Asymmetric Hydrogenation

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Asymmetric Hydrogenation of Aromatic, Aliphatic, and α,β-Unsaturated Acyl Silanes Catalyzed by Tol-binap/Pica Ruthenium(II) Complexes: Practical Synthesis of Optically Active α-Hydroxysilanes**

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Optically active α-hydroxysilanes are regarded as a kind of chiral organometallic compound with a functional group. These molecules and their derivatives have been utilized for stereocontrolled C–C bond formation and rearrangement, which resulted in a variety of chiral organic compounds.[1–5] Asymmetric reduction of acyl silanes is a straightforward method to produce the chiral secondary α-hydroxysilanes. Hydroboration with *B*-chlorodiisopinocampheylborane (Ipc_2BCl) is the most widely used method for this important transformation.[1,3a,4d–h,5–7] The chiral oxazaborolidine reagent is effective for the reaction of acetylenic acyl silanes.[4i,j,5] A chiral lithium amide reduces α,β-unsaturated acyl silanes with excellent enantioselectivity.[8] However, these procedures require more than one equivalent of the chiral reagent to the substrate.

A recently reported transfer hydrogenation catalyzed by an arene/*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (Ts-dpen) Ru^{II} complex using 2-propanol as a reducing agent is effective for aromatic acyl silanes.[3c] Although this is the only catalytic chemical process for this reaction, the substrate-to-catalyst molar ratio (S/C) of 33–200 is not satisfactory for practical use. Asymmetric microbial reductions are reported to exhibit high stereoselectivity merely for specific acyl silane substrates.[3b,9] Thus, the development of an efficient procedure for the catalytic asymmetric reduction of acyl silanes is highly desirable. Hydrogenation possesses advantages over many other reduction methods from the atom-economical and practical points of view.[10]

Herein, we disclose for the first time the highly enantioselective hydrogenation of acyl silanes catalyzed by Tol-binap/pica Ru^{II} complexes.[11,12] The reaction is conducted with a S/C value as high as 10000 under 10 atm of H_2. A series of benzylic, aliphatic, and allylic α-hydroxysilanes is obtained in up to 99% *ee*.

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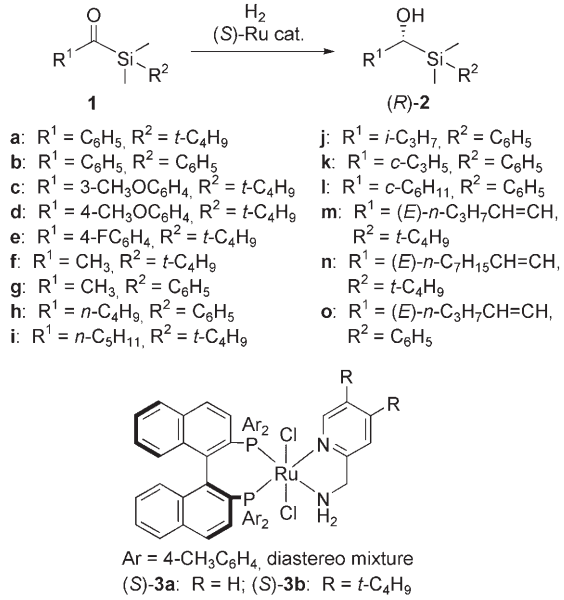
[**] This work was supported by a Grant-in-Aid from the Japan Society for the Promotion of Science (JSPS) (No. 18350046). Tol-binap = 2,2′-bis(di-4-tolylphosphanyl)-1,1′-binaphthyl; pica = α-picolylamine.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Benzoyl-*tert*-butyldimethylsilane (**1a**; Scheme 1), prepared by a reported procedure,[3c] was selected as a typical substrate for screening the reaction conditions. Hydrogenation of **1a** (0.42 g, 0.48 M) in ethanol with [$RuCl_2${(*S*)-Tol-binap}(pica)] [(*S*)-**3a**;[13] 0.94 mg, 0.24 μM, S/C = 2000] and *t*-C_4H_9OK (1.0 M in *tert*-butyl alcohol, 40 μL, 10 mM) at 24 °C under H_2 (10 atm) was completed in 1 h to afford the (*R*)-α-hydroxysilane (*R*)-**2a** in 96% *ee* and 96% yield of isolated product (Scheme 1 and Table 1, entry 1). When the concentration of base was increased to 50 mM, the yield of **2a** was slightly decreased with formation of the benzyl silyl ether as a by-product (Table 1, entry 2). This is because cleavage of the Si–C(OH) bond of **2a** through a Brook-type rearrangement occurred under the conditions of higher base concentration.[14]



Scheme 1. Asymmetric hydrogenation of acyl silanes.

The 1 mM concentration of base was not enough to activate the precatalyst **3a** for conversion to the active RuH species (Table 1, entry 3).[11,15] KOH was usable instead of *t*-C_4H_9OK (Table 1, entry 4), but employment of the less basic K_2CO_3 or DBU decreased the reactivity, even at a higher concentration of base (40 mM; Table 1, entries 5 and 6). $NaBH_4$, a metal hydride, also activated **3a**, although the efficiency was much less than that of *t*-C_4H_9OK (Table 1, entry 7).[11,16] The Ru complex **3b** with 4,5-di-*tert*-butylpicolyl-

Table 1: Asymmetric hydrogenation of **1a**.[a]

Entry	Ru catalyst	S/C[b]	Activator [mM]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	(*S*)-**3a**	2000	*t*BuOK (10)	1	96	96
2	(*S*)-**3a**	2000	*t*BuOK (50)	1	92[e]	95
3	(*S*)-**3a**	1000	*t*BuOK (1)	1	<1[f]	nd[g]
4	(*S*)-**3a**	1600	KOH (10)	1	94	96
5	(*S*)-**3a**	30	K_2CO_3 (40)	6	92	95
6	(*S*)-**3a**	400	DBU (40)[h]	6	94	96
7	(*S*)-**3a**	300	$NaBH_4$ (10)	10	94	97
8	(*S*)-**3b**	1200	*t*BuOK (10)	6	91	97
9	[i]	500	*t*BuOK (20)	3	1	nd[g]

[a] Unless otherwise stated, reactions were conducted using 1.0–2.1 mmol of **1a** (0.4–0.5 M) in ethanol containing a Ru catalyst and an activator at 20–25 °C under 10 atm of H_2. [b] Substrate/catalyst molar ratio. [c] Yield of isolated (*R*)-**2a**. [d] Data for (*R*)-**2a** determined by chiral HPLC analysis. [e] A benzyl silyl ether was obtained as a by-product. [f] Conversion determined by ^{1}H NMR analysis. [g] Not determined. [h] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [i] $[RuCl_2\{(S)\text{-binap}\}\{(S,S)\text{-dpen}\}]$ was used as a catalyst in 2-propanol.

Table 2: Asymmetric hydrogenation of acyl silanes.[a]

1	Ru catalyst	S/C[b]	*t* [h]	(*R*)-**2** Yield [%][c]	*ee* [%][d]
1a[e]	(*S*)-**3a**	10000	2.5	96	95
1b	(*S*)-**3a**[f]	900	1	80	96
1c	(*S*)-**3a**	1000	3.5	90	96
1d	(*S*)-**3a**	500	5	90	96
1e	(*S*)-**3a**	1600	1.5	96	96
1f	(*S*)-**3a**	2000	3	88	98
1f	(*S*)-**3b**	800	3	99	98
1g	(*S*)-**3a**[g]	1100	1	85	93
1h	(*S*)-**3a**	600	1	88	97
1i	(*S*)-**3a**	1200	6	99	91
1i	(*S*)-**3b**[h]	500	6	97	95
1j	(*S*)-**3a**	900	4	77	99
1k	(*S*)-**3a**	600	1	83	98
1l	(*S*)-**3a**	600	1.5	94	99
1m	(*S*)-**3a**	350	1	84	89
1n	(*S*)-**3a**	300	1	82[i]	87[j]
1o	(*S*)-**3a**	350	1	54	90

[a] Unless otherwise stated, reactions were conducted using 0.9–1.4 mmol of ketone **1** (0.4–0.7 M) in ethanol containing a Ru catalyst **3** and *t*-C_4H_9OK (10 mM) at 20–26 °C under 10 atm of H_2. [b] Substrate/catalyst molar ratio. [c] Yield of isolated product. [d] Chiral GC or HPLC analysis. [e] Reaction using 18.4 mmol (4.05 g) of **1a**. [f] The concentration of *t*-C_4H_9OK was 5 mM. [g] $NaBH_4$ (15 mM) was used as catalyst activator. [h] CH_3OH/*t*-C_4H_9OH (3:7) was used as solvent. [i] Determined by ^{1}H NMR analysis. [j] Determined after conversion to the *N*-phenylcarbamate.

amine (DTB-pica) instead of the original pica showed comparably high enantioselectivity, while the activity was relatively lower (Table 1, entry 8).

Notably, a catalyst system consisting of *trans*-$[RuCl_2\{(S)\text{-binap}\}\{(S,S)\text{-dpen}\}]$ and *t*-C_4H_9OK in 2-propanol, which shows high activity and enantioselectivity for the hydrogenation of simple ketones, was virtually inert for this transformation (Table 1, entry 9).[17,18] The flat pyridine moiety of the pica ligand is crucial to achieve high reactivity for the hydrogenation of sterically hindered acyl silanes. Thus, we chose the following standard reaction conditions: precatalyst, **3**; activator, *t*-C_4H_9OK (10 mM); solvent, ethanol; H_2 pressure, 10 atm; temperature, 20–25 °C.

The catalyst system hydrogenated aromatic, aliphatic, and α,β-unsaturated acyl silanes with high reactivity and enantioselectivity. Absolute configurations of new hydroxysilanes were estimated by a modified Mosher method (see the Supporting Information).[19] Hydrogenation of **1a** (0.75 M) with (*S,S*)-**3a** at a S/C value of 10000 in ethanol containing *t*-C_4H_9OK (10 mM) at 23 °C under H_2 (10 atm) produced (*R*)-**2a** in 95% *ee* and 96% yield of isolated product (Table 2). Although benzoyldimethylphenylsilane (**1b**) is more base-labile than **1a**, it was also hydrogenated with high enantioselectivity under a lower concentration of base (5 mM).

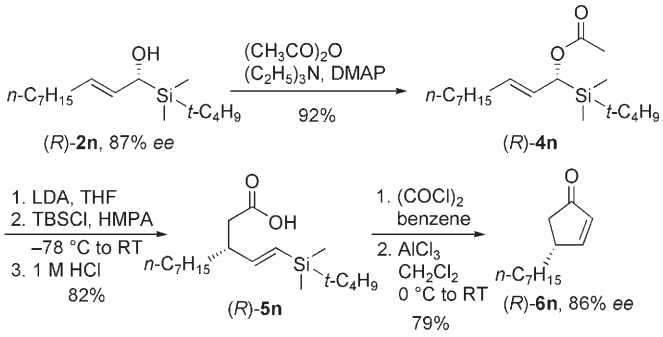
Benzoyl substrates with an electron-donating CH_3O group or an electron-attracting F atom at the *meta* or *para* position of the phenyl ring (**1c–e**) were converted to the α-hydroxysilanes **2c–e** in the same *ee* of 96%. The electronic features of the aromatic moieties did not affect the enantioselectivity, while introduction of the electron-withdrawing function accelerated the reaction rate. Hydrogenation of acetyl-*tert*-butyldimethylsilane (**1f**), a simple aliphatic substrate, mediated by (*S*)-**3a** in base-containing ethanol afforded the (*R*)-α-hydroxysilane (*R*)-**2f** in 98% *ee*. The sense of enantioselection was the same as that in the reaction of benzoylsilane **1a**. The Tol-binap/DTB-pica Ru complex **3b** showed the same enantioselectivity.

Acetyldimethylphenylsilane (**1g**), which is extremely labile in basic alcoholic media, was hydrogenated with (*S*)-**3a** using $NaBH_4$ (15 mM) as an activator to give (*R*)-**2g** in 93% *ee* and 85% yield of isolated product. Hydrogenation of pentanoyldimethylphenylsilane (**1h**) afforded the hydroxysilane **2h** in 97% *ee*; *t*-C_4H_9OK (10 mM) could be used as an activator in this reaction. Hexanoyl-*tert*-butyldimethylsilane (**1i**) was hydrogenated with **3a** in 91% optical yield. When the reaction was conducted with complex **3b**, the optical yield was increased to 95%. Use of a CH_3OH/*t*-C_4H_9OH (3:7) mixed solvent gave slightly better stereoselectivity. The "remote effect" of *tert*-butyl groups on the pyridine ring (see the catalyst structure) may originate from suitable fixation of the catalyst conformation for enantioface selection of this substrate. Hydrogenation of secondary alkyl acyl silanes **1j–l** in the presence of (*S*)-**3a** afforded the (*R*)-α-hydroxysilanes (*R*)-**2j–l** in >98% *ee*. Tri-*n*-butyl(propanoyl)stannane,[20] a tin analogue of **1**, was not converted under the standard hydrogenation conditions.

Complex **3a** also effects asymmetric hydrogenation of α,β-unsaturated acyl silanes to the optically active allylic α-hydroxysilanes, although these conjugated acyl silanes readily undergo 1,4-reduction in general.[1,3c] Hydrogenation of (*E*)-2-hexenoyl-*tert*-butyldimethylsilane (**1m**) in the presence of (*S*)-**3a** (S/C = 350) and *t*-C_4H_9OK (10 mM) in ethanol under H_2 (10 atm) was completed in 1 h to afford the *R* allylic α-hydroxysilane (*R*)-**2m** in 89% *ee* and 84% yield of isolated product (Table 2). The 1,2-reduction occurred exclusively over the 1,4-reduction, while conjugate addition of ethoxide occurred as a side reaction in less than 5% yield. Such predominant 1,2-reduction selectivity for α,β-unsaturated acyl silanes is achieved only by this hydrogenation catalyzed by a Tol-binap/pica Ru complex, hydroboration with

Ipc_2BCl,[1,3a,4d–h] and a chiral lithium amide[8] reduction. In the same manner, hydrogenation of (*E*)-2-decenoyl-*tert*-butyldimethylsilane (**1n**) afforded (*R*)-**2n** in 87% *ee* and 82% yield. When (*E*)-2-hexenoyldimethylphenylsilane (**1o**) was hydrogenated with (*S*)-**3a** under the standard conditions, (*R*)-**2o** was obtained in 90% *ee* and 54% yield accompanied by messy by-products as a result of the extreme lability of **1o**.[21]

The chiral allylic α-hydroxysilane (*R*)-**2n** was readily converted to (*R*)-4-*n*-heptyl-2-pentenone [(*R*)-**6n**][22] through the Ireland–Claisen rearrangement[4a] without loss of enantioselectivity (Scheme 2). Acetylation of (*R*)-**2n** in 87% *ee* under standard conditions gave (*R*)-**4n** in 92% yield. Deprotonation of **4n** with LDA followed by treatment with $t\text{-}C_4H_9(CH_3)_2SiCl$ in the presence of HMPA at −78 °C, warming to room temperature, and hydrolysis with an acid afforded the chiral 5-silyl-4-pentenonic acid (*R*)-**5n** in 82% yield. Intramolecular vinylation of the acid anhydride of **5n** mediated by $AlCl_3$ resulted in the chiral enone (*R*)-**6n** in 86% *ee* and 79% yield (see the Supporting Information).[23]



Scheme 2. Conversion of α-hydroxysilane to cyclopentenone with retention of configuration. DMAP = 4-dimethylaminopyridine; LDA = lithium diisopropylamide; TBSCl = *tert*-butyldimethylsilyl chloride; HMPA = hexamethylphosphoramide.

In conclusion, we report here the first example of the highly reactive and enantioselective hydrogenation of acyl silanes catalyzed by Tol-binap/pica Ru^{II} complexes **3** with a base or a metal hydride activator in ethanol. A series of aromatic, aliphatic, and α,β-unsaturated acyl silanes is converted to the corresponding α-hydroxysilanes in excellent *ee*. Allylic α-hydroxysilanes with high enantio- and regioselectivity are obtained in the reaction of α,β-unsaturated compounds. Thus, this method provides a new, efficient, and practical route to producing chiral silane compounds.

Experimental Section

General procedure for hydrogenation of acyl silanes: Hydrogenation of **1a** illustrates the typical reaction procedure using standard Schlenk techniques. A degassed (three freeze–thaw cycles) solution of solid (*S*)-**3a** (1.7 mg, 1.8 μmol), $t\text{-}C_4H_9OK$ (24.5 mg, 0.22 mmol), and **1a** (4.05 g, 18.4 mmol) in ethanol (20 mL) was placed in a 100-mL glass autoclave equipped with a teflon-coated magnetic stirring bar. Hydrogen was introduced into the autoclave at a pressure of 10 atm, and then the reaction mixture was vigorously stirred at 23 °C for 2.5 h. After carefully venting the hydrogen gas, the solvent was removed under reduced pressure. The residue was purified by silica-gel column chromatography with ethyl acetate/hexane (1:20) as eluent to give (*R*)-**2a** (faintly yellow oil, 3.94 g, 96% yield, 95% *ee*). The *ee* of **2a** was determined by HPLC analysis: column, Chiralcel OD-H; eluent, hexane/2-propanol (9:1); flow rate, 0.5 mL min^{-1}; column temperature, 40 °C; retention time (t_R) of (*R*)-**2a**, 17.5 min (97.6%); t_R of (*S*)-**2a**, 11.4 min (2.4%). $[\alpha]_D^{20} = +95.4$ ($c = 1.08$, CH_2Cl_2); literature[3c] $[\alpha]_D^{24} = -81.6$ ($c = 1.02$, CH_2Cl_2), 82% *ee* (*S*).

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