in DME (0.1 M of alcohol). [f] The reactions were performed in THF (0.5 M of amino alcohol), with 2.5 equiv of MMA and 0.1 mol% of [Rh(trop$_2$N)(PPh$_3$)].

In addition to these intermolecular amidation reactions, complex **1a** is also capable of promoting the intramolecular dehydrogenative coupling of α,ω-aminoalcohols. A simple and direct synthesis of medium-sized ring lactams can be developed (entries 6–8, Table 2). The five and six member ring lactams **9f** and **9g** are obtained in especially excellent yields under very mild conditions. The cationic complex [Rh(OTf)(trop$_2$NH)(PPh$_3$)] (**1a-TfOH**) shows remarkable stability in water or water-containing solvents and can be used in combination with a base as a convenient precatalyst for the synthesis of carboxylates from primary alcohols and water.[9c–e] This is a significant advantage over most catalytic systems which require the use of an organic solvent. An efficient dehydrogenative coupling of polyols to the corresponding sodium carboxylates can be performed with **1a-TfOH**,

NaOH as the base, and a ketone as the hydrogen acceptor (Table 3). It is convenient to use cyclohexanone as a hydrogen acceptor in these reactions because the formation of cyclohexanol is exergonic, and this by-product can be easily recycled with hydrogen peroxide using polytungstate as the catalyst.[18]

Table 3. Scope of rhodium catalyzed DHC of polyols to carboxylic acids.[a]



entry	Alcohol	Product	Time at rt	Yield (%)[b]
1	 **8g**	 **10a**	2 h	99
2	 **8h**	 *rac*-**10b**	18 h	89[c]
3	 **8i**	 **10c**	10 h	95[c]
4	 (*R*)-**8a**	 **10b**	5 h	91 (85)[d]
5	 **8j**	*rac*-**10b**	14 h	92[e]
6	 **8b**	**10c**	8 h	98
7	 **8k**	 **10d**	12 h	97
8	 **8c**	 **10e**	12 h	66[f]

[a] A mixture of the alcohol (1.31 mmol, 1 equiv), cyclohexanone (3.37 mmol, 2.5 equiv), H_2O (1.5 mL), NaOH (1.57 mmol, 1.2 equiv), and [Rh(OTf)(trop$_2$NH)(PPh$_3$)] (0.1 mol%) was stirred for the indicated time at room temperature. [b] Yield of isolated product after acidic workup of the recrystallized sodium salts. [c] With 2.4 equiv of NaOH. [d] The reaction was performed with 5 equiv of acetone. [e] The reaction was carried out with 1.5 equiv of cyclohexanone at 60 °C. [f] The reaction was performed at 40 °C with THF as the cosolvent.

Moreover, we assume that the finely dispersed droplets of the hydrogen acceptor, cyclohexanone, serve as a solvent for the transition-metal complex in the course of the reaction. Ethylene glycol (**8g**) and 1,2-propanediol (**8a**), major commodity chemicals from the hydrogenolysis of biodiesel-derived glycerol, are chemoselectively and quantitatively converted to 2-hydroxy acetic acid (**10a**, entry 1, Table 3) and 2-hydroxypropionic acid (*rac*-**10b**)[19] in excellent yields after a simple acidic workup of the reaction mixture. Remarkably, acetone can also be used as an efficient hydrogen acceptor for the DHC of **8a** to lactic acid and, under these conditions, the reaction proceeds homogeneously, although a slightly lower yield (85%) is obtained in this transformation (entry 4, Table 3). The high efficiency of the hydrogen transfer from a primary alcohol to a ketone in an intramolecular process is also noteworthy. This is represented by the transformation of 1-hydroxy-2-propanone (**8j**) to the lactic acid *rac*-**10b**, which requires only 1.5 equivalents of an additional external hydrogen acceptor (entry 5, Table 3). Otherwise, lactic acid can also be obtained in very good yields from propylene oxide (entry 2, Table 3). This reaction involves a catalytic tandem reaction, in which epoxide opening is coupled to a DHC process. The dehydrogenative coupling of glycerol with the present catalytic system is highly selective, and one of the primary hydroxy functions of the molecule is exclusively converted, affording glyceric acid in 98% yield (entry 6, Table 3). To our knowledge, this marks the highest isolated yield reported to date for the selective oxidation to a monoacid. Alternatively, glyceric acid (**10c**) can also be prepared with excellent yield from the epoxide (**8i**) in the presence of an excess of base (entry 3, Table 3). Importantly, enantiomerically pure substrates were selectively converted to monocarboxylates without loss of the stereochemical information; the configuration at the stereocenter was completely retained. (*R*)-1,2-dihydroxypropane (*R*-**8a**) was converted in 91% yield to give the *R*-configured isomer of lactic acid (*R*-**10b**) in 5 h at room temperature (entry 4, Table 3). Furthermore, the enantiomerically pure amino alcohol (**8k**) was quantitatively converted to β-hydroxy-α-aminoacid (**10d**) without epimerization (entry 7, Table 3). In order to transform unprotected polyols with more than three free hydroxy groups, a slight modification of the reaction conditions was necessary; THF was added as a cosolvent. Under these conditions, the mono-methylated sugar substrate (**8c**) could be converted to the glucoronic acid (**10e**) with an acceptable yield (entry 8, Table 3). The vicinal unprotected secondary alcohol functions remained unchanged, and keto-sugars could not be detected. Finally, in order to determine the efficiency of the catalytic system, the catalyst loading was reduced to 0.01 mol% in the DHC between 1,2-dihydroxypropane and water and under identical conditions, and a conversion of 70% to lactic acid was achieved.

Conclusion

The catalytic system composed of the diolefin amide rhodium(I) complex (**1a**) and a hydrogen acceptor (**A**) provides a convenient route for the preparation of a wide range of carboxylic acid derivatives from primary alcohols under mild conditions. Activated olefins for the synthesis of carboxylic acids, can be employed as suitable hydrogen acceptors. As shown in this work, a wide range of different polyhydroxylated substrates can be used in this dehydrogenative coupling reaction, including polyols derived from renewable feedstock. The coupling reaction with primary amines proceeds with especially high yields (>80%) under mild conditions.

Medium size lactams, commonly embedded in the skeletons of bioactive natural products, can be synthesized in one step from the corresponding amino alcohol, providing an efficient strategy for their synthesis. The high chemoselectivity in the transformation of polyhydroxy compounds is remarkable. The discrimination between primary and secondary OH groups very likely has kinetic reasons. The primary and sterically less hindered hydroxyl groups simply interact faster with the Rh–N group, the active site in the catalyst. On the other hand, the formation of the monoacids 2-hydroxy acetic acid (**10a)** and glyceric acid (**10c**) may be partly due to the biphasic reaction conditions. The amide catalyst (**1a**) and the substrate are mainly dissolved in the droplets of the hydrogen acceptor together with sufficient amounts of water to allow a fast DHC reaction while the product is dissolved in the aqueous phase and is thereby removed from further conversion. This assumption is supported by the fact that, in glycerol, both primary hydroxyl groups are amidated to the corresponding bisamide (**9b**) which is considerably less hydrophilic. The simplicity of the catalytic process, allowing the direct chemoselective introduction of a carboxylic acid or amide functionality in an aqueous reaction medium, is appealing. Especially when a device can be developed, in which an electrode surface acts as a hydrogen acceptor, and the formal release of hydrogen leads to a direct production of an electrical current as a "by-product". Indeed, we recently succeeded in the preparation of organometallic fuel cells (OMFC), in which such reactions can possibly be performed, and investigations along these lines are under way.[20]

Experimental Section

General: All of the reactions were carried out in flame-dried glassware under an argon atmosphere using standard Schlenk techniques (for the synthesis of acids) or in an argon filled glove box (Braun MB 150 B-G system; for the synthesis of amides). Methyl methacrylate was carefully distilled from mol sieves. Cyclohexanone was distilled from calcium hydride and acetone from calcium sulfate. The alcohols employed for the synthesis of acids were used as received. The alcohols and amines employed for the synthesis of amides were distilled and dried prior use. All of these reagents and the organometallic complexes were stored and weighed in the glove box. The complexes [RuH(PNN)(CO)],[11j] [RuH(IEt_2Me_2)$_4$][BAr^F_4],[14] [RuH(dppe)$_2$][OTf],[15] [{Rh($trop_2$NH)Cl}$_2$],[21] [Rh(OTf)($trop_2$NH)(PPh_3)],[21][Rh($trop_2$N)(PPh_3)],[21][Rh(OTf)($trop_2$NH)(P(OPh)$_3$)],[9c] [Rh($trop_2$NMe)(PPh_3)][OTf],[22] [Rh(OTf)($trop_2$NH)(IMe)] (IMe =1,3,4,5-tetramethylimidazole-2-ylidene),[9e] and [Rh($trop_2$PPh)(PPh_3)][BAr^F] ($trop_2$PPh = bis(5-*H*-dibenzo-[*a*,*d*]cyclohepten-5-yl)phenylphosphane)[23] were synthesized according to previously reported procedures. Analytical thin-layer chromatography was performed using E. Merck silica gel 60 F254 plates (0.25 mm thickness). Chromatographic purification of the amides was performed by flash chromatography (Brunschwig silica 32–63, 60 Å) using the indicated solvents as eluents. Optical rotations were measured in a Jasco DIP-1000 polarimeter operating at the sodium D line with a 100 mm path length cell and are reported as follows: $[\alpha]_D^T$, concentration (g per 100 mL). ^{1}H NMR spectra were recorded at 300 or 250 MHz and chemical shifts were referenced to the residual solvent peak. ^{13}C NMR spectra are proton decoupled and were recorded at 75.5 MHz; chemical shifts were referenced to the solvent. Coupling constants *J* are given in Hertz [Hz] as absolute values, unless specifically stated. The data is reported as: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet or unresolved, br = broad signal, coupling constant(s) in Hz, integration, interpretation. Mass spectrometric measurements were performed by the mass spectrometry service of the LOC at the ETH Zürich. ETHZ on Bruker's maXis (ESI/NanoSpray-Qq-TOF) for high resolution measurements. IR spectra were measured on a Perkin–Elmer 2000 FTIR spectrometer with a KBr beam splitter. Melting points were determined on a Büchi melting point apparatus and are reported uncorrected.

General procedure for the catalyzed dehydrogenative coupling of alcohols to amides (Table 2): The alcohol (1.31 mmol, 1 equiv), amine (3.93–10.48 mmol, 3–8 equiv), methyl methacrylate (3.93–7.86 mmol, 3–6 equiv), and [Rh($trop_2$N)(PPh_3)] (**1a**, 2 mg, 0.0026 mmol, 0.2 mol %) in THF (1 mL) were stirred at room temperature for the time indicated in Table 1. The reactions of **8c** were performed with $BnNH_2$ (281 g, 2.62 mmol, 2 equiv), MMA (393 mg, 3.93 mmol, 3 equiv) and powdered 4 Å MS in DME (0.1 M of alcohol). The reactions were monitored by TLC. All of the volatile materials were removed under reduced pressure, and the pure amide was isolated by chromatographic purification (**9b–d** and **9f–h**) or recrystallization (**9a** and **9e**).

General procedure for the catalyzed dehydrogenative coupling of alcohols to acids (Table 3): A mixture of the alcohol (1.31 mmol, 1 equiv), water (1.5 mL), sodium hydroxide (380 mg, 6.55 mmol, 1.2 equiv), and cyclohexanone (321 mg, 3.28 mmol, 2.5 equiv) or acetone (380 mg, 6.55 mmol, 5 equiv) were combined in a Schlenk flask under an argon atmosphere. The mixture was degassed by purging with argon for 10 min prior to the addition of [Rh(OTf)($trop_2$NH)(PPh_3)] (0.00131 mmol, 1 mg, 0.001 equiv) under a stream of argon. After the reaction times indicated in Table 3 (the progress of each reaction was monitored by NMR spectroscopy), water was added (20 mL), and the mixture was extracted with diethyl ether (2×20 mL). The aqueous phase was then evaporated and the corresponding sodium salts were recrystallized and dried. Aqueous solutions of the sodium salts were acidified with 1N HCl and the pure acids were filtered from NaCl and dried (**10a–10d**). Compound **10e** was isolated by chromatographic purification.

Physical and spectroscopic data for the synthesized compounds 9a–9h and 10a–10e: Amides **9a**, **9b**, and **9f–h** and carboxylic acids **10a–e** were identified by comparison with data stored in the Aldrich NMR spectra database or with previously reported data. The ^{1}H and ^{13}C NMR spectra of **9a–h** and **10a–e** are shown in the Supporting Information.

Synthesis of compounds 9a–h and 10a–e

***N*-Benzyl lactamide (9a)**: After the workup, the product was recrystallized from THF affording a white solid (211 mg, 90 %). M.p. 48–50 °C; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.32–7.17 (m, 5H), 7.11 (bs, 1H), 4.44 (d, $^3J_{H,H}$ = 6.0 Hz, 2H), 4.17 (q, $^3J_{H,H}$ = 6.8 Hz, 1H), 1.45 ppm (d, $^3J_{H,H}$ = 6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ = 174.8 (C), 137.9 (C), 128.7 (CH), 128.6 (CH), 127.6 (CH), 68.4 (CH), 43.1 (CH_2), 21.2 ppm (CH_3);[24] ESI MS: *m*/*z* 180.1 $[M+1]^+$.

***N*,*N*-Dibenzyl-2-hydroxymalonamide (9a)**: After the workup, the residue was purified by flash column chromatography (ethyl acetate (EtOAc)/methanol (MeOH) 10:1 to 1:1), affording the diamide as a white solid (234 mg, 60 %). M.p. 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (bs, 2H), 7.35–7.23 (m, 10H), 4.50 (d, $^3J_{H,H}$ = 2.9 Hz, 1H), 4.40 (s, 1H), 4.46 ppm (d, $^3J_{H,H}$ = 6.8 Hz, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 167.3 (C), 137.7 (C), 128.7 (CH), 127.6 (CH), 127.5 (CH), 71.1 (CH), 43.6 ppm (CH_2);[25] ESI MS: *m*/*z* 299.2 $[M+1]^+$.

N-Benzyl-2,3-dihydroxypropionamide was isolated from the crude reaction mixture described above as a white solid (25 mg, 10 %). M.p. 83–85 °C; ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 8.20 (t, $^3J_{H,H}$ = 6.3 Hz, 1H), 7.30–7.10 (m, 5H), 5.55 (d, $^3J_{H,H}$ = 5.6 Hz, 1H), 4.70 (t, $^3J_{H,H}$ = 5.7 Hz, 1H), 4.17 (d, $^3J_{H,H}$ = 6.3 Hz, 2H), 3.91–3.83 (m, 1H), 3.59–3.45 (m, 1H), 3.39–3.32 ppm (m, 1H); ^{13}C NMR (75.5 MHz, [D_6]DMSO): δ = 172.1 (C), 139.3 (C), 128.2 (CH), 127.6 (CH), 127.0 (CH), 73.40 (CH), 63.9 (CH_2), 41.9 ppm (CH_2);[26] ESI MS: *m*/*z* 196.1 $[M+1]^+$.

***N*-Benzyl-*O*-methyl-β-D-glucopyranuronamide (9c)**: The residue obtained was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to afford a pale solid (331 mg, 85 %). M.p. 167–169 °C; $[\alpha]^{20}_D$ = +93.3 (*c* = 0.75 % in DMSO); ^{1}H NMR (300 MHz, CD_3CN/D_2O): δ = 7.61–7.53 (m, 5H), 5.06 (d, $^3J_{H,H}$ = 3.5 Hz, 1H), 4.64 (s, 2H), 4.24 (d, $^3J_{H,H}$ = 9.0 Hz,

1H), 3.88–3.75 (m, 3H), 3.62 ppm (s, 3H); ^{13}C NMR (75.5 MHz, CD_3CN/D_2O): δ=171.1 (C), 138.1 (C), 129.0 (CH), 127.7 (CH), 127.6 (CH), 100.0 (CH), 73.0(CH), 71.9(CH), 71.4 (CH), 71.2 (CH), 55.7 (CH_3), 42.9 ppm (CH_2); HRMS (ESI) calcd for $C_{14}H_{20}NO_6$ $[M+H]^+$ 298.1285, found 298.1282; ATR IR: $\tilde{\nu}$=3285 w, 2923 w, 2355 w, 1665 s, 1540 m, 1460 w, 1045 s, 1003 m, 945 m, 730 m cm^{-1}.

***N*-(4-Chlorobenzyl)-*O*-methyl-β-D-glucopyranuronamide (9d)**: The residue obtained was purified by flash chromatography (CH_2Cl_2/MeOH 9:1) to afford a white solid (352 mg, 81%). M.p. 165–167°C; $[\alpha]^{20}_D$ = +135.4 (c=0.75% in DMSO);^{1}H NMR (300 MHz, CD_3CN/D_2O): δ=7.32–7.21 (m, 4H), 4.72 (d, $^3J_{H,H}$=3.0 Hz, 1H), 4.33 (s, 2H), 3.72 (s, 1H), 3.60–3.43 (m, 3H), 3.33 ppm (s, 3H); ^{13}C NMR (75.5 MHz, CD_3CN/D_2O): δ=173.7 (C), 140.0 (C), 138.0 (CH), 131.9 (CH), 131.2 (CH), 102.7 (CH), 75.6 (CH), 74.6 (CH), 73.8 (CH), 73.6 (CH), 58.1 (CH_3), 44.5 ppm (CH_2); HRMS (ESI-TOF) calcd for $C_{14}H_{19}ClNO_6$ $[M+H]^+$ 332.0895, found 332.0906; ATR IR: $\tilde{\nu}$=3280 w, 2931 w, 2359 w, 1661 s, 1542 m, 1459 w, 1047 s, 1013 s, 971 s cm^{-1}.

***N*-Isopropyl-*O*-methyl-β-D-glucopyranuronamide (9e)**: The residue obtained was recrystallized from MeOH to afford a pale solid (293 mg, 90%). M.p. 135–137°C; $[\alpha]^{20}_D$ = +43.9 (c=0.75% in DMSO); ^{1}H NMR (300 MHz, CD_3CN/D_2O): δ=4.72 (d, $^3J_{H,H}$=3.2 Hz, 1H), 3.96 (sept, $^3J_{H,H}$=3.6 Hz, 1H), 3.83 (d, $^3J_{H,H}$=9.8 Hz, 1H), 3.53–3.39 (m, 2H), 3.36 (s, 3H), 1.11 ppm (d, $^3J_{H,H}$=3.2 Hz, 6H); ^{13}C NMR (75.5 MHz, CD_3CN/D_2O): δ=172.9 (C), 102.7 (CH), 75.7 (CH), 74.9 (CH), 74.0 (CH), 72.8 (CH), 58.0 (CH_3), 43.8 (CH), 24.2 ppm (CH_3); HRMS (ESI-TOF): calcd for $C_{10}H_{20}NO_6$ $[M+H]^+$ 250.1285, found 298.1281. ATR IR: $\tilde{\nu}$= 3307 w, 2929 w, 1636 s, 1565 m, 1460 w, 1354 w, 1073 s, 1054 s, 1000 s, 800 w, 634 w cm^{-1}.

2-Pyrrolidinone (9f): Purification by flash column chromatography with CH_2Cl_2/MeOH (100:1) as eluent afforded the product as a colorless oil (102 mg, 92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.51 (bs, 1H), 3.08 (t, $^3J_{H,H}$=7.0 Hz, 2H), 2.02–2.94 (m, 2H), 1.80–1.76 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=179.3 (C), 42.1 (CH_2), 30.0 (CH_2), 20.4 ppm (CH_2);[27] ESI MS: m/z 86.0 $[M+1]^+$.

Piperidine-2-one (9g): Purification by flash column chromatography with CH_2Cl_2/MeOH (100:1) as eluent afforded the product as a colorless oil (125 mg, 96%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.40 (bs, 1H), 3.20–3.15 (m, 2H), 2.25–2.19 (m, 2H), 1.66–1.62 ppm (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=172.8 (C), 41.9 (CH_2), 31.3 (CH_2), 22.1 (CH_2), 20.1 ppm (CH_2);[28] ESI MS: m/z 100.1 $[M+1]^+$.

Azepan-2-one (9h): Purification by flash column chromatography with CH_2Cl_2/MeOH (100:1) as eluent afforded the product as a white solid (55 mg, 37%). M.p. 70–72°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.44 (bs, 1H), 3.09–3.04 (m, 2H), 2.33–2.29 (m, 2H), 1.60–1.47 ppm (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=179.5 (C), 42.5 (CH_2), 36.7 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 23.14 ppm (CH_2).[29] ESI MS: m/z 114.1 $[M+1]^+$.

Glycolic acid (10a): Obtained as a white solid (98 mg, 99%). M.p. 78–80°C; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ =3.91 ppm (s, 2H); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ=174.6 (C), 59.9 ppm (CH_2).

D-(−)-Lactic acid (10b): Obtained as a colorless oil (107 mg, 91%). $[\alpha]^{20}_D$ = +13.8 (c=2.5% in 1N NaOH); (lit. $[\alpha]^{20}_D$ = +13.5); ^{1}H NMR (300 MHz, D_2O): δ=3.75 (q, $^3J_{HH}$=6.9 Hz, 1H), 1.15 ppm (d, $^3J_{HH}$= 6.8 Hz, 3H); ^{13}C NMR (75.5 MHz, D_2O): δ=177.9 (C), 63.9 (CH), 15.5 ppm (CH_3).[30]

Glyceric acid (10c): After evaporation of the aqueous phase, the white crystals of sodium glycerate were obtained by washing with acetone and methanol. Glyceric acid was obtained, after acidification with 1N HCl, as a viscous oil (136 mg, 98%, from glycerol; 129 mg, 95% from glycidol). ^{1}H NMR (300 MHz, D_2O): δ=4.25 (t, $^3J_{HH}$=3.1 Hz, 1H),), 3.73 ppm (d, $^2J_{HH}$ $^3J_{HH}$=3.1 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O): δ=177.2 (C), 72.0 (CH), 64.2 ppm (CH_2).[31]

(2*S*, 3*R*)-2-Amino-3-hydroxy-3-phenylpropanoic acid (10d): After acidification with 2N HCl solution, the water was evaporated under pressure. After addition of water (2×10 mL) and subsequent evaporation, all of the possible remaining HCl was removed. The residue was crystallized from absolute ethanol. To isolate the pure amino acid, the pH of an aqueous solution was adjusted to 7 by slow addition of 25% aqueous ammonia. The mixture was kept at −4°C overnight, and the solid was collected and washed with a mixture of water/EtOH (1:10) to afford the pure β-hydroxyamino acid as a white solid (230 mg, 97%). M.p. 185–187°C; $[\alpha]^{20}_D$ = −31.0 (c=0.1, H_2O); lit. $[\alpha]^{20}_D$ −32.8 (c=0.1, H_2O); ^{1}H NMR (300 MHz, D_2O): δ=7.43–7.37 (m, 5H), 5.26 (d, $^3J_{HH}$=4.2 Hz, 1H), 4.10 (d, $^3J_{HH}$=4.1 Hz, 1H); ^{13}C NMR (75.5 MHz, D_2O): δ=171.6 (C), 139.4 (C), 129.0 (CH), 129.0 (CH), 125.9 (CH), 71.2 (CH), 60.9 ppm (CH).[32]

Methyl-β-D-glucopyranosiduronic acid (10e): The residue was purified by flash column chromatography on a short plug of silica gel (EtOAc:-MeOH 10:1 to 1:1), affording the acid as an oil (180 mg, 66%). ^{1}H NMR (300 MHz, D_2O): δ=4.23 (d, $^3J_{H,H}$=8.0 Hz, 1H), 3.62 (dd, $^3J_{H,H}$=9.0 Hz, $^3J_{H,H}$=6.0 Hz, 1H), 3.45 (s, 3H), 3.38–3.30 (m, 2H), 3.28–3.14 ppm (m, 1H); ^{13}C NMR (75.5 MHz, D_2O): δ=173.1 (C), 100.9 (CH), 74.2 (CH), 73.6 (CH), 73.6 (CH), 70.6 (CH), 58.2 ppm (CH_3).[33]

Acknowledgements

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