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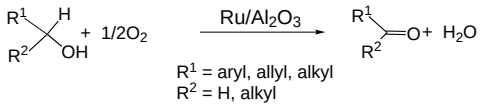
Supported Ruthenium Catalyst for the Heterogeneous Oxidation of Alcohols with Molecular Oxygen**

Kazuya Yamaguchi and Noritaka Mizuno*

Although catalytic oxidation of alcohols to carbonyl compounds has attracted much attention both in industrial processes and in organic syntheses,[1–3] alcohols are traditionally oxidized by non-catalytic methods with stoichiometric oxidants such as dichromate and permanganate.[1–3] These methods produce enormous amounts of metal salts as wastes. Much effort has been made to develop homogeneous catalytic systems to solve these problems.[4–6] However, most systems are applicable only for the oxidation of activated benzylic and allylic alcohols, or large quantities of additives such as NaOAc, NaOH, and K_2CO_3 are needed.[7–10] There is little known about the oxidation of alcohols with molecular oxygen, which could be applied to a wide range of alcohols. If these oxidation reactions could be performed by using solid-supported catalysts (heterogeneous catalysis), they would be considerably cheaper and environmentally more friendly because of the ease with which the catalysts could be separated from products and recycled.[11–14] Examples of solid-supported catalysts that have been tested include tetrapropylammonium perruthenate (TPAP)/MCM-41,[15] Ru/CeO_2,[16] Ru-hydrotalcite,[17] Ru-hydroxyapatite,[18] $[RuCl_2(p\text{-cymene})]_2$/activated carbon,[19] Pd-hydrotalcite,[20] and Pd or Pt on activated carbon.[21] However, heterogeneous oxidation reactions are limited to activated alcohols and/or have turn over numbers (TONs) which are very low (less than 20).[15–21] If oxidation reactions could be carried out without solvents, then the system would facilitate the separation of catalyst from products. Despite the advantage of using solid catalysts without solvents or additives for oxidation of both activated and non-activated alcohols, nothing has been reported on the use of highly active solvent-free heterogeneous catalysts with only molecular oxygen. Herein we report an effective aerobic heterogeneous oxidation reaction of both activated and non-activated alcohols, which may have a sulfur atom, a nitrogen atom, or a carbon-carbon double bond, by using molecular oxygen or air catalyzed by Ru supported on alumina (Ru/Al_2O_3) and demonstrate the use of solvent-free oxidation reactions [Eq. (1)]. The results we present offer a strategy for the design of heterogeneous alcohol-oxidation catalysts for use in conjunction with molecular oxygen.



(1)

The Ru/Al_2O_3 system had high catalytic activities for the oxidation of activated and non-activated alcohols with only 1 atm of O_2 as shown in Table 1. Reaction selectivity was over 97% in all cases and all primary and secondary benzylic alcohols were converted quantitatively into the corresponding benzaldehydes and ketones, respectively. Primary and secondary allylic alcohols afforded the corresponding enals or enones without intramolecular hydrogen transfer or geometrical isomerization of the double bonds. Additionally, the catalytic system efficiently oxidized non-activated alcohols to the corresponding carbonyl compounds: for the oxidation of 2-octanol, 2-octanone was produced in a 91% yield (entry 14). Similarly, alicyclic alcohols such as cyclopentanol and cyclooctanol were selectively oxidized to the corresponding cyclic ketones (entries 15 and 16). Less reactive aliphatic primary alcohols, 1-octanol and 1-decanol, were also oxidized. However, increasing the reaction time did not improve the yields of the aldehydes because of successive oxidation to the corresponding carboxylic acids. The addition of a small amount of hydroquinone (1 equiv based on Ru) completely

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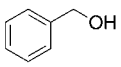
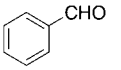
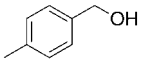
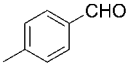
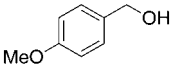
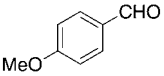
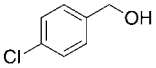
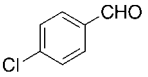
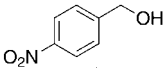
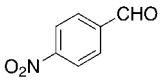
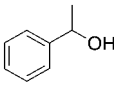
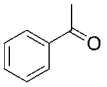
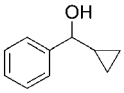
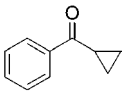
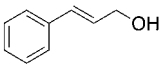
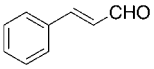
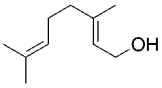
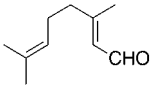
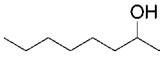
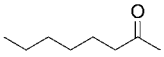
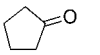
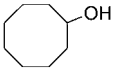
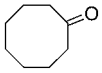
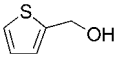
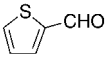
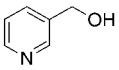
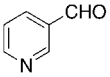
Table 1. Results of oxidations of various alcohols catalyzed by Ru/Al_2O_3 with molecular oxygen.[a]

Entry	Substrate	Product	t [h]	Conv. [%]	Selectivity [%]
1			1	> 99	> 99
2			1	> 99	> 99
3			1	> 99	> 99
4			1	> 99	> 99
5			3	97	> 99
6			1	> 99	> 99
7			1	> 99	> 99
8			1.5	> 99	98
9[b]			6	84	> 99
10			6	89	97
11[b,c]	$C_7H_{15}CH_2OH$	$C_7H_{15}CHO$	4	87	98
12[b,c]	$C_9H_{19}CH_2OH$	$C_9H_{19}CHO$	4	71	99
13			5	90	> 99
14			2	91	> 99
15[b]			8	92	> 99
16[b]			6	81	> 99
17			1.5	> 99	> 99
18[b]			2	93	> 99

[a] Reaction conditions were as follows: alcohol (1 mmol), Ru/Al_2O_3 (Ru: 2.5 mol %),$PhCF_3$ (1.5 mL), 356 K, under 1 atm of O_2: conversion and selectivity were determined by gas chromatography with an internal standard. [b] Ru/Al_2O_3 (Ru: 5 mol %). [c] Hydroquinone (1 equiv based on Ru) was added.

suppressed the over-oxidation, which afforded only aliphatic aldehydes in fairly good yields. Ru/Al_2O_3 catalyzed the oxidation of alcohols also containing nitrogen or sulfur atoms to the corresponding aldehydes in high yields (entries 17 and 18), while monomeric Ru complexes cannot affect catalytic oxidation of these alcohols because of the strong coordination to the metal center.[10]

Among various Ru catalysts tested, Ru/Al_2O_3 showed the highest catalytic activity for the oxidation of benzyl alcohol at 356 K. $Ru(OH)_3{\cdot}n\,H_2O$ gave benzaldehyde in a 29 % yield (TON = 12) after 20 h and other Ru compounds of $RuCl_3{\cdot}n$-H_2O, $[RuCl_2(PPh_3)_3]_2$, $[RuCl_2(p\text{-cymene})]$, and RuO_2 showed no catalytic activity.

The heterogeneous oxidation of alcohols without solvents would be more feasible for industrialized processes. The Ru/Al_2O_3 catalyst system efficiently facilitated the oxidation of non-activated 2-octanol and activated 1-phenylethanol without the use of solvents. The solvent-free oxidation of 2-octanol, and 1-phenylethanol at 423 K had turn over frequencies (TOFs) of 300 h^{-1} and 340 h^{-1}, and TONs of 950 and 980, respectively [Eq. (2)]. These TOFs and TONs are higher than those reported for the aerobic oxidation of 2-octanol by other Ru catalysts: ($[RuCl_2(PPh_3)_3]$/TEMPO (TON and TOF, 466 and 104 h^{-1}),[10] Ru/quinone/Co–salen (194, 97 h^{-1}),[8] TPAP (20, 6 h^{-1}),[15] Ru/CeO_2 (30, 5 h^{-1}),[16] Ru–Co–hydrotalcite (9, 5 h^{-1}),[17] and Ru–hydroxyapatite (6, 1 h^{-1})[18]). Furthermore,

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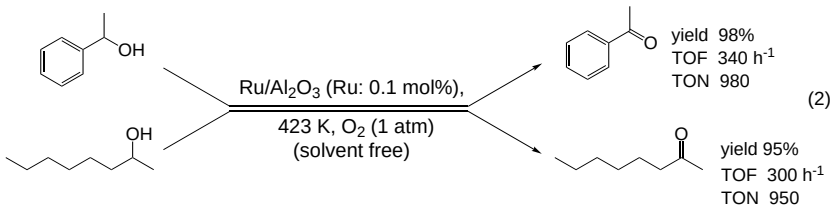


(2)

air can be used instead of molecular oxygen in the present system without changes in conversion and selectivity values.

It was confirmed by induced coupled plasma techniques (ICP) that the Ru content of the used Ru/Al_2O_3 catalyst was the same as that of the fresh catalyst and that no Ru was in the filtrate. In addition, the oxidation of benzyl alcohol was completely stopped by the removal of Ru/Al_2O_3 from the reaction solution. These results indicate that any Ru species that leached into the reaction solution is not an active homogeneous catalyst and that the observed catalysis is truly heterogeneous in nature.[22] The Ru/Al_2O_3 catalyst system is reusable (Figure 1). When the oxidation of benzyl alcohol was repeated seven times with the same sample of catalyst, benzaldehyde was quantitatively produced at the same rate as that of the first run.

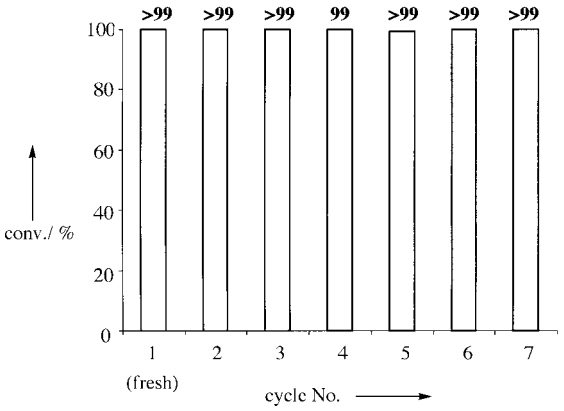


Figure 1. Recycling of Ru/Al_2O_3 catalyst for the oxidation of benzyl alcohol. Reaction conditions were as follows: benzyl alcohol (1 mmol), Ru/Al_2O_3 (Ru: 2.5 mol%), $PhCF_3$ (1.5 mL), 356 K, under 1 atm of O_2, 1 h.

The conversion and selectivity were not changed by the addition of a free-radical trap, for example, 2,6-di-*tert*-butyl-4-methylphenol, and hydroquinone. The skeletal isomerization of a cyclopropyl ring used as a radical clock did not proceed at all. This evidence shows that a radical is not involved in the oxidation reaction. Primary alcohols were selectively oxidized even in the presence of secondary ones, an equimolar mixture of benzyl alcohol and 1-phenylethanol gave a mixture of benzaldehyde and acetophenone in 90% and 24% yields, respectively. Similarly, competitive oxidations of 1-octanol and 4-octanol showed 84 and 8% conversions, respectively. These faster oxidations of primary alcohols show that Ru–alcoholate **II** (see scheme 1) is formed as an intermediate, since the formation of metal–alcoholate species is well known for such selective oxidation of primary hydroxy groups.[23,24] Competitive oxidations of *para*-substituted benzyl alcohols gave a Hammett ρ value of -0.461 ($r^2 = 0.99$; Figure 2), which suggests that hydride abstraction from **II** to form the carbocation-type intermediate is involved in the oxidation path.

The number of moles of water produced was equivalent to that of acetone produced for the oxidation of 2-propanol (19.6 mmol, at 343 K) by using Ru/Al_2O_3 and molecular oxygen. This 1:1 stoichiometry suggests that the simple dehydrogenation does not proceed. Under anaerobic conditions, the number of moles of acetone produced was approximately the same as those of Ru loaded on Al_2O_3,

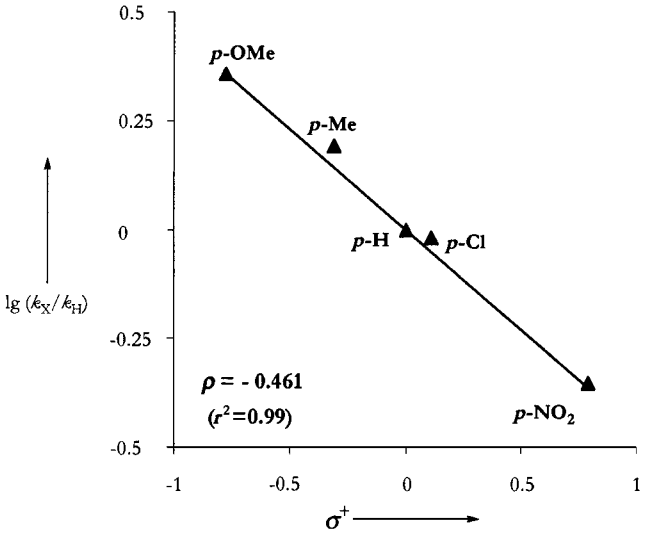
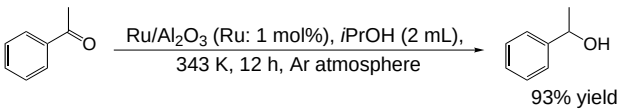


Figure 2. Hammett plots for the aerobic oxidation of *p*-substituted benzyl alcohols by using Ru/Al_2O_3 catalyst. Reaction conditions were as follows: alcohol (1 mmol), Ru/Al_2O_3 (1 mol%), $PhCF_3$ (1.5 mL), 333K, under 1 atm O_2..

and water produced. When acetophenone (1M) was treated in 2-propanol under Ar, almost equimolar amounts of acetone and 1-phenylethanol were produced, which shows that transfer hydrogenation takes place [Eq. (3)].[25] These facts suggest that a Ru-H species **III** is formed. On the basis of all the results, Scheme 1 is proposed: Ru–alcoholate species **II** is formed by ligand exchange between Ru–hydroxide **I** then, an alcohol undergoes typical β elimination to afford the corresponding carbonyl compound and **III**. The hydride species is then reoxidized by molecular oxygen.[26]



(3)

The rate did not change with a decrease in oxygen partial pressure (P_{O_2}) from 1.0 to 0.2 atm (air). Kinetic data could well be expressed by the Michaelis-Menten type equation.[27] The kinetic isotope effects (k_H/k_D) were 5.0 and 2.4 for the intramolecular competitive oxidation of α-deuterio-*p*-methylbenzyl alcohol and for the intermolecular competitive

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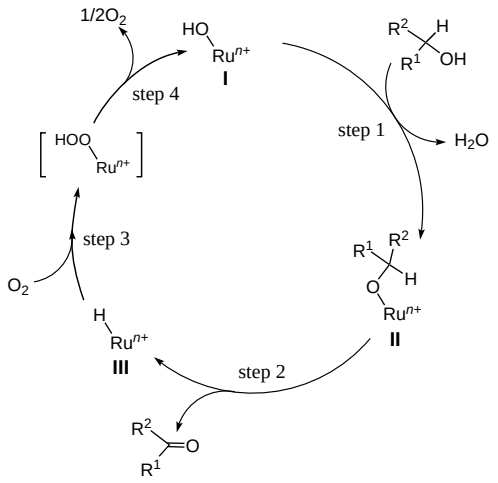

Scheme 1.

oxidation of benzyl alcohol and benzyl [D_7]alcohol ($C_6D_5CD_2OH$) at 333K, respectively. The apparent activation energies for steps 1 (alcoholate formation) and 2 (β elimination) were 40.0 and 54.9 kJ mol^{-1}, respectively. On the basis of these facts, step 2 is rate-determining.

In summary, Ru/Al_2O_3 can act as an efficient heterogeneous catalyst for the oxidation of alcohols with 1 atm of molecular oxygen or air, without additives. The high activity of, and ease with which, the catalyst can be recovered and reused raise the prospect of using this type of simple supported catalyst for organic syntheses and the industrial oxidation of alcohols. The catalyst would be considerably cheaper than organometallic and inorganic compounds.

Experimental Section

The Ru/Al_2O_3 catalyst was prepared by the modification of a literature preparation of $Ru(OH)_3{\cdot}nH_2O$:[28] γ-Al_2O_3 (2.0 g, JRC-ALO-4, BET surface area: 174 m^2 g^{-1}) was vigorously stirred with an aqueous solution of $RuCl_3$ (60 mL, 8.3×10^{-3} M) for 15 min at room temperature. The initially brown aqueous phase became lighter, and the alumina powder turned dark gray. The solid was separated by filtration and washed with a large amount of water, then dried in vacuo. This solid was added to deionized water (30 mL), the pH of the solution was adjusted to 13.2 by the addition of an aqueous solution of NaOH (1.0 M) and the resulting slurry was stirred for 24 h. During this period, the powder changed from dark gray to dark green. The solid was separated by filtration and copiously washed with water, then dried in vacuo to afford 2.1 g of Ru/Al_2O_3 as a dark green powder. The contents of ruthenium and chloride was 1.4 and 0 wt%, respectively, and the BET surface area was 182 m^2 g^{-1}. The ESR spectrum had a signal at $g=2.11$, which is assigned to Ru^{3+} with low-spin d^5 electron configuration.[29] The XRD pattern was the same as that of the γ-Al_2O_3 support and no signals arising from ruthenium metal or dioxide were observed. Particles of ruthenium metal or dioxide were not detected by TEM. The IR spectrum showed a very broad ν(OH) band in the range of 2900–3700 cm^{-1}. These facts suggest that ruthenium(III) hydroxide is highly dispersed on γ-Al_2O_3. Thus, the Ru/Al_2O_3 catalyst can be easily prepared in a quantitative yield and the content of Ru can be controlled.

Oxidations of alcohols were typically carried out as follows. A suspension of Ru/Al_2O_3 (0.11 g, Ru: 2.5 mol%) in trifluorotoluene (1.5 mL) was stirred for 5 min. Benzyl alcohol (0.108 g, 1 mmol) was added to the reaction mixture and the suspension was purged with molecular oxygen. The resulting mixture was heated at 356 K for 1 h, and benzaldehyde was produced in >99% yield determined by GC. After the reaction, the catalyst was separated by filtration (or centrifugation) and was further washed with acetone. The filtrate was evaporated in vacuo, and the crude product was purified by column chlomatography on silica gel, which gave 0.101 g of pure benzaldehyde (95% yield). The separated Ru/Al_2O_3 was washed with an aqueous solution of NaOH (1.0 M) and water (30 mL), and dried in vacuo before recycling.

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[4] CuCl/Phen/K_2CO_3[5] and $Pd(OAc)_2$/bathophenanthroline disulfonate/NaOAc[6] systems are reported to be efficient examples. In the former system, the turnover number (TON, moles of product per mol of catalyst) and turnover frequency (TOF, TON hr^{-1}) for the oxidation of 2-undecanol are 9 and 5 h^{-1}, respectively. In the latter system, the TON and TOF for the oxidation of 2-pentanol are 400 and 100 h^{-1}, respectively. Even in these systems, large quantities of additives such as NaOAc, NaOH, or K_2CO_3 (0.05–2 equivalents based on alcohol) are needed to acheive high yields of carbonyl conpounds. In addition, the $Pd(OAc)_2$/PhenS*/NaOAc system can not oxidize sulfur, nitrogen, carbon–carbon double-bond-containing alcohols because of the strong coordination to the metal center.

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[26] While step 3 may proceed via the formation of hydrogen peroxide, the filtrate for the oxidation of benzyl alcohol with molecular oxygen showed a negative peroxide test (Quantofix test stick, detection limit 1 mg L^{-1} hydrogen peroxide). The catalytic oxidation of benzyl alcohol with hydrogen peroxide hardly proceeded because of the rapid decomposition of hydrogen peroxide, in agreement with the rapid decomposition of Ru^{n+}-OOH without contributing to the oxidation of alcohols in Scheme 1.

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[27] The catalytic rate (R) of the oxidation of benzyl alcohol was expressed by $R = k_2[C]/\{1 + k_2/(k_1[A])\}$, where [C] and [A] are the amount of Ru/Al_2O_3 and the concentration of benzyl alcohol, respectively, and k_1 and k_2 are the rate constants for step 1 and step 2, respectively, and at 356 K these were 38 $h^{-1}g^{-1}$ and 42 M $h^{-1}g^{-1}$, respectively.
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Direct Asymmetric Aldol Reactions of Glycine Schiff Base with Aldehydes Catalyzed by Chiral Quaternary Ammonium Salts**

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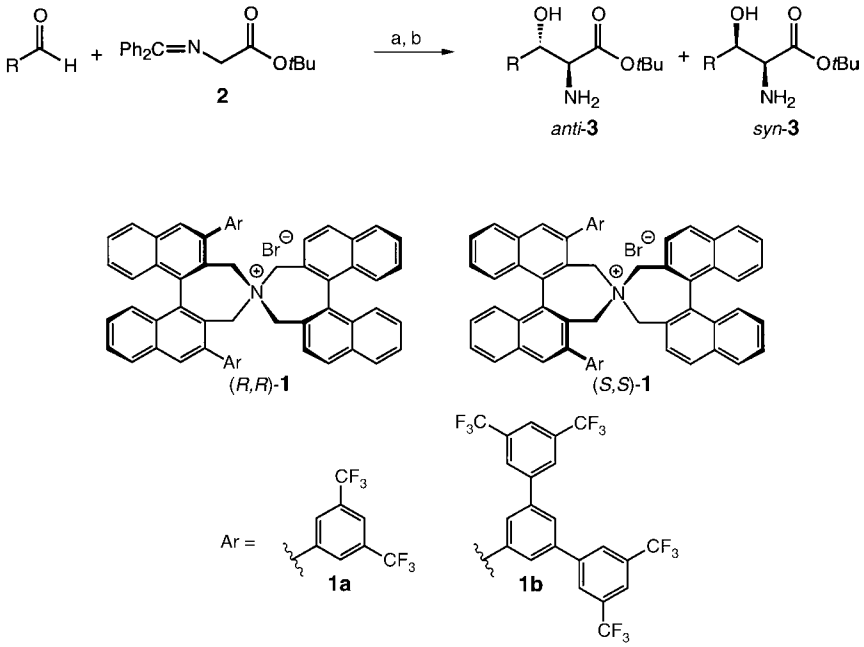
As naturally occurring α-amino acids as well as components of many complex biologically active cyclic peptides and enzyme inhibitors, optically active β-hydroxy-α-amino acids are extremely important chiral units, especially from the pharmaceutical viewpoint.[1] Furthermore, they are useful chiral building blocks in organic synthesis[2] as exemplified by their transformation into β-lactams,[3] β-halo-α-amino acids,[4] and aziridines.[5] Accordingly, numerous methods for the asymmetric synthesis of β-hydroxy-α-amino acids have been elaborated, most of which unfortunately involve multistep procedures and/or the inevitable use of a stoichiometric amount of chiral auxiliaries.[6–8] In this regard, the construction of their primary structure with the correct stereochemistry by the direct catalytic asymmetric aldol reaction of a glycine donor with aldehyde acceptors has been considered to be an ideal protocol.[9] However, there have been few successful examples to date,[10,11] except for the chemoenzymatic process with glycine-dependent aldolases.[9b,12] We report herein an efficient and direct asymmetric aldol reaction of glycine Schiff base **2**[13] with aldehydes under organic/aqueous biphasic conditions by using enantiomerically pure, C_2-symmetric chiral quaternary ammonium salt **1**[14] as a phase-transfer catalyst (Scheme 1). This approach provides a practical and environmentally benign chemical process for the synthesis of optically active β-hydroxy-α-amino acids.

Initially, we examined the direct asymmetric aldol reaction of prochiral glycine Schiff base **2** and 3-phenylpropanal as a representative acceptor under phase-transfer conditions. Thorough optimization of the catalyst structure and reaction conditions revealed that treatment of **2** with 3-phenylpropanal (2 equiv) in toluene/aqueous NaOH (1%) (*v*/*v* 1.25:1; 2 equiv of base for **2**) in the presence of chiral quaternary ammonium salt (*R*,*R*)-**1a** (2 mol%)[14d] at 0°C for 2 h and subsequent hydrolysis with HCl (1N) in THF resulted in the formation of the corresponding β-hydroxy-α-amino ester **3** (R = $PhCH_2CH_2$) in 76% yield with the *anti*/*syn* ratio of 3.3:1. The enantiomeric excess of the major *anti* isomer was determined to be 91% by chiral HPLC analysis (Table 1, entry 1). Significantly, use of (*R*,*R*)-**1b** (which contains a 3,5-bis(3,5-bis(trifluoromethyl)phenyl)phenyl substituent) as a catalyst enhanced both diastereo- and enantioselectivities in this system (*anti*/*syn* 12:1; 96% *ee* for *anti* isomer) (Table 1, entry 2).[15]



Scheme 1. Direct catalytic asymmetric aldol reaction of glycine Schiff base **2** with aldehydes in the presence of **1** under phase-transfer conditions. a) (*R*,*R*)-**1** (2 mol%), toluene/aqueous NaOH (1%), 0°C, 2 h; b) HCl (1N)/THF.

A variety of aldehydes were examined for this direct asymmetric aldol reaction with (*R*,*R*)-**1** and the results are listed in Table 1. Generally, the reaction proceeded smoothly at 0°C for 2 h to afford the *anti* isomer predominantly, with excellent enantioselectivity. Heptanal, an aliphatic aldehyde with a long hydrocarbon chain, was found to be a good candidate (Table 1, entry 3), thus indicating the feasibility of direct asymmetric synthesis of a variety of lipo β-hydroxy-α-amino acids, a useful component for the preparation of lipophilic peptides and glycopeptides with characteristic high

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