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A Base-controlled Chemoselective Transfer Hydrogenation of α,β-Unsaturated Ketones Catalyzed by $[IrCp^*Cl_2]_2$ With 2-Propanol

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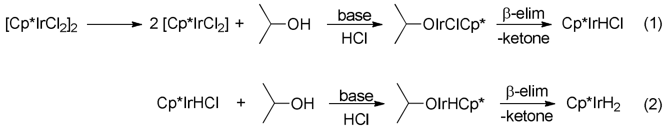
A simple homogeneous catalyst system based on commercially available $[IrCp^*Cl_2]_2$ has been developed for the conjugate reduction of α,β-unsaturated ketones. Under the optimized conditions, a wide range of α,β-unsaturated ketones was reduced to saturated ketones in 83-98% yield. While switching the base from K_2CO_3 to KOH, saturated alcohols was selectively obtained.

The catalytic transfer hydrogenation of unsaturated organic compounds is an attractive methodology in synthetic organic chemistry.[1] Chemoselective reduction of α,β-unsaturated carbonyl compounds is one of the most important subjects in this field. Since the second half of the 20th century, a number of protocols have been developed for the transfer hydrogenation of α,β-unsaturated ketones with the aim of avoiding the use of hazardous hydrogen gas[2-3] and other costly hydrogen sources (hydrosilanes,[4] $NaBH_4$,[5] Hantzsch ester[6] etc.). This type of transformation has been achieved by the use of transition metals derived from ruthenium,[7-8] rhodium,[9-10] palladium,[11] iridium,[12] and nickel.[13] The use of alcohols, formic acid and its salts is oftentimes preferred. Among them, 2-propanol is the most attractive hydrogen donor due to it's good solvent properties, less expensive, and easy to remove from the reaction system as itself or the generated acetone.[1c]

Despite all these advances, considering the constitution of these catalyst systems, most of the catalysts required tedious steps of synthesis or additive ancillary ligands. Only a few processes directly applied the commercially available catalyst, and most of them also suffered from drawbacks such as low yields, high temperature, and the use of toxic solvents.[8-9] In this respect, the search for simple and practical catalyst system especially consisting of commercially available catalyst is still in high demand.

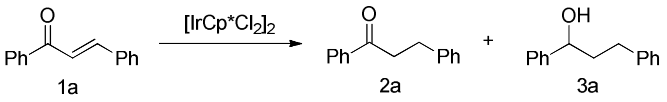
As part of our continuing interest in homogeneous iridium catalysts for organic transformations,[14] we herein reported the potential of commercial available catalyst $[IrCp^*Cl_2]_2$ in transfer hydrogenation of α,β-unsaturated ketones with 2-propanol as hydrogen source and solvent.

We began our studies by utilizing chalcone **1a** as a model substrate in the presence of $[IrCp^*Cl_2]_2$[15] under various conditions (Table 1). Treatment of **1a** with catalytic amount of $[IrCp^*Cl_2]_2$ and K_2CO_3 in MeOH at 85 °C for 5 h gave the conjugate reduction product **2a** in 31 % yield with none of the double hydrogenation product **3a** (Table 1, entry 1). A screening on other straight-chain fatty alcohols, that is, EtOH, 1-PrOH, and 1-BuOH, gave **2a** in 36%, 70%, and 57% yields, respectively (entries 2-4). To our delight, when 2-PrOH was used, the reaction proceeded smoothly, yielding the **2a** in 92% yield with excellent chemoselectivity (entry 5). To further improve the yield, a series of bases was then screened and Na_2CO_3 gave the similar result to K_2CO_3 (entry 6). Interestingly, in the case of Cs_2CO_3, the generated **2a** was further hydrogenated to the saturated alcohol **3a** in 64% yield (entry 7). Other strong bases, such as KOH and NaOH, gave **3a** in 86 , 84% yields, respectively (entries 8-9). Organic base NEt_3 exhibited inhibitory effect on the reaction and resulted in a low yield (entry 10). It should be noted that decreasing the amount of K_2CO_3 to 5 mol% led to full conversion of **1a** and 99 % of the **2a** was obtained within 5 h (Table 1, entry 11). However, in the absence of K_2CO_3, the reaction proceeded sluggishly (entry 12).



Base on the above findings and the literature data, we inferred that the role of the base was to generate a highly active Cp^*IrH_2 catalyst from the dichloride (eqns. (1) and (2)).[16] In addition, an excess of base resulted in low solubility of the substrate, which ultimately led to low yield. To validate our assumption, a series of controlled experiments based on the volume of 2-PrOH was carried out under the condition of entry 5, as showed in Figure 1. As expected, the yield of **2a** was merely moderate when the concentration of K_2CO_3 was high. Increasing the volume of 2-PrOH improved the yield of **2a**. A full conversion of **1a** and 99% yield of **2a** was achieved when the amount of 2-PrOH was increasing to 2 mL. Continue increasing the volume of 2-PrOH to 5 mL did not change the yield of **2a**.

Table 1. Optimization of reaction conditions in transfer hydrogenation of chalcone[a]



Entry	Solvent	Base	Yield (%)[b]	
			2a	**3a**
1	MeOH	K_2CO_3	31	0
2	EtOH	K_2CO_3	36	0
3	1-PrOH	K_2CO_3	70	0
4	1-BuOH	K_2CO_3	57	0
5	2-PrOH	K_2CO_3	92	0
6	2-PrOH	Na_2CO_3	89	0
7	2-PrOH	Cs_2CO_3	16	64
8	2-PrOH	KOH	2	86
9	2-PrOH	NaOH	3	84
10	2-PrOH	NEt_3	14	0
11[c]	2-PrOH	K_2CO_3	99	0
12	2-PrOH	-	66	0

[a] Reactions conditions: **1a** (0.2 mmol), $[IrCp^*Cl_2]_2$ (1 mol%), base (0.5 equiv.), solvent (1 mL), 85 °C, 5 h. [b] GC yield. [c] 5 mol% K_2CO_3 was used. Cp^*: 1,2,3,4,5-pentamethylcyclopentadiene.

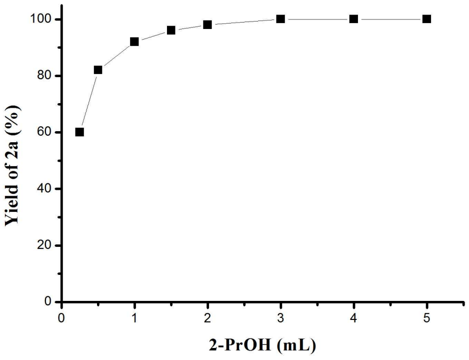
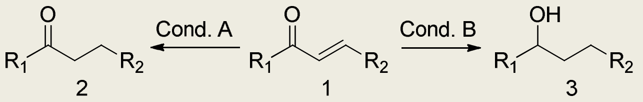


Figure 1. Effect of the volume of 2-PrOH on the catalytic transfer hydrogenation of chalcone with $[IrCp^*Cl_2]_2$.

With the optimized conditions in hands, various α,β-unsaturated ketones were then subjected to the reaction to establish the scope and generality of this protocol (Table 2). Firstly, a series of substituted chalcones were investigated (entries 2-16). The chalcones bearing electron-donating group Me and MeO on the 4' position respectively required a higher catalyst loading and temperature to achieve satisfactory results (entries 2-3); while the chalcones bearing Me and MeO groups on the 4 position respectively were easy to reduce cleanly (entries 10-11). The transformations of halogen- and trifluoromethyl-substituted chalcones afforded desired products in 92-98% yields, and the position of the substituted groups did not significantly affect the reactivity (entries 4-7, 12-15). A similar result was observed in the case of 4',2-disubstituted chalcone (entry 16). We also studied the cases of heterocyclic α-enones. To our delight, it still exhibited high activity and good selectivity, provided the desired products in excellent yields (entries 17-18). When the R^2 group was occupied by H or alkyl groups, the reaction also proceeded smoothly in good to excellent yields (entries 19-21). Activated α,β-unsaturated ketones **1v** and **1w**, which have been proved to be good substrates in the previous reports, were also reduced in high yields (entries 22-23). Furthermore, the present catalytic system also displayed high catalytic efficiency for the reduction of cyclic enones (entries 24-25). However, α,β,γ,ε-unsaturated enone **1z** was proved to be sluggish substrate and only trace amount of **2z** was observed (entry 26). The transfer hydrogenations of α,β-unsaturated ketones to the corresponding alcohols were also investigated by applying KOH as the base. As expected, the desired

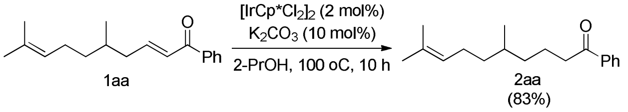
Table 2. $[IrCp^*Cl_2]_2$ catalyzed transfer hydrogenation of α,β-unsaturated ketones[a]



Entry	1	R^1	R^2	Yield (%)	
				2[b]	**3**[c]
1	**1a**	Ph	Ph	97 (**2a**)	88 (82)
2[d]	**1b**	*p*-MeC_6H_4	Ph	90 (**2b**)	83
3[d]	**1c**	*p*-$MeOC_6H_4$	Ph	85 (**2c**)	78
4	**1d**	*p*-FC_6H_4	Ph	92 (**2d**)	85
5	**1e**	*p*-ClC_6H_4	Ph	98 (**2e**)	91
6	**1f**	*p*-BrC_6H_4	Ph	92 (**2f**)	88
7	**1g**	*m*-ClC_6H_4	Ph	94 (**2g**)	84
8	**1h**	*o*-MeC_6H_4	Ph	96 (**2h**)	90
9	**1i**	2-naphthyl	Ph	95 (**2i**)	85
10	**1j**	Ph	*p*-MeC_6H_4	94 (**2j**)	84
11	**1k**	Ph	*p*-$MeOC_6H_4$	93 (**2k**)	85
12	**1l**	Ph	*p*-ClC_6H_4	97 (**2l**)	89
13	**1m**	Ph	*p*-$CF_3C_6H_4$	96 (**2m**)	
14	**1n**	Ph	*m*-$CF_3C_6H_4$	95 (**2n**)	
15	**1o**	Ph	*o*-$CF_3C_6H_4$	94 (**2o**)	
16	**1p**	*p*-ClC_6H_4	*o*-$CF_3C_6H_4$	93 (**2p**)	
17	**1q**	furanyl	Ph	93 (**2q**)	
18	**1r**	thiophenyl	Ph	97 (**2r**)	
19	**1s**	Ph	H	87 (**2s**)	
20	**1t**	Ph	$Ph(CH_2)_2$	96 (**2t**)	
21	**1u**	Ph	$CH_3(CH_2)_5$	94 (**2u**)	
22	**1v**	Me	Ph	95 (**2v**)	92[e]
23	**1w**	Me	furanyl	94 (**2w**)	
24	**1x**	$-C_3H_6-$		91 (**2x**)	
25	**1y**	$-C_2H_4-$		97[c] (**2y**)	
26	**1z**	Ph	PhCH=CH	trace (**2z**)	

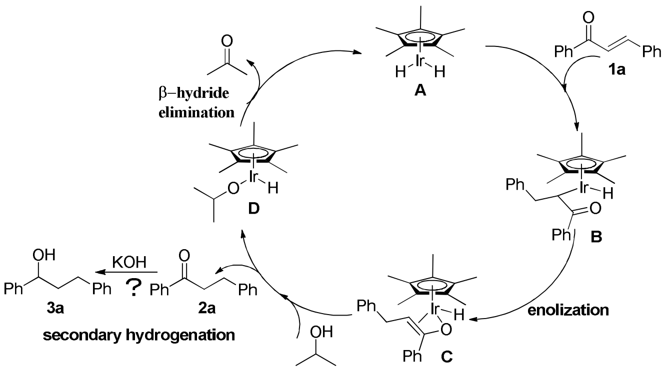
[a] Condition **A**: **1** (0.4 mmol), $[IrCp^*Cl_2]_2$ (1 mol%), K_2CO_3 (5 mol%), 2-PrOH (4 mL), 85 °C, 5 h; condition **B**: **1** (0.4 mmol), $[IrCp^*Cl_2]_2$ (1 mol%), KOH (50 mol%), 2-PrOH (4 mL), 85 °C, 5 h. [b] Isolated yield. [c] Yields were determined by GC analysis using *n*-hexadecane as internal standard (yield in parentheses is the isolated yield). [d] $[IrCp^*Cl_2]_2$ (2 mol%), K_2CO_3(10 mol%), 100 °C, 10 h. [e] 8 h.

saturated alcohols were obtained in 78-92% yields, which established our findings on the base-controlled chemoselectivity (entries 1-12, 22). Finally, an α,β-unsaturated ketone **1aa** bearing a non-polarized double bond was subjected to the condition (eqn. (3)). To our delight, the present catalytic system selectively reduced the enone and kept the non-polarized double bond.



(3)

A plausible mechanism is proposed in Scheme 1 to explain the selective transfer hydrogenation of α,β-unsaturated ketones to the saturated ketones or alcohols.[17] In the initial step, the active catalyst **A** was generated *via* the sequences showed in eqns. (1) and (2). The α-enone **1a** then coordinated to **A**, followed by a hydride transfer to give intermediate **B**, which underwent an enolization to produce **C**. The resulting Ir-enolate **C** was protonated by 2-PrOH to give product **2a** and produced the catalytic species **D**, which sequently underwent a β-elimination to reproduce the active catalyst **A**. Although detailed mechanism for the secondary hydrogenation of the resulting ketones in the presence of KOH is not clear. A base promoted Meerwein-Ponndorf-Verley type reaction may be responsible for this unexpected results.[18] More detailed studies are required to clarify the detailed mechanism.



Scheme 1. Proposed Catalytic Cycle.

Conclusions

We have demonstrated that $[IrCp^*Cl_2]_2$ was a highly effective and versatile catalyst for the transfer hydrogenation of α,β-unsaturated ketones with 2-PrOH. The simplicity of this protocol employing commercially available catalyst makes it attractive for laboratory hydrogenations without the need for hazardous H_2 and other costly hydrogen sources. By changing the base from K_2CO_3 to KOH, the products could be switched from saturated ketones to saturated alcohols.

Experimental section

An Ar purged flame-dried Schlenk tube (25 mL) containing α,β-unsaturated ketone **1** (0.40 mmol, 1 equiv), $[IrCp^*Cl_2]_2$ (1 mol%), and K_2CO_3 (5 mol%) were added 2-PrOH (4 mL). The reaction mixture was stirred at 85 °C for 5 h unless stated otherwise. After the reaction was complete, the solvent was removed under reduced pressure. The crude residue was purified by flash column silica gel chromatography (petroleum ether/ ethyl acetate: 95:5 to 90:10) to yield the product **2**.

Notes and references

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Electronic Supplementary Information (ESI) available: Experimental details, ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR spectra of all isolated products. See DOI: 10.1039/c000000x/

1 Selected reviews: (a) R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, *Chem. Rev.* 1985, **85**, 129; (2) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* 1997, **30**, 97; (c) J.-i. Ito, H. Nishiyama, *Tetrahedron Lett.* 2014, **55**, 3133.

2 (a) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley-VCH, Weinheim, 1994; (b) M. Bartók, A. Molnár, *Heterogeneous Catalytical Hydrogenation*, Wiley-VCH, Weinheim, Chapter 16. pp. 843-908, 1997; (c) S. Nishimura, *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*, Wiley-VCH, Weinheim, 2001; (d) *Fine Chenicals through Heterogeneous Catalysis*, Eds: R. A. Sheldon, H. van Bekkum, Wiley-VCH, Weinheim, 2001.

3 Selected reference see: (a) G. Szöllösi, B. Török, L. Baranyi and M. Bartók, *J. Catal.* 1998, **179**, 619; (b) G. Szöllősi, Á. Mastalir, Á. Molnár and M. Bartók, *React. Kinet. Catal. Lett.* 1996, **57**, 29; (c) A. Mori, Y. Miyakawa, E. Ohashi, T. Haga, T. Maegawa, H. Sajiki, *Org. Lett.* 2006, **8**, 3279; (d) S. Jagtap, Y. Kaji, A. Fukuoka, K. Hara, *Chem. Commun.* 2014, **50**, 5046.

4 (a) M. Sugiura, N. Sato, S. Kotani, M. Nakajima, *Chem. Commun.* 2008, 4309; (b) A. Pelss, E. T. Kumpulainen, A. M. Koskinen, *J. Org. Chem.* 2009, **74**, 7598; (c) M. Benohoud, S. Tuokko, P. M. Pihko, *Chem. Eur. J.* 2011, **17**, 8404; (d) J.-Y. Shang, F. Li, X.-F. Bai, J.-X. Jiang, K.-F. Yang, G.-Q. Lai, L.-W. Xu, *Eur. J. Org. Chem.* 2012, 2809.

5 (a) B. C. Ranu, S. Samanta, *J. Org. Chem.* 2003, **68**, 7130; (b) A. T. Russo, K. L. Amezcua, V. A. Huynh, Z. M. Rousslang, D. B. Cordes, *Tetrahedron Lett.* 2011, **52**, 6823.

6 Q. Liu, J. Li, X.-X. Shen, R.-G. Xing, J. Yang, Z. Liu, B. Zhou, *Tetrahedron Lett.* 2009, **50**, 1026.

7 (a) S. Bolaño, L. Gonsalvi, F. Zanobini, F. Vizza, V. Bertolasi, A. Romerosa, M. Peruzzini, *J. Mol. Catal. A: Chem.* 2004, **224**, 61; (b) C. A. Mebi, R. P. Nair, B. J. Frost, *Organometallics* 2007, **26**, 429; (c) S. Naskar, M. Bhattacharjee, *Tetrahedron Lett.* 2007, **48**, 465.

8 (a) Y. Sasson, J. Blum, *Tetrahedron Lett.* 1971, **12**, 2167; (b) J. Blum, Y. Sasson, S. Iflah, *Tetrahedron Lett.* 1972, 13, 1015; (c) Y. Sasson, J. Blum, *J. Org. Chem.* 1975, **40**, 1887; (d) I. Ryu, T. Doi, T. Fukuyama, J. Horiguchi, T. Okamura, *Synlett* 2006, 721;

9 (a) D. Beaupere, P. Bauer and R. Uzan, *Can. J. Chem.* 1979, **57**, 218; (b) Z. Baán, Z. Finta, G. Keglevich, I. Hermecz, *Green Chem.* 2009, **11**, 1937.

10 X. Li, L. Li, Y. Tang, L. Zhong, L. Cun, J. Zhu, J. Liao, J. Deng, *J. Org. Chem.* 2010, **75**, 2981.

11 (a) B. Basu, M. H. Bhuiyan, P. Das and I. Hossain, *Tetrahedron Lett.* 2003, **44**, 8931; (b) B. Basu, S. Das, P. Das, A. K. Nanda, *Tetrahedron Lett.* 2005, **46**, 8591; (c) K. Fujimoto, T. Yoneda, H. Yorimitsu, A. Osuka, *Angew. Chem. Int. Ed.* 2014, **53**, 1127; (d) D. B.

Bagal, B. M. Bhanage, *RSC Adv.* 2014, **4**, 32834; (e) L.-H. Gong, Y.-Y. Cai, X.-H. Li, Y.-N. Zhang, J. Su, J.-S. Chen, *Green Chem.* 2014, **16**, 3746; (f) N. M. Patil, T. Sasaki, B. M. Bhanage, *Catalysis Letters* 2014, **144**, 1803.

12 (a) S. Sakaguchi, T. Yamaga, Y. Ishii, *J. Org. Chem.* 2001, **66**, 4710; (b) Y. Himeda, N. Onozawa-Komatsuzaki, S. Miyazawa, H. Sugihara, T. Hirose, K. Kasuga, *Chem. Eur. J.* 2008, **14**, 11076; (c) J. Li, Y. Zhang, D. Han, G. Jia, J. Gao, L. Zhong, C. Li, *Green Chem.* 2008, **10,** 608.

13 N. Castellanos-Blanco, M. Flores-Alamo, J. J. García, *Organometallics* 2012, **31**, 680.

14 S. –J. Chen, G. -P. Lu, C. Cai, *Synthesis* 2014, **46**, 1717.

15 $[IrCp^{*}Cl_2]_2$ was an efficient catalyst for the hydrogen autotransfer (or hydrogen-borrowing) process, for reviews, see: (a) G. Guillena, J. R. D, M. Yus, *Chem. Rev.* 2010, **110**, 1611; (b) Y. Ishii, Y. Obora, *Synlett* 2011, 30; (c) S. Bähn, S. Imm, L. Neubert, M. Zhang, H. Neumann, M. Beller, *ChemCatChem* 2011, **3**, 1853; d) T. Suzuki, *Chem. Rev.* 2011, **111**, 1825; (e) A. C. Marr, *Catal. Sci. Technol.* 2012, **2**, 279.

16 A. Aranyos, G. Csjernyik, K. J. Szabó, J.-E. Bäckvall, *Chem. Commun.* 1999, 351.

17 (a) K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka, R. Yamaguchi, *Org. Lett.* 2005, **7**, 4017; (b) C. Löfberg, R. Grigg, M. A. Whittaker, A. Keep, A. Derrick, *J. Org. Chem.* 2006, **71**, 8023; (c) S. Whitney, R. Grigg, A. Derrick, A. Keep, *Org. Lett.* 2007, **9**, 3299; (d) S. Bhat, V. Sridharan, *Chem. Commun.* 2012, **48**, 4701.

18 For base promoted reactions of ketones or alcohols under transition-metal-free conditions, see: (a) C. Walling, L. Bollyky, *J. Am. Chem. Soc.* 1964, **86**, 3750; (b) A. Berkessel, T. J. S. Schubert, T. N. Mu¨ller, *J. Am. Chem. Soc.* 2002, **124**, 8693; (c) Y.-F. Liang, X.-F. Zhou, S.-Y. Tang, Y.-B. Huang, Y.-S. Feng, H.-J. Xu, *RSC Adv.* 2013, **3**, 7739, and references therein.