Transfer Hydrogenation in Water: Enantioselective, Catalytic Reduction of (E)- β , β -Disubstituted Nitroalkenes

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Received June 14, 2009

ABSTRACT

ٌCp جCO₂S

NO

Me

H₂O

SO42

NO₂

Me



5 equiv HCO₂H, H₂O 0.2 M, pH = 2.0, 24 h, rt

The study of catalytic, asymmetric methods is at the forefront of research in chemical synthesis. In general, the field is propelled by the discovery of novel catalysts, by the identification of new modes of reactivity, and by enabling simple access routes to useful building blocks. Enantioselective, catalytic hydrogenation is the most widely applied catalytic method in industry. Asymmetric transfer hydrogenation (ATH)^{1,2} methods are attractive because of the simplification that can result from their implementation. In this respect, we were intrigued

10.1021/ol901332e CCC: 40.75 $\hfill \odot$ 2009 American Chemical Society Published on Web 08/26/2009

some years ago by the development of chiral aqua Ir(III) complexes³ in enantioselective transfer hydrogenations. The benefits of such a process can be appreciated on several fronts, including the cost and ease of using low molecular weight, organic reductants in aqueous media⁴ at ambient temperature and pressure. Herein, we report an efficient and convenient method for asymmetric reduction of β , β -disubstituted nitroalkenes with diamine derived iridium(III) complexes **2** (Scheme 1).⁵ The method delivers chiral









Vol. 11, No. 18

ORGANIC

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nitroalkanes in good to excellent selectivity under operationally straightforward conditions.

There is ample precedence for the use of diamine derived Ru complexes in transfer hydrogenation reactions, as exemplified by the catalyst systems developed by Novori and Ikariya.^{1b,2} In contrast, there was little precedence available to guide our initial investigations with Ir catalysts in water. Recent studies by Ogo and Fukuzumi document watersoluble [Cp*Ir(bpy)(H₂O)](SO₄) catalysts that perform achiral reductions of simple ketones in water at pH 5.³ Yet, whether the ligands in the parent complex could be replaced by chiral donors without altering the stability or reactivity of the Ir complex was unclear at the time that we commenced our studies.⁶ Initial screening and optimization studies relied upon preparation of iridium(III) complexes derived from optically active diamines.⁷ To our delight, the corresponding complexes 3 are simply prepared by combining the known Ir(III) trihydrate complex 1 with a donor ligand 2 of choice in aqueous methanol at ambient temperature. Solvent evaporation furnished aqua Ir complexes as air stable solids in quantitative yields (Scheme 1).

Since many of the studies about asymmetric transfer hydrogenations are limited to the reduction of acetophenones and related compounds,^{1,2,6} we were interested in expanding the scope of this powerful methodology to other substrate classes, such as conjugate reduction of activated double bonds. We choose nitroalkenes⁸ as valuable targets since these substrates have only been studied to a limited extent, namely in enzymatic,^{5a-c} metal-catalyzed,^{5d-f} and organocatalytic^{5g} reductions. Our initial studies commenced with nitroolefin **4** as a test substrate and a broad range of ligands, with aqua Ir(III) complexes in water. Monotosylated 1,2-diphenyldiamines provided a leading result and warranted closer scrutiny (Table 1, entry 1). The use of strongly electron



 a Reactions carried out with 0.1 mmol of ketone. b Determined by $^1\mathrm{H}$ NMR of unpurified product. c ee was determined by chiral HPLC.

withdrawing groups on mono-*N*-tosylated diamines led to remarkable improvement in selectivity and reactivity. In particular, stilbene diamine ligands derivatized as perfluorinated sulfonamides were notable (Table 1, entries 2–7). Finetuning of the aryl-groups and re-examination of the sulfonyl-group led to a modest but significant increase in selectivity (Table 1, entry 7). Interestingly, this reactivity trend stands in sharp contrast to what is observed with the typical Ru(II) based catalyst systems and molecular hydrogen as well as the Ir(III) based catalysts in water and formic acid.^{2b,6}

We then proceeded to examine the scope of nitroalkenes which would undergo selective and efficient reduction. As displayed in Table 2, reduction with catalyst **5** provided

Table 2. Substrate Scope

	$\begin{array}{c} F_{3}CO_{2}S\\ cat \qquad H\\ F \swarrow \\ R & \qquad F \checkmark \\ Me & \qquad 5 equ \\ 0.2 \end{array}$	SO Cp^* H_2O NH_2 F_5F F	A^{2-}	
$entry^{a,b}$	R	mol % cat.	yield, c %	ee, d,e %
1	C_6H_5	1.0	90	90
2	p-F-C ₆ H ₄	1.0	82	94
3	p-Cl-C ₆ H ₄	1.0	92	90
4	$p ext{-}Br ext{-}C_6H_4$	1.0	92	92
5	m-Cl-C ₆ H ₄	1.0	94	91
6	p-CH ₃ -C ₆ H ₄	1.0	78	90
7	p-CH ₃ O-C ₆ H ₄	1.5	94	92
8	p-CN-C ₆ H ₄	1.0	87	92
9	p -t Bu -C $_{6}H_{4}$	1.0	77	89
10 ^f	2-naphthyl	1.5	56	92

^{*a*} Reactions carried out with 0.5 mmol of nitroalkene. ^{*b*} 1.0 M formic acid solutions were utilized. ^{*c*} Isolated yields. ^{*d*} Determined by chiral HPLC. ^{*e*} Absolute configuration established by correlation to known compounds, see the Experimental Section in the Supporting Information. ^{*f*} 40 °C.

excellent yields and good selectivity for a variety of nitroalkenes, including those substituted with electron with-drawing and donating groups (Table 2, entries 6–8). A series

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of substrates with halogens underwent clean reduction with excellent yield and selectivity (Table 2, entries 2-5).

In conclusion, we have developed a mild and convenient method for the selective reduction of β , β -disubstituted nitroalkenes. The catalyst developed is readily prepared, air stable, and utilizes formic acid as an inexpensive, safe, and readily available reductant. The operational simplicity of this reaction is an attractive advantage over existing methods

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since additional precautions with regard to degassing of solvents and moisture are not necessary. The reaction provides good selectivities and yields of chiral nitroalkanes within reasonable reaction time (24 h). Ongoing studies in this arena look to gain a better understanding of the factors affecting the reactivity and selectivity of these catalysts such that more efficient and selective systems may be developed.

Acknowledgment. This research was supported through generous support in the form of a grant by Sumitomo Chemicals, Japan.

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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