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pH-Independent Transfer Hydrogenation in Water: Catalytic, Enantioselective Reduction of β-Keto Esters

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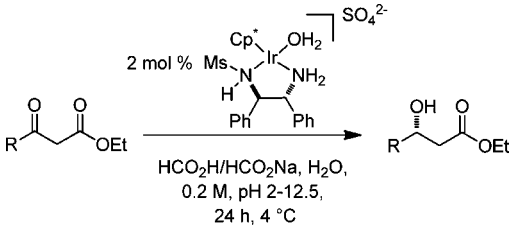
ABSTRACT



A pH-independent asymmetric transfer hydrogenation of β-keto esters in water with formic acid/sodium formate is described. The reaction is conducted open to air and gives access to β-hydroxy esters in excellent yields and selectivities.

In recent decades, the development of methods for catalytic asymmetric synthesis has gained increasing importance in chemistry. Within this area, asymmetric transfer hydrogenation (ATH) plays an important role in accessing small building blocks with procedures that are a simple vis-à-vis preparation of starting materials and experimental implementation. Additionally, ATH constitutes an attractive alternative to the use of protocols prescribing molecular hydrogen.[1]

The pioneering studies of Noyori disclosing the ability of Ru(II) complexes bearing monosulfonylated diamine complexes to catalyze hydrogen transfer reactions[2] were significant, as it provided new opportunities for asymmetric catalysis. A few years later Ogo documented Ir(III) diamine complexes, which are able to reduce simple ketones and aldehydes in water, a reaction which was noted to be pH-dependent.[3]

We recently described Ir(III) catalyzed ATH reactions of nitroalkenes and cyano- and nitro-substituted acetophenones employing monosulfonylated diamines as well as diamine ligands.[4] Herein, we report the pH-independent iridium-catalyzed ATH of β-keto esters[5] in water with formic acid as a reductant. Although the enantiomeric excess observed when the reaction is conducted under very

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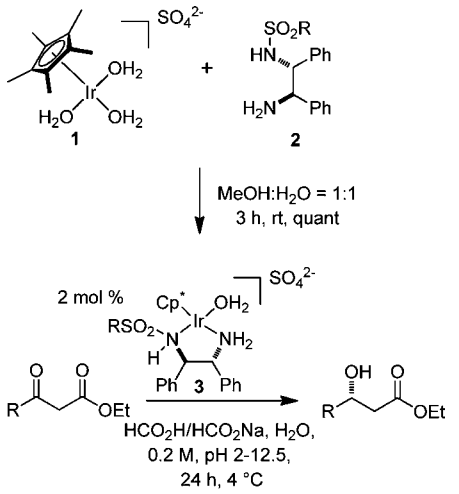
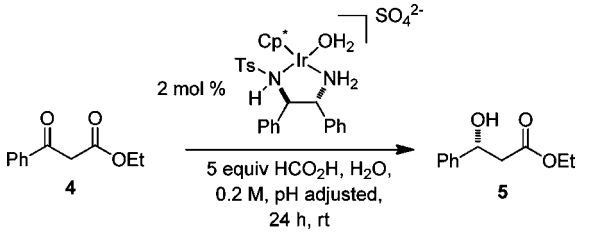
acidic conditions is moderate, the reaction is shown to tolerate a wide pH-range. Additionally, no retro-aldol reaction was observed, even at pH > 10.5. The fact that the reactions can be conducted over a broad window of conditions provides a process in which the conditions may be adapted for a given substrate. This underscores the robustness of the catalyst, a prerequisite for the concept we have termed extreme catalysis, in which the inherent preferences of a substrate and not the catalyst dictate the optimal reaction conditions.[6]

Scheme 1. pH Independent ATH Reactions



The family of catalysts employed in this study (**3**) are easily prepared by combining iridium(III) trihydrate **1** with an equimolar amount of monosulfonylated diamine **2** in water/methanol solutions at ambient temperature (Scheme 1). Evaporation of the solvents then furnished the complexes as air- and moisture-stable solids. We were impressed by the fact that initial pH-screening of unsubstituted β-keto ester **4** with the traditional monotosylated diphenyl ethane diamine derived catalyst revealed that the reaction could be conducted over a broad pH range (Table 1). Experiments involving screening were performed to examine the effect of substituents on the sulfonyl group (Table 2). Ligands incorporating nonfluorinated *N*-sulfonyl groups proved superior to their fluorinated counterparts (compare Table 2, entries 1−3 with entries 4−6), which stands in contrast to our previously published work involving the reduction of nitroalkenes and α-cyano- and α-nitro-ketones.[4a,b] In addition, we observed that the use of ligands with moderate electron-donating substituents (Me) is favorable, in contrast to what has been reported for Ru-mediated reductions.

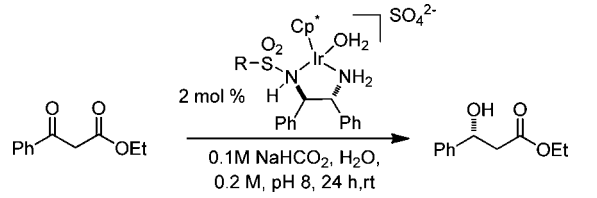
Table 1. Initial Screening over a Wide pH Range



entry[a,b]	pH	conversion %[c]	ee[d]
1	2.0	100	70
2	3.5	100	70
3	5.0	100	94
4	8.0	100	95
5	10.5	100	94
6	12.5	78	nd

[a] Reactions carried out with 0.1 mmol of ketoester. [b] Medium initially 1.0 M formic acid prior to adjustment of pH. [c] Determined by ^{1}H NMR of the unpurified reaction mixture. [d] Determined by chiral SFC (Chiralpak I-A column).

Table 2. Investigation of Effect of Ligand *N*-Sulfonyl Group



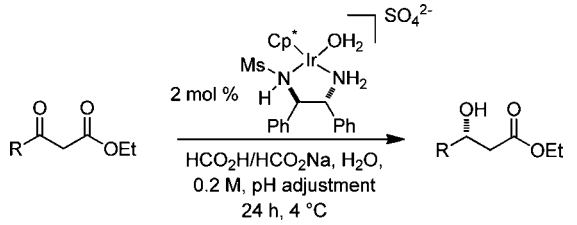
entry[a]	R	ee[b]
1	Me	96
2	C_6H_4Me	94
3	C_6H_4OMe	90
4	CF_3	90
5	$C_6H_4CF_3$	90
6	$C_6H_4OCF_3$	86

[a] Reactions carried out with 0.1 mmol of ketoester; the data are reported at full conversion for all entries. [b] Determined by chiral SFC (Chiralpak I-A column).

With the optimal catalyst and conditions in hand, the substrate scope was investigated (Table 3). The temperature of the reaction could be lowered to 4 °C, without any appreciable loss in rate. The reaction tolerates substrates with both electron-donating and -withdrawing substituents in the *para*- and *meta*-position, but substitution in the *ortho*-position significantly reduces enantioselectivity,

(6) For recent work from our laboratory involving extreme catalysis, see: (a) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4294. (b) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 938. (c) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1101. (d) Morandi, B.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 9085. (e) Morandi, B.; Cheang, J.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 3080. (f) Morandi, B.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 5984. (g) Künzi, S. A.; Morandi, B.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 1900. (h) Morandi, B.; Dolva, A.; Carreira, E. M. *Org. Lett.* **2012**, *14*, 2162. (i) Morandi, B.; Carreira, E. M. *Science* **2012**, 1471.

Table 3. Substrate Scope



entry[a,b]	R	pH	yield %[c]	ee[d,f]
1	C_6H_5	8.0	96	96
2	C_6H_5	3.5	98[g]	92
3	C_6H_5	5.0	98[g]	96
4	C_6H_5	10.0	97[g]	96
5	*p*-F-C_6H_4	8.0	95	94
6	*p*-Cl-C_6H_4	8.0	94	92
7	*p*-Br-C_6H_4	8.0	96	94
8	*p*-I-C_6H_4	8.0	91	93
9	*m*-Cl-C_6H_4	8.0	92	93
10	*o*-Cl-C_6H_4	8.0	97	70
11	*p*-OMe-C_6H_4	8.0	97	95
12	*p*-NO_2-C_6H_4	8.0	99	87
13	2-naphthyl	8.0	96	94
14	3-pyridyl	8.0	77	73[e]
15	2-furyl	8.0	90	96

[a] Reactions carried out with 2 mmol of ketoester. [b] Medium initially 1.0 M formic acid prior to adjustment of pH. [c] Isolated yields. [d] Determined by chiral SFC (Chiralpak I-A column). [e] Chiralpak I-B column. [f] Absolute configuration established by correlation to known compounds. [g] Reactions conducted at 1 mmol scale of ketoester.

albeit without affecting reactivity. Electron-poor arenes as substrates lead to products with significantly lower selectivity (Table 3, entry 12), whereas electron-rich arenes result in useful yields and selectivity. We also examined the reduction of **4** at various pH's. As shown in Table 3, entries 2–4, changes in pH did not significantly impact the enantioselectivity of the reaction. From pH 3.5 up to pH 10.0, the reaction proceeds smoothly with full conversion and excellent enantiomeric excess.

In conclusion, we have documented a pH-independent catalytic method for the asymmetric transfer hydrogenation of β-ketoesters in water at 4 °C. The catalyst used in this reaction is readily prepared and moisture- and air-stable. Additionally, the use of sodium formate as the reductant as well as the fact that the reaction is conducted in water simplifies the execution of reaction and isolation of the products. The work underscores the effect of subtle ligand alterations on the Ir catalyst, allowing for a wide range of conditions to be considered when reducing keto esters. In a broader context the work highlights the discovery and development of catalysts and processes that are robust, throughout a range of pH, including pH 2 and pH 12.5, enabling the selection of conditions dictated by the substrate as opposed to the catalyst. Further investigations in this area are ongoing and will be reported as results emerge.

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Supporting Information Available. Full experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.