Asymmetric Hydrogenation of Polysubstituted Aromatic Ketones Catalyzed by the DIPSkewphos/PICA Derivative–Ruthenium(II) Complexes

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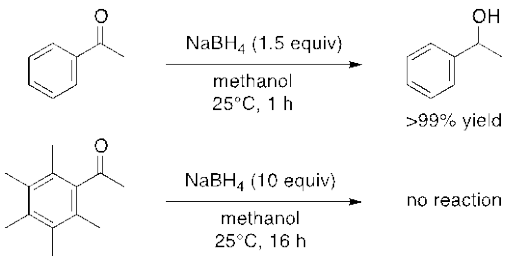
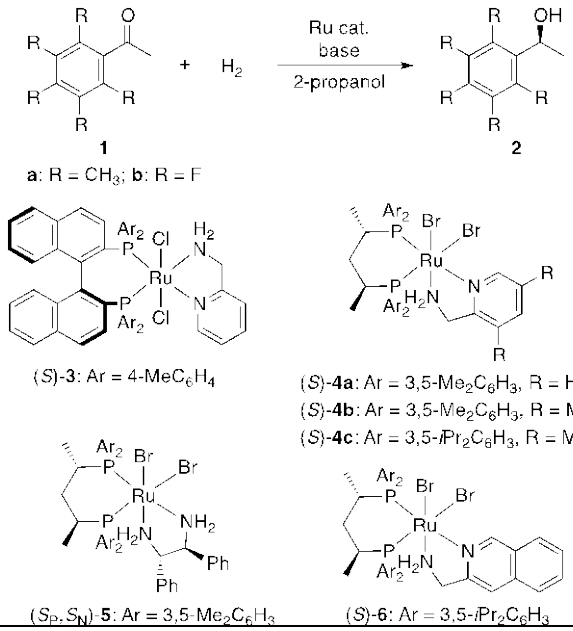
Abstract: The DIPSkewphos/PICA derivative–Ru(II) complexes catalyzed asymmetric hydrogenation of significantly sterically hindered 2',3',4',5',6'-pentamethylacetophenone, which was not reduced with $NaBH_4$ at 25°C, with a substrate-to-catalyst molar ratio (S/C) of 2000 under 50 atm of H_2 in a base-containing 2-propanol to afford the alcohol in 99% *ee* quantitatively. A series of polysubstituted aromatic ketones was smoothly reacted with an S/C of 300–10,000 under 10–50 atm of H_2, yielding the alcoholic products in up to 99% *ee*. The catalyst system achieved an industrial-scale (50 kg) hydrogenation of 2',6'-dichloro-3'-fluoroacetophenone, affording the alcohol in 96% isolated yield and in 98% *ee*. The obtained alcoholic product is known as a key intermediate for the synthesis of the medicine crizotinib.

Asymmetric hydrogenation of ketones affording optically-enriched secondary alcohols has remarkably contributed to fine stereoselective synthesis of a wide variety of biologically active compounds, such as medicines, agrochemicals, and perfumes.[1] The high atom-efficiency and operational simplicity allow the reaction to be conducted on an industrial scale.[2] Acetophenone, a simple aromatic ketone, has frequently been used as a standard substrate to evaluate the efficiency of hydrogenation catalysts. However, the reactivity of the carbonyl group is drastically changed by introducing substituents on the phenyl ring. For example, acetophenone itself is readily reduced with $NaBH_4$ (1.5 equiv) in methanol to give 1-phenylethanol quantitatively (Scheme 1). In contrast, in our hands, the reduction of 2',3',4',5',6'-pentamethylacetophenone resulted in no reaction with ten equivalents of $NaBH_4$ in 16 h. Development of efficient catalysts to hydrogenate such sterically hindered aromatic ketones is a challenging scientific subject. Moreover, several medicinal compounds synthesized from optically active polysubstituted 1-arylethanols have been developed in recent years.[3] Thus, we began an investigation of the asymmetric hydrogenation of polysubstituted aromatic ketones by our original Ru(II) catalysts.[4] The hardly reducible ortho-substituted ketones were the primary targets.



Scheme 1. Reduction of acetophenones with $NaBH_4$.

Table 1. Asymmetric hydrogenation of pentasubstituted acetophenones **1** catalyzed by chiral Ru complexes.[a]



Entry	1	Ru cat.	S/C[b]	Base	H_2 [atm]	Yield [%][c]	*ee* [%][d]
1	**1a**	(*S*)-**3**	200	*t*BuOK	10	<1	Nd[e]
2	**1a**	(*S*)-**4a**	200	*t*BuOK	10	83	88
3	**1a**	(*S*)-**4b**	200	*t*BuOK	10	94	93
4	**1a**	(S_P,S_N)-**5**	200	*t*BuOK	10	<1	Nd[e]
5	**1a**	(*S*)-**4c**	200	*t*BuOK	10	96	94
6	**1a**	(*S*)-**6**	200	*t*BuOK	10	98	99
7	**1a**	(*S*)-**6**	200	*t*BuONa	10	96	99
8	**1a**	(*S*)-**6**	500	*t*BuONa	10	95	99
9	**1a**	(*S*)-**6**	2000	*t*BuONa	50	>99(96)[f]	99
10	**1b**	(*S*)-**6**	300	*t*BuOK	10	20	96
11	**1b**	(*S*)-**6**	300	*t*BuOK	50	92(85)[f]	96

[a] Unless otherwise stated, the reactions were carried out under H_2 at 40°C for 21 h using ketone **1** (1.0 M) in 2-propanol containing a Ru complex and a base (30 mM). [b] Substrate-to-catalyst molar ratio. [c] Determined by GC

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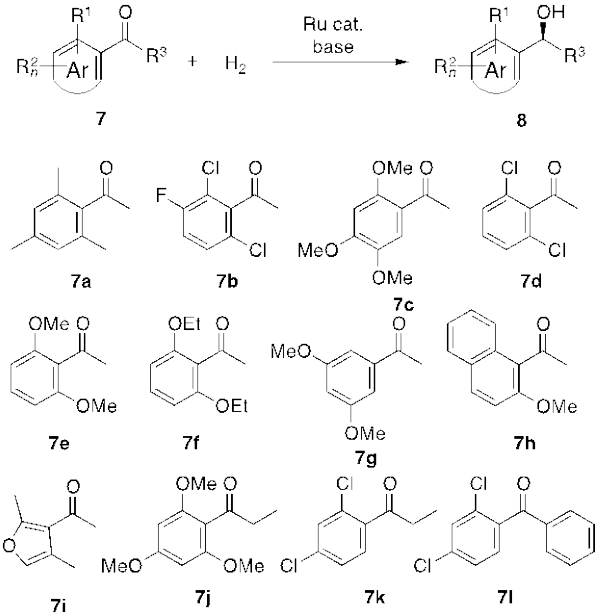
or ^{1}H NMR analysis. [d] Determined by chiral GC or HPLC analysis. [e] Not determined. [f] Isolated yields of **2** are indicated in parentheses.

We selected 2',3',4',5',6'-pentamethylacetophenone (**1a**) as a standard substrate to evaluate the efficiency of a series of catalysts. The hydrogenation of **1a** was conducted with a Ru(II) complex at a substrate-to-catalyst molar ratio (S/C) of 200 in a *t*BuOK-containing 2-propanol ($[\mathbf{1a}]_0$ = 1.0 M, [*t*BuOK] = 30 mM) under 10 atm of H_2 at 40°C in 21 h (Table 1). Only trace amounts of the alcoholic product **2a** were observed in the reaction with $RuCl_2$[(*S*)-tolbinap](pica) ((*S*)-**3**), which showed high catalytic activity in the hydrogenation of the sterically hindered *tert*-alkyl ketones and acylsilanes (Entry 1).[5,6] The catalytic activity was dramatically increased by using the (*S*,*S*)-Xylskewphos/PICA–Ru(II) complex (*S*)-**4a** to afford (*S*)-**2a** in 83% yield and 88% *ee* (Entry 2).[6–9] Introduction of methyl groups at the 3 and 5 positions on the PICA-pyridine ring (3,5-Me_2PICA)[6] improved both the catalytic activity and enantioselectivity (Entry 3). The (*S*,*S*)-XylSkewphos/(*S*,*S*)-DPEN–Ru(II) complex ((S_P,S_N)-**5**) showed marginal catalytic activity, indicating the importance of the PICA structure for this reaction (Entry 4).[6,10] The more sterically demanding diphosphine (*S*,*S*)-DIPSkewphos matched with 3,5-Me_2PICA ((*S*)-**4c**) to yield (*S*)-**2a** in 94% *ee* (Entry 5).[6] The Ru(II) complex combined with DIPSkewphos and 3-aminomethylisoquinoline (3-AMIQ) ((*S*)-**6**) exhibited even higher enantioselectivity under the regular conditions to afford (*S*)-**2a** in 99% *ee* (Entry 6).[6,11,12] The reaction using *t*BuONa instead of *t*BuOK as a base gave a comparable result (Entry 7). The high catalytic activity of the (*S*)-**6**/*t*BuONa system enabled the hydrogenation with an S/C of 500 under 10 atm of H_2 and an S/C of 2000 under 50 atm of H_2 with maintenance of the excellent enantioselectivity (Entries 8 and 9). The reaction of 2',3',4',5',6'-pentafluoroacetophenone (**1b**), another penta-substituted acetophenone, with an S/C of 300 under 10 atm of H_2 was slow, but the desired alcohol **2b** in 96% *ee* was obtained with a high yield of 92% under 50 atm of H_2 (Entries 10 and 11).[13]

We next applied the catalyst systems to the asymmetric hydrogenation of a range of polysubstituted aromatic ketones **7** in 2-propanol or ethanol (Table 2). In most cases the DIPSkewphos/3-AMIQ–Ru(II) complex **6** achieved the best enantioselectivity. The reaction of 2',4',6'-trimethylacetophenone (**7a**) catalyzed by **4c** or **6** with *t*BuOK or *t*BuONa was completed even at an S/C of 2000 under 10 atm of H_2 in 21 h to give the alcohol **8a** in 98% *ee* (Entries 1–3).[14] The marked difference in the reaction rate between the ketones **1a** and **7a** suggests that the meta-substituents on the phenyl ring influence the catalytic activity. 2',6'-Dichloro-3'-fluoroacetophenone (**7b**) was quantitatively converted with **4b**, **4c**, or **6** to the alcohol **8b** in 98–99% *ee* (Entries 4–6).[15] The reaction of 2',4',5'-trimethoxyacetophenone (**7c**), an electron-rich ketone, quantitatively yielded the alcohol **8c** in 99% *ee* under the regular conditions (Entries 7–9). 2',6'-Dichloro- and -dimethoxyacetophenones, **7d** and **7e**, were also appropriate substrates for this reaction, resulting in the alcohols **8d** and **8e** in up to 99% *ee* quantitatively regardless of the electronic properties of the substituents (Entries 10–14). The more sterically hindered 2',6'-diethoxyacetophenone (**7f**) was a difficult substrate to hydrogenate with high reactivity and enantioselectivity with **4b** and **4c** (Entries 15 and 16).

Table 2. Asymmetric hydrogenation of polysubstituted aromatic ketones **7**.[a]



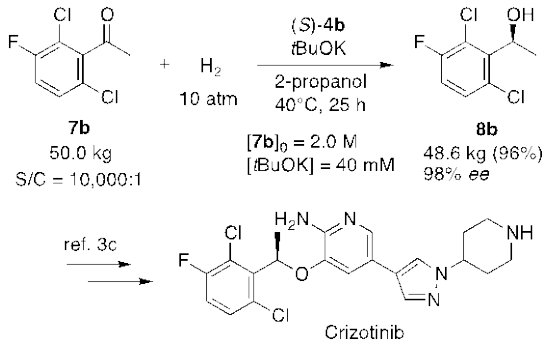
Entry	7	Ru cat.	S/C[b]	Base	Solvent	Yield [%][c]	*ee* [%][d]
1	**7a**	(*S*)-**4c**	2000	*t*BuOK	*i*PrOH	98(97)	98
2	**7a**	(*S*)-**6**	2000	*t*BuOK	*i*PrOH	>99(99)	98
3	**7a**	(*S*)-**6**	2000	*t*BuONa	*i*PrOH	>99(97)	98
4	**7b**	(*S*)-**4b**	1000	*t*BuOK	*i*PrOH	>99	98
5	**7b**	(*S*)-**4c**	1000	*t*BuOK	*i*PrOH	>99	98
6	**7b**	(*S*)-**6**	1000	*t*BuOK	*i*PrOH	>99(93)	99
7	**7c**	(*S*)-**4c**	2000	*t*BuOK	EtOH	>99(98)	99
8	**7c**	(*S*)-**6**	2000	*t*BuOK	EtOH	>99(99)	99
9	**7c**	(*S*)-**6**	2000	*t*BuONa	EtOH	>99(98)	99
10	**7d**	(*S*)-**4c**	2000	*t*BuOK	*i*PrOH	99(95)	99
11	**7d**	(*S*)-**6**	2000	*t*BuOK	*i*PrOH	>99(99)	99
12	**7e**	(*S*)-**4c**	2000	*t*BuOK	*i*PrOH	>99(95)	96
13	**7e**	(*S*)-**6**	2000	*t*BuOK	*i*PrOH	>99(99)	98
14	**7e**	(*S*)-**6**	2000	*t*BuONa	*i*PrOH	>99(99)	98
15	**7f**	(*S*)-**4b**	500	*t*BuOK	*i*PrOH	91	93
16	**7f**	(*S*)-**4c**	500	*t*BuOK	*i*PrOH	98	92
17	**7f**	(*S*)-**6**	500	*t*BuOK	*i*PrOH	>99(97)[e]	95
18	**7g**	(*S*)-**4c**	2000	*t*BuOK	EtOH	>99[f,g]	97
19	**7g**	(*S*)-**6**	2000	*t*BuOK	EtOH	>99(100)[f,g]	98
20	**7h**	(*S*)-**4c**	1000	*t*BuOK	*i*PrOH	>99(97)	99
21	**7h**	(*S*)-**6**	1000	*t*BuOK	*i*PrOH	>99(99)	99
22	**7i**	(*S*)-**4c**	1000	*t*BuOK	*i*PrOH	91	97
23	**7i**	(*S*)-**6**	1000	*t*BuOK	*i*PrOH	99(93)[h]	95
24	**7j**	(*S*)-**4c**	1000	*t*BuOK	*i*PrOH	98(94)[i]	99
25	**7j**	(*S*)-**6**	1000	*t*BuOK	*i*PrOH	>99(97)[e]	99
26	**7k**	(*S*)-**4c**	1000	*t*BuOK	*i*PrOH	99(99)	99
27	**7k**	(*S*)-**6**	1000	*t*BuOK	*i*PrOH	93(92)	99
28	**7l**	(*S*)-**6**	1000	*t*BuOK	*i*PrOH	96(93)[g]	37

[a] Unless otherwise stated, the reactions were carried out under 10 atm of H_2 at 40°C for 21–24 h using ketone **7** (0.5–2.0 M) in solvent containing a Ru complex and a base (20–30 mM). [b] Substrate-to-catalyst molar ratio. [c] Determined by GC or ^{1}H NMR analysis. Isolated yields of **8** are indicated in

parentheses. [d] Determined by chiral GC or HPLC analysis. [e] Reaction for 36 h. [f] Reaction at 30–33°C [g] Reaction for 16 h. [h] Reaction for 8 h. [i] Reaction for 30 h.

Fortunately, the desired alcohol **8f** was quantitatively obtained with a high level of enantiomeric purity of 95% in the presence of **6** with an S/C of 500 under 10 atm of H_2 in 36 h (Entry 17). Less hindered 3',5'-dimethoxyacetophenone (**7g**) was smoothly hydrogenated with an S/C of 2000 to afford **8g** in up to 98% *ee* (Entries 18 and 19). The reaction of 2'-methoxy-1'-acetonaphthone (**7h**) with a fused ring structure in the presence of **4c** or **6** at an S/C of 1000 quantitatively afforded the **8h** in 99% *ee* (Entries 20 and 21). 3-Acetyl-2,4-dimethylfuran (**7i**), a disubstituted heteroaromatic ketone, was also hydrogenated with 95%–97% enantioselectivity (Entries 22 and 23). The enantiomeric purity of the alcohol **8i** was gradually reduced with a prolonged reaction time in the hydrogenation using **4c** (Entry 22). In contrast, the reaction in the presence of **6** was completed in 8 h with the maintenance of high enantiomeric purity (Entry 23). The polysubstituted propiophenone derivatives, **7j** and **7k**, were also smoothly converted with **4c** or **6** at an S/C of 1000 to the corresponding alcohols, **8j** and **8k**, both in 99% *ee* (Entries 24–27). The hydrogenation of 2,4-dichlorobenzophenone (**7l**) gave the benzhydrol **8l** with modest enantioselectivity (Entry 28).[16]

Finally, we applied the catalyst system to an industrial-scale hydrogenation of **7b** (Scheme 2). The reaction was conducted in a 200-L stainless steel autoclave by using 50.0 kg of **7b** and (*S*)-**4b** (23.0 g, S/C = 10,000) in 85 L of *t*BuOK (542 g)-containing 2-propanol ($[\mathbf{7b}]_0$ = 2.0 M, [*t*BuOK] = 40 mM) under 10 atm of H_2 at 40°C in 25 h to afford the alcohol (*S*)-**8b** (48.6 kg, 96% yield) in 98% *ee* (see the Supporting Information in detail). The alcohol (*S*)-**8b** is a key intermediate in the synthesis of crizotinib, a medicine for the treatment of locally advanced or metastatic non-small cell lung cancer.[3c,17]



Scheme 2. Practical-scale hydrogenation of **7b**.

The *cis*-RuH_2[(*S*)-dipskewphos](3-amiq) ((*S*)-**9**) is proposed to be the active species derived from (*S*)-**6**/*t*BuONa catalytic system based on the related previous studies.[4,8–10,18] Scheme 3 illustrates the molecular models of (*S*)-**9** and plausible diastereomeric transition states (TSs) $\mathbf{TS}_{\boldsymbol{Re}}$ and $\mathbf{TS}_{\boldsymbol{Si}}$ in the hydrogenation of the pentamethylphenyl ketone **1a**. The more nucleophilic H_A connecting to Ru at the *trans* position to the PAr_2 group reacts as a hydride. The hydrogenation of **1a** proceed through the six-membered metal–ligand cooperated TS, $\mathbf{TS}_{\boldsymbol{Re}}$ or $\mathbf{TS}_{\boldsymbol{Si}}$ in which the $C^{\delta+}=O^{\delta-}$ dipole of ketone interacts with the $H_A^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H_{ax}^{\delta+}$ quadrupole of the catalyst.[4,18] The $\mathbf{TS}_{\boldsymbol{Si}}$ suffers significant steric repulsion between the pentamethylphenyl ring of **1a** and the diisopropylphenyl group of the catalyst. In contrast, the $\mathbf{TS}_{\boldsymbol{Re}}$ has no such repulsion because the hindered pentamethylphenyl ring is placed above the flat isoquinoline group of the catalyst. Therefore, the $\mathbf{TS}_{\boldsymbol{Re}}$ is much favored over $\mathbf{TS}_{\boldsymbol{Si}}$, and it affords (*S*)-**2a**. Low activity of the catalyst derived from XylSkewphos/DPEN–Ru complex **5** may be due to insufficient reaction area to accept the hindered ketone **1a** around the catalytic species.

In conclusion, we here reported asymmetric hydrogenation of polysubstituted aromatic ketones with the DIPSkewphos/PICA derivative–Ru(II) catalysts in a base (*t*BuOK or *t*BuONa)-containing 2-propanol or ethanol. Significantly sterically hindered 2',3',4',5',6'-pentamethylacetophenone, which was not reduced with $NaBH_4$ at 25°C, was quantitatively hydrogenated with an S/C of 2000 under 50 atm of H_2 to afford the alcohol in 99% *ee*. Both Skewphos and PICA ligand-structures were crucial to achieve high catalytic activity and enantioselectivity. A range of polysubstituted aromatic ketones was smoothly hydrogenated with an S/C of 300–10,000 under 10–50 atm of H_2 to give the chiral alcohols in 99% *ee* in the best cases. The high catalyst efficiency achieved an industrial-scale (50 kg) hydrogenation of 2',6'-dichloro-3'-fluoroacetophenone to afford the alcoholic product in 96% isolated yield and 98% *ee* as a key intermediate for the synthesis of the medicine crizotinib.

Experimental Section

Asymmetric hydrogenation of 1a with Ru complex (*S*)-6 at an S/C of 2000 under 50 atm of H_2 (Table 1, Entry 9)

The ruthenium complex (*S*)-**6** (1.0 mg, 0.84 μmol), *t*BuONa (4.9 mg, 51 μmol), ketone **1a** (318.9 mg, 1.68 mmol), and a Teflon-coated stirring bar were placed in a 30 mL glass test tube inside a stainless autoclave that had been filled with argon. The reaction vessel was then evacuated and refilled with argon. 2-Propanol (1.7 mL) that had been degassed by three freeze–thaw cycles was transferred into the autoclave through a Teflon cannula. Hydrogen was initially introduced into the autoclave at a pressure of 20 atm before being reduced to 5 atm. This procedure was repeated five times. The autoclave was then pressurized with H_2 gas (50 atm), and the solution was stirred vigorously at 40°C for 21 h. After careful release of the hydrogen, the solution was concentrated under reduced pressure. Purification by a preparative TLC (developed with hexane/ethyl acetate = 2:1) gave (*S*)-1-(2,3,4,5,6-pentamethylphenyl)ethanol ((*S*)-**2a**) (309.5 mg, 1.61 mmol, 96%, 99% *ee*).

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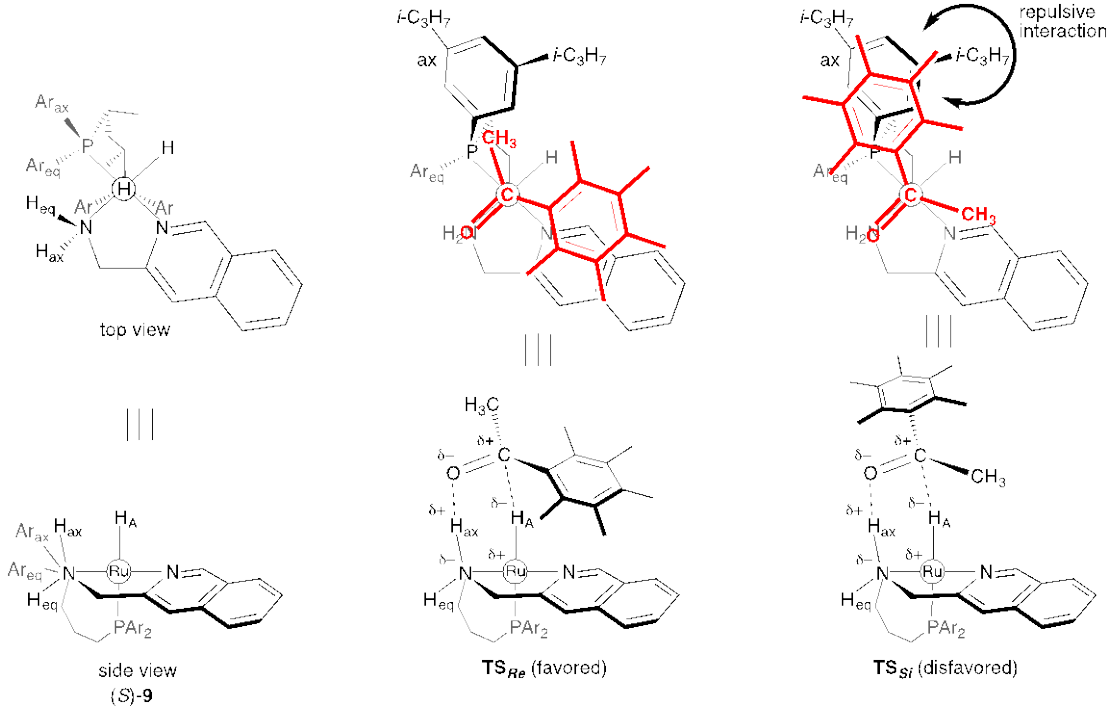
Keywords: alcohol • asymmetric catalysis • hydrogenation • ketone • ruthenium



Scheme 3. Structure of RuH_2 complex (*S*)-**9** derived from (*S*)-**6** and diastereomeric TS models in the hydrogenation of **1a**. The structures are simplified for clarity. Ar = 3,5-*i*Pr$_2$C$_6$H$_3$.

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[3] For example, see: a) M. M. Zhao, J. M. McNamara, G.-J. Ho, K. M. Emerson, Z. J. Song, D. M. Tschaen, K. M. J. Brands, U. Dolling, E. J. J. Grabowski, P. J. Reider, I. F. Cottrell, M. S. Ashwood, B. C. Bishop, *J. Org. Chem*. **2002**, *67*, 6743–6747; b) H. Takemoto, M. Takayama, T. Shiota, Jpn. Kokai Tokkyo Koho P4145655, **2008**; c) P. D. de Koning, D. McAndrew, R. Moore, I. B. Moses, D. C. Boyles, K. Kissick, C. L. Stanchina, T. Cuthbertson, A. Kamatani, L. Rahman, R. Rodriguez, A. Urbina, A. Sandoval (née Accacia), P. R. Rose, *Org. Process Res. Dev*. **2011**, *15*, 1018–1026; d) M. Takayama, N. Kurose, Jpn. Kokai Tokkyo Koho P5164181, **2013**; e) M. R. Leleti, Y. Li, V. R. Mali, J. Powers, J. Yang, PCT Int. WO 2013/082429 A1, **2013**.

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[6] TolBINAP = 2,2'-bis(di-4-tolylphosphino)-1,1'-binaphthyl. PICA = α-picolylamine. XylSkewphos = 2,4-bis(di-3,5-xylylphosphino)pentane. 3,5-Me$_2$PICA = 2-aminomethyl-3,5-dimethylpyridine. DPEN = 1,2-diphenylethylenediamine. DIPSkewphos = 2,4-di(bis(3,5-diisopropylphenyl)phosphino)pentane.

[7] T. Katayama, K. Tsutsumi, K. Murata, T. Ohkuma, N. Arai, Jpn. Kokai Tokkyo Koho P2015-24975, **2015**.

[8] The Ru(II) complex (*S*)-**4a** was utilized in the industrial synthesis of (*R*)-3-quinuclidinol, which is a key building block of the medicine solifenacin. See: K. Tsutsumi, T. Katayama, N. Utsumi, K. Murata, N. Arai, N. Kurono, T. Ohkuma, *Org. Process Res. Dev*. **2009**, *13*, 625–628.

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[12] Asymmetric reduction of **1a** with 4 equivalents of poly(methylhydroxysilane) in THF at 65°C for 24 h catalyzed by a chiral Fe complex with an S/C of 20 gave **2a** in 45% yield and 99% *ee*. See: N. S. Shaikh, S. Enthaler, K. Junge, M. Beller, *Angew. Chem*. **2008**, *120*, 2531–2535; *Angew. Chem. Int. Ed*. **2008**, *47*, 2497–2501.

[13] Transfer hydrogenation of **1b** with the chiral Re catalyst at an S/C of 100 in 2-propanol at 80°C for 20 h afforded **2b** in 46% *ee* quantitatively. See: E. Mejía, R. Aardoom, A. Togni, *Eur. J. Inorg. Chem*. **2012**, 5021–5032.

[14] Hydrogenation of **7a** with the chiral bis(oxazolinyl)phenyl–Ru(II) dimer including a $ZnCl_4$ bridge at an S/C of 100 under 30 atm of H_2 in 24 h gave **8a** in 98% yield and 95% *ee*. See: a) J. Ito, S. Ujiie, H. Nishiyama, *Organometallics* **2009**, *28*, 630–638; b) J. Ito, T. Teshima, H. Nishiyama, *Chem. Commun*. **2012**, *48*, 1105–1107.

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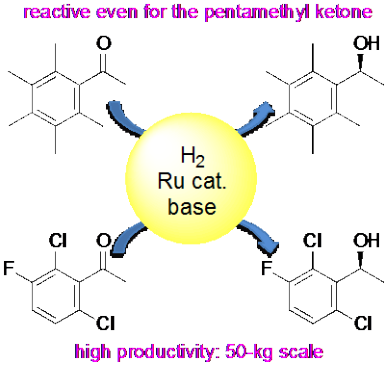
COMMUNICATION

Asymmetric hydrogenation of polysubstituted aromatic ketones was achieved by using the DIPSkewphos/PICA derivative–Ru(II) catalysts. Significantly sterically hindered 2',3',4',5',6'-pentamethyl-acetophenone was quantitatively converted to the alcohol in 99% *ee*. Industrial-scale (50 kg) reaction of 2',6'-dichloro-3'-fluoroacetophenone afforded the alcoholic product, which is a key synthetic intermediate of the medicine crizotinib, in 98% *ee*.



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