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Transfer Hydrogenation in Water: Enantioselective, Catalytic Reduction of α-Cyano and α-Nitro Substituted Acetophenones

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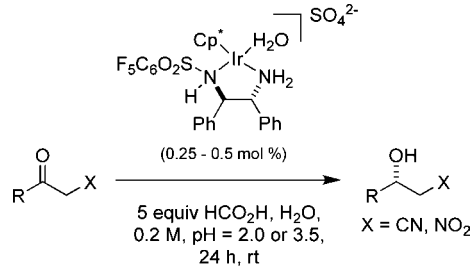
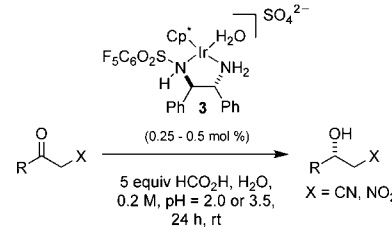
ABSTRACT



Catalytic reduction of α-substituted acetophenones under conditions involving asymmetric transfer hydrogenation in water is described. The reaction is conducted in water and open to air, and formic acid is used as reductant.

The number of catalytic asymmetric methods has increased dramatically in recent years, and these have proven invaluable for the synthesis of natural products, chiral starting materials, and intermediates. In the past decade, asymmetric transfer hydrogenation (ATH)[1] has flourished as a result of the pioneering studies of Noyori and co-workers.[2] We wish to report a convenient and efficient method for enantioselective reduction of α-cyanoketones and α-nitroketones with iridium(III) diamine aqua complexes **3** (Scheme 1).[3] The methodology described herein delivers functionalized chiral alcohols in good to excellent selectivities and conversions. Also, the products derived from these reductions have

Scheme 1. Reduction of Acetophenones



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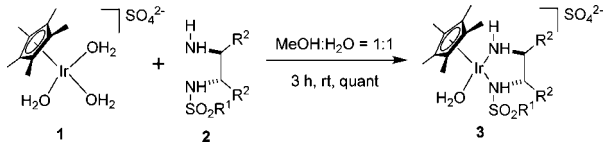
substantial flexibility for further transformations. Finally, the operational convenience of these reactions is noteworthy as they are carried out at ambient temperature, in water, and open to air.

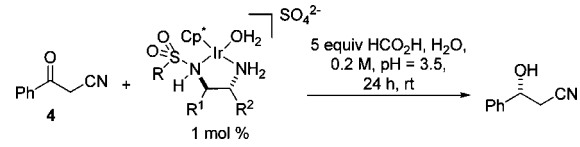
Scheme 2. Catalyst Formation



Recent studies by Ogo, Fukuzumi, and colleagues have yielded water-soluble pH-dependent catalysts that perform achiral reductions in aqueous medium.[4] We were intrigued at the prospect of utilizing chiral aqua complexes derived from iridium(III) trihydrate precatalysts[4a] for the catalytic, enantioselective reduction of ketones (Scheme 2). Asymmetric reductions with such catalysts would be beneficial on several fronts, including both cost of reductant (HCO_2H) and solvent (H_2O), as well as ease of operation. The advantage with regard to safety of formic acid as compared to molecular hydrogen is also apparent when considering conducting large-scale reactions. The benefits of working with water as a reaction medium is also noteworthy, and processes utilizing water as a reaction medium are on the rise.[5]

Initial catalyst screening and optimization relied upon preparation of chiral iridium(III) complexes such as **3** (Scheme 2). These catalysts are prepared by combining the known Ir(III) trihydrate complex **1** with a ligand of choice in a water/methanol solution at ambient temperature. Removal of the solvent yielded aqua complexes as air-stable solids in quantitative yields. After screening a broad selection of bidentate ligands for the reduction of a standard α-cyano ketone 3-oxo-3-phenylpropanenitrile **4**, it was clear that monosulfonylated 1,2-diphenyl diamines,[6] such as Noyori's Ts-DPEN ligand, served as

Table 1. Initial Catalyst Screening



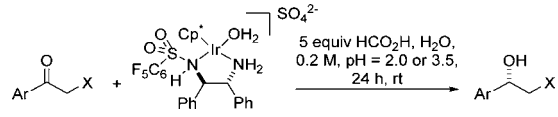
entry[a]	R	R^1, R^2	conversion %[b]	ee %[c]
1	*p*-Tol	-$(CH_2)_4$-	46	15
2	F_5C_6	Cy	0	ND
3	F_5C_6	-$(CH_2)_4$-	<5	ND
4	*p*-Tol	Ph	81	84
5	CF_3	Ph	>90	90
6	F_5C_6	Ph	>90	94

[a] Reactions were carried out with 0.5 mmol of ketone. [b] Determined by ^{1}H NMR of crude reaction after workup. [c] Enantiomeric excess was determined by chiral HPLC.

leads for further optimization (Table 1, entry 4). A screen of sulfonamides with a broad range of steric and electronic properties proved fruitful. Ligands bearing strong electron-deficient sulfonamides yielded catalysts with improved selectivity and reactivity. Perfluorinated sulfonamides in particular displayed remarkable reactivity, which is in contrast to what has been observed with Ru(II) based catalysts (Table 1, entries 5 and 6).[2b]

Examination of the scope of α-cyano ketones indicated a well-tolerated reaction at pH = 3.5 (Table 2). In many cases catalyst loadings as low as 0.25 mol % proved sufficient for

Table 2. Scope of α-Substituted Ketones



entry[a,b]	Ar	X	mol % cat.	yield %[c]	ee %[d]
1	C_6H_5	CN	0.25	96	94
2	*m*-Cl-C_6H_4	CN	0.25	90	90
3	*m*-CH_3O-C_6H_4	CN	0.25	96	95
4	*p*-F-C_6H_4	CN	0.50	95	91
5	*p*-CH_3-C_6H_4	CN	0.50	96	93
6[e]	2-naphthyl	CN	0.5	95	96
7	2-furyl	CN	0.25	83	96
8	2-thiophenyl	CN	0.5	94	92
9	*p*-CN-C_6H_4	CN	0.25	97	86
10	C_6H_5	NO_2	0.5	94	93
11	*p*-^{t}Bu-C_6H_4	NO_2	0.5	92	99
12	*m*-Br-C_6H_4	NO_2	0.5	54	91
13	*m*-Cl-C_6H_4	NO_2	0.5	95	95
14[e]	2-naphthyl	NO_2	0.5	53	93
15	*o*-CH_3O-C_6H_4	NO_2	0.5	93	83
16	C_6H_5	Cl	0.25	93	91

[a] Reactions were carried out with 0.5 mmol of ketone. [b] For X = CN, Cl, pH = 3.5; for X = NO_2, pH = 2.0. [c] Isolated yield, [d] Enantiomeric excess was determined by chiral HPLC. [e] Addition of 10 mol % hexafluoroisopropanol.

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(5) For discussions of water as a reaction medium, see: (a) Lindström, U. M. *Chem. Rev.* **2002**, *102*, 2751. (b) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095. For examples of ATH in water, see: . (c) Soltani, O.; Ariger, M. A.; Carreira, E. M. *Org. Lett.* **2009**, *11*, 4196. (d) Wu, X.; Liu, J.; Li, X.; Zanotti-Gerosa, A.; Hancock, F.; Vinci, D.; Ruan, J.; Xiao, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6718. (e) Li, X.; Blacker, J.; Houson, I.; Wu, X.; Xiao, J. *Synlett* **2006**, *8*, 1155. (f) Wu, X.; Li, X; King, F.; Xiao, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3407. (g) Wu, X.; Li, X.; Hems, W.; King, F.; Xiao, J. *Org. Biomol. Chem.* **2004**, *2*, 1818. (h) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.; Yu, B. *Chem. Commun.* **2006**, 1766.

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complete conversion.[7] Electron-donating and -withdrawing groups at the *meta* and *para* positions did not adversely affect the selectivity or conversion (Table 2, entries 2−5). Heteroaromatic substrates such as the furan and thiophene substituted ketones proved to be outstanding substrates (Table 2, entries 7 and 8). Also worth noting, complete reduction of 2-naphthyl ketone required addition of 10 mol % hexafluoroisopropanol as a cosolvent, presumably because of poor interaction between the catalyst and substrate in the aqueous medium employed.

Examining the scope of α-nitroketones in this reduction led to similarly fruitful results. A modest increase in catalyst loading (0.5 mol %), as compared to the reduction of α-cyano ketones, was required for full conversion. Also, a slightly more acidic medium (pH = 2.0) was necessary to minimize side reactions. Enhancement in selectivity was observed with a substrate containing a bulky group at the *para* positon (entry 11). As it was observed with α-cyano ketones, substitution of the aryl ring with bulky electron-withdrawing halogens at the *meta* position was tolerated (entries 12 and 13). Finally, α-chloroketone was shown to undergo reduction in excellent yield and selectivity (entry 17). Such chloroalcohols are accessible precursors to terminal epoxides.[5c]

In summary, we have documented a catalytic method for the enantioselective reduction of α-cyanoketones and α-nitroketones. The designed catalysts are readily prepared and are stable to moisture and air. Furthermore, the use of formic acid as reductant underlines the convenience of the method because it is inexpensive, readily available, and operationally simple to employ. Low catalyst loadings (0.25−0.5 mol %) provide excellent yields of chiral cyanoketones and nitroketones.

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Supporting Information Available: Experimental procedures and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Repeating the reaction of **4** with 0.1 mol % catalyst after 72 h gives 83% yield and 94% ee in addition to unreacted starting material.