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1 Regioselective Iridium-Catalyzed Asymmetric Monohydrogenation 2 of 1,4-Dienes

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6 **S** Supporting Information

7 **ABSTRACT:** A highly efficient regio- and enantioselective
8 monohydrogenation of 1,4-dienes has been realized using an
9 iridium catalyst with a chiral N,P-ligand under mild conditions.
10 The substrate scope was studied and included both unfunctional-
11 ized as well as functionalized substituents on the *meta*- or *para*-
12 position. Substrates having substituents with functionalities such
13 as silyl protected alcohols or ketals were monohydrogenated in
14 high regioselectivity and high enantiomeric excess (up to 98%
15 ee).

16 ■ INTRODUCTION

17 Synthesis of enantiopure products by asymmetric catalysis of
18 organic reactions represents an important area in modern
19 synthetic chemistry. Among many successful examples,
20 asymmetric hydrogenation has been most extensively studied
21 in academia and widely applied in industry,^{1,2} as affirmed by the
22 award of the 2001 Nobel Prize in chemistry to Knowles and
23 Noyori.³ Today, asymmetric hydrogenation is still one of the
24 most widely used, reliable catalytic methods for the preparation
25 of optically active compounds.⁴ In the past few decades,
26 significant progress has been made toward the asymmetric
27 hydrogenation of $\text{C}=\text{C}$, $\text{C}=\text{N}$, and $\text{C}=\text{O}$ ^{4d,7} utilizing
28 transition-metal chiral-ligand complexes.^{4,8} The reduction of
29 olefins containing an adjacent polar group (i.e., dehydro-amino
30 acids) by Rh- and Ru-catalyst precursors modified with
31 phosphorus ligands has a long history. Rhodium and ruthenium
32 catalysts have a strong preference to hydrogenate olefins having
33 a polar functional group next to the $\text{C}=\text{C}$ bond which can
34 coordinate to the metal center and help in achieving high levels
35 of activity and stereocontrol.⁹

36 Asymmetric hydrogenation of unfunctionalized olefins has
37 attracted considerable interest recently,¹⁰ and chiral Ir-P,N
38 complexes have been found to be extremely useful catalytic
39 precursors for the asymmetric hydrogenation of minimally
40 functionalized di- and trisubstituted olefins.^{11,12} However,
41 despite the development of highly *enantioselective* protocols,
42 *regioselectivity*, or the ability to hydrogenate only one out of
43 several olefins in a certain substrate is still a generally unsolved
44 task.^{2a,4c,5e,10e}

45 A few examples have been reported and consist almost
46 exclusively of Rh- and Ru-catalyzed hydrogenations of an olefin
47 having a polar substituent in preference over an unfunctional-
48 ized olefin in the same substrate. An early example of

regioselective hydrogenation of (*E*)-3,7-dimethylocta-2,6-di-
enoic acid was reported in 1980 by Toth using a chiral Rh
monophosphine complex (Scheme 1).¹³ The hydrogenation
was highly selective for the olefin close to the carboxyl group
and proceeded without isomerization within the limits of
detection. The pioneering work of regioselective asymmetric
hydrogenation of allylic alcohols by Noyori in 1987 using Ru
dicarboxylate complexes containing BINAP ligands follows a
similar trend. Although the allylic and nonallylic double bonds
in geraniol are both trisubstituted, the monohydrogenated
product was accompanied by less than 0.5% of dihydroci-
tronellol.¹⁴

In 2005 Minnaard and co-workers reported the asymmetric
hydrogenation of enol carbamate using a Rh precursor with
chiral monodentate phosphoramidites. It was found that the
double bond adjacent to the carbamate functional group was
hydrogenated but the double bond that is further away from the
functional moiety was not reduced.¹⁵ These examples illustrate
that the regioselective hydrogenation using Rh and Ru catalysts
might be explained by a mechanism that requires a chelating
group adjacent to the $\text{C}=\text{C}$ bond. Ir, on the other hand, is
believed to operate via a mechanism involving an η^2 -
bonded olefin and an extra molecule of dihydrogen coordinated
to the metal that is necessary for the first migratory insertion
step.¹⁶ Overall, the regioselective asymmetric hydrogenation
using transition metals remains unexplored and the reported
examples of substrates are still rare and limited.

Herein, we report on the Ir-catalyzed highly regioselective
asymmetric hydrogenation of two trisubstituted olefins on
cyclic diene structures.

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Scheme 1. Regioselective Asymmetric Hydrogenation Using Transition Metals

79 ■ RESULTS AND DISCUSSION

80 Our initial investigation began with the hydrogenation of **1a**. It
81 was found that the regioselectivity between the two olefins was

Table 1. Optimization of Asymmetric Hydrogenation Conditions^a Using **1a**

entry	cat.	time	base	conv (%) ^b	(1a') ee (%) ^c	1a' / 1a'' ^c
1	A	12 min	no	91	83	79/21
2	A	30 min	no	98	81	47/53
3	A	2 h	no	99	N.D. ^d	1/99
4	B	12 min	no	50	83	99/1
5	B	3 h	no	99	N.D. ^d	3/97
6	B	3 h	PVP	98	84	97/3

^aReaction conditions: 0.125 mmol of substrate, 0.5 mol % catalyst, 10 mol % base, H₂, and rt unless otherwise stated. ^bDetermined by ¹H NMR spectroscopy. ^cDetermined by chiral GC analysis; see [Supporting Information](#) for details. ^dN.D. = Not Determined.

Figure 1. Catalysts used in this study. COD = 1,5-cyclooctadiene.

Table 2. Optimization of Asymmetric Hydrogenation Conditions^a Using **2a**

entry	cat.	pressure (bar)	solvent	base	conv (%) ^b	2a' / 2a'' ^c	(2a') ee (%) ^c
1	A	20	DCM	PVP	99	65/35	90
2	B	20	DCM	PVP	99	93/7	78
3	C	20	DCM	PVP	99	67/33	82
4	D	20	DCM	PVP	99	81/19	90
5	E	20	DCM	PVP	99	27/73	94
6	F	20	DCM	PVP	99	78/22	95
7	F	20	DCM	K ₃ PO ₄	99	72/28	91
8	F	20	benzene	K ₃ PO ₄	99	40/60	91
9	F	20	toluene	K ₃ PO ₄	99	41/59	94
10	F	20	Ph-CF ₃	K ₃ PO ₄	99	85/15	96
11	F	10	Ph-CF ₃	K ₃ PO ₄	99	93/7	96

^aReaction conditions: 0.125 mmol of substrate, 0.5 mol % catalyst, 10 mol % base, H₂, 16 h, and rt unless otherwise stated. ^bDetermined by ¹H NMR spectroscopy. ^cDetermined by chiral GC analysis; see [Supporting Information](#) for details.

Table 3. Asymmetric Hydrogenation with Different Types of Protecting Groups^a

Entry	Substrate	Conv. ^b	Product	P1 ee (%) ^c / ^d	P1 / P2 ^d
1	EOM	65	EOM	96(R)	99/1
2	EE	93	EE	97(R)	94/6
3	THP	70	THP	83(R)	99/1
4	TIPS	73	TIPS	97(R)	99/1
5	TES	99	TES	96(R)	86/14
6	TBDM	99	TBDM	96(R)	93/7

^aReaction conditions: 0.125 mmol of substrate, 0.5 mol % catalyst, 10 mol % base, H₂, 12 h, and rt unless otherwise stated. THP = tetrahydropyranyl acetal. TIPS = triisopropyl silyl ether. ^bDetermined by ¹H NMR spectroscopy. ^cDetermined by chiral GC analysis; see [Supporting Information](#) for details. ^dAbsolute configuration of the hydrogenated product was assigned on the basis of elution order of hydrolysis product compared with commercially available (R)-(+)-3-methylcyclohexanone.

modest when using the standard hydrogenation conditions 82 (Table 1, entries 1–3). However, the regioselectivity was found 83 to depend on the catalyst and especially on the addition of base. 84 Thus, when using catalyst B (Figure 1) and poly(4-vinylpyridine) (PVP) as the base, it was possible to run the reaction 85 to completion with a regioselectivity of 97:3. Interestingly, the 86 selectivity observed was opposite to what is normally reported 87 for Rh- and Ru-catalyzed hydrogenations (Scheme 1a,b); with 88 the Ir-catalyst, the unfunctionalized olefin was hydrogenated in 89 preference over the enol ether. One possible explanation for the 90

Table 4. Asymmetric Hydrogenation of Different Silyl Protected Substrates^a

$ \begin{array}{c} \text{R}^1\text{O} \\ \\ \text{C}_6\text{H}_3 \\ \\ \text{R}^2 \\ \\ \text{R}^3 \quad \text{R}^4 \end{array} \xrightarrow[\text{Ph-CF}_3, \text{K}_3\text{PO}_4, \text{H}_2, \text{r.t., 12 h}]{0.5 \text{ mol \% Ir catalyst}} \begin{array}{c} \text{R}^1\text{O} \\ \\ \text{C}_6\text{H}_3 \\ \\ \text{R}^2 \\ \\ \text{R}^3 \quad \text{R}^4 \end{array} $					
Entry	Substrate	Catalyst	Product	Yield (%)	ee (%) ^d
1		F		58 ^b	96(<i>R</i>) ^e
2		F		79 ^{c,f}	96(<i>R</i>) ^e
3		E		56 ^{c,f}	99(<i>S</i>)
4		F		54 ^b	92(<i>R</i>)
5		F		55 ^c	95(<i>R</i>)
6		F		78 ^b	96(<i>R</i>)
7		F		70 ^b	95(<i>R</i>)
8		F		45 ^b	80(<i>R</i>)
9		F		75 ^{c,f}	95(<i>R</i>)
10		F		56 ^{c,f}	92(<i>R</i>)
11		E		81 ^c	95(<i>S</i>)

^aReaction conditions: 0.25 mmol of substrate, 0.5 mol % catalyst, 2 mL of Ph-CF₃, 10 bar H₂, 12 h, and rt unless otherwise stated. ^bNMR yield using internal standard 1,3,5-trimethoxybenzene. ^cIsolated yield. ^dDetermined by chiral GC or SFC analysis, see [Supporting Information](#) for details. ^eAbsolute configuration of the hydrogenated product was assigned on the basis of elution order of hydrolysis product compared with commercially available (*R*)-(+)-3-methylcyclohexanone. ^fObserved 5–10% over reduction product, see [Supporting Information](#) for details. ^gConversion determined by ¹H NMR spectroscopy. ^hReaction conditions: 0.25 mmol of substrate, 0.5 mol % catalyst, 2 mL of Ph-CF₃, 20 bar H₂, 24 h, and rt.

92 observed selectivity for Ir to preferentially hydrogenate the
93 olefin and not the enol ether could originate from the
94 possibility of the enol ether to form an eta-3 (η^3) coordination,
95 which would compete with the coordination of the dihydrogen
96 molecule to the iridium catalyst.

97 In order to improve the usefulness of the method, the silyl
98 enol ether **2a** was chosen as the model substrate for this study
99 since it is easily deprotected.

100 A screening of some Ir N₂P-ligand catalysts revealed that silyl
101 enol ether **2a** gave full conversion and good to high
102 enantioselectivities (Table 2, entries 1–6). The best
103 enantioselectivity was obtained for catalyst F, which gave **2a'**
104 in 95% ee (entry 6). Next, the reaction was optimized with
105 regards to solvent effects, base, and pressure. The combination
106 of Ph-CF₃ as solvent and K₃PO₄ as base under 10 bar of
107 hydrogen was the most suitable reaction condition for this
108 reaction (entry 11). (See [Supporting Information](#) for results of
109 hydrogenations carried out at shorter time intervals.)

110 With the optimized reaction conditions established, the effect
111 of the different protecting groups was evaluated (Table 3).

Table 5. Asymmetric Hydrogenation of Different Silyl Protected Substrates^{a,f}

Entry	Substrate	Catalyst	Product	Isolated Yield (%)	ee (%) ^e
17		B		81	--
18		B		78 ^g	--
19		F		82 ^c	99 (<i>R</i>)
20		Ent-A		93 ^d	98 (<i>R</i>)

^aReaction conditions: 0.178 mmol of substrate, 0.5 mol % catalyst, 2 mL of Ph-CF₃, 5 bar H₂, 14 h, and rt unless otherwise stated. ^bReaction time, 3 h ^c0.120 mmol of substrate. ^d0.089 mmol of substrate. ^eDetermined by chiral GC or SFC analysis; see [Supporting Information](#) for details. ^fObserved 2–5% over reduction product; see [Supporting Information](#) for details.

Figure 2. Examples of total syntheses of biologically active compounds originating from chiral **7a''**.

112 Interestingly, the type of protecting group used had relatively
113 little influence on the regio- and enantioselectivities observed.
114 The EOM (methoxy methyl acetal), EE (ethoxy ethyl acetal),
115 and the silyl protecting groups (entries 1, 2, and 4–6) all
116 resulted in high enantioselectivities. Of all the protecting
117 groups, TES (triethyl silyl ether) and TBDMS (*tert*-butyl
118 dimethyl silyl ether) showed optimal results and were used to
119 investigate the scope of the reaction.

120 A number of 1,4-diene substrates were prepared in high yield
121 using the Birch reduction and were selectively hydrogenated to
122 the corresponding protected silyl enol olefins in high yield and
123 good to excellent enantioselectivities. Having the substituent at
124 the *meta* position in the silyl protected enol ethers resulted in
125 all cases in very high enantioselectivities (between 95% to 99%,
126 t4

Table 6. Synthesis of α,β -Unsaturated Ketones^a

Entry	Substrate	Product	Yield (%)	ee (%) ^d
1	TES-O-C ₆ H ₄ -CH=CH ₂ (7a')	7a''	86 ^b	95(R)
2	TES-O-C ₆ H ₄ -CH=CH-CH ₃ (14a')	14a''	68 ^b	95(R)
3	TES-O-C ₆ H ₄ -CH=CH-CH ₂ -n-Pr (15a')	15a''	78 ^b	92(R)
4 ^f	TBDMSO-C ₆ H ₄ -CH=CH-OTBDMS (18a')	18a''	59 ^c	97(R) ^{g,21}
5 ^g	TBDMSO-C ₆ H ₄ -CH=CH-OTBDMS (19a')	19a''	56 ^c	95(R)
6 ^g	TBDMSO-C ₆ H ₄ -CH=CH-OTBDMS (20a')	20a''	51 ^c	98(R)
7 ^f	TBDMSO-C ₆ H ₄ -CH=CH-OTBDMS (21a')	21a''	62 ^c	94(S)

^aReaction conditions: 0.25 mmol of substrate, 10 mol % Pd(OAc)₂, 5 mL of DMSO, balloon O₂, 16 h, and rt. ^bNMR yield using internal standard 1,3,5-trimethoxybenzene. ^cIsolated yield. ^dDetermined by chiral GC or SFC analysis, see [Supporting Information](#) for details. ^eAbsolute configuration of the hydrogenated product was tentatively assigned based on specific optical rotation compared with literature. ^f0.25 mmol of substrate, 20 mol % Pd(OAc)₂, 5 mL of DMSO, balloon O₂, 24 h, and rt. ^g0.25 mmol of substrate, 30 mol % Pd(OAc)₂, 5 mL of DMSO, balloon O₂, 48 h, and rt.

prochiral substrates, and products **24a'** and **25a'** were isolated in 99% ee and 98% ee, respectively (Table 5).

Although the chiral, *meta* or *para* substituted enol ethers constitute a useful class of building blocks in their own right, the usefulness of the regioselective hydrogenation could be further demonstrated by conversion of the enol ether into the corresponding α,β -unsaturated ketone. This facilitates a straightforward, yet flexible route to chiral cyclohexenones, which have served as starting materials in a large number of total syntheses of biologically active compounds and natural products (Figure 2).^{17,18}

The conversion of the enol ethers into α,β -unsaturated ketones was realized by a Saegusa-type oxidation.¹⁹ The best method for the relatively volatile compounds in this study was the recently reported modification by Herzon²⁰ using 10% Pd and O₂ as the oxidant. A range of *meta* or *para* substituted enol ethers having alkyl or functionalized side chains was oxidized using this protocol. In all cases the corresponding chiral α,β -unsaturated ketones could be isolated in good yields and with full preservation of the chiral centers (Table 6).

CONCLUSION

We have described a new and efficient regio- and highly enantioselective hydrogenation of 1,3- and 1,4-disubstituted 1,4-cyclohexadienes resulting in chiral, silyl protected enol ethers. A variety of substituents were tolerated on both the *meta* and *para* positions demonstrating the broad scope of the reaction. Oxidation of the chiral enol ethers was performed using a Saegusa-type reaction and led to the corresponding chiral α,β -unsaturated ketones in good isolated yields with preserved enantiomeric purity.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b06829.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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