Article

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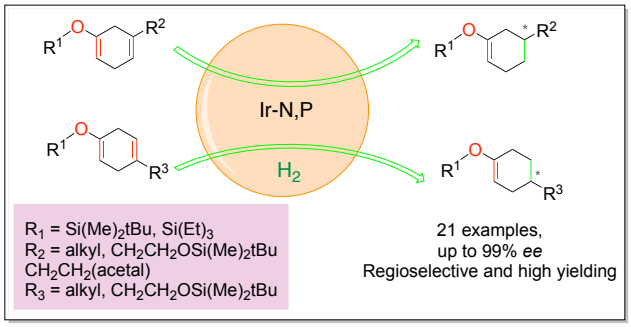
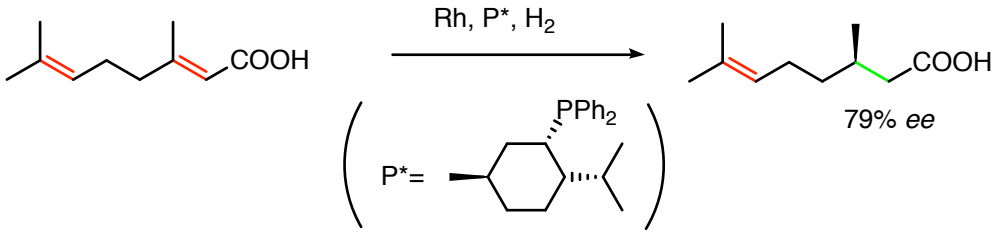
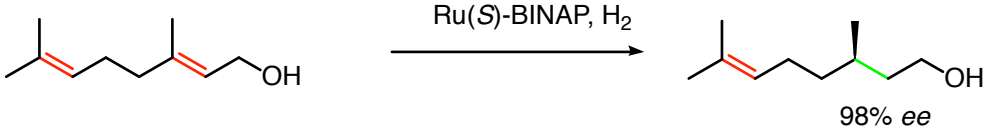
J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b06829 • Publication Date (Web): 20 Sep 2017


Ir-N,P
H2
R1 = Si(Me)2tBu, Si(Et)3
R2 = alkyl, CH2CH2OSi(Me)2tBu
CH2CH2(acetal)
R3 = alkyl, CH2CH2OSi(Me)2tBu
21 examples,
up to 99% ee
Regioselective and high yielding

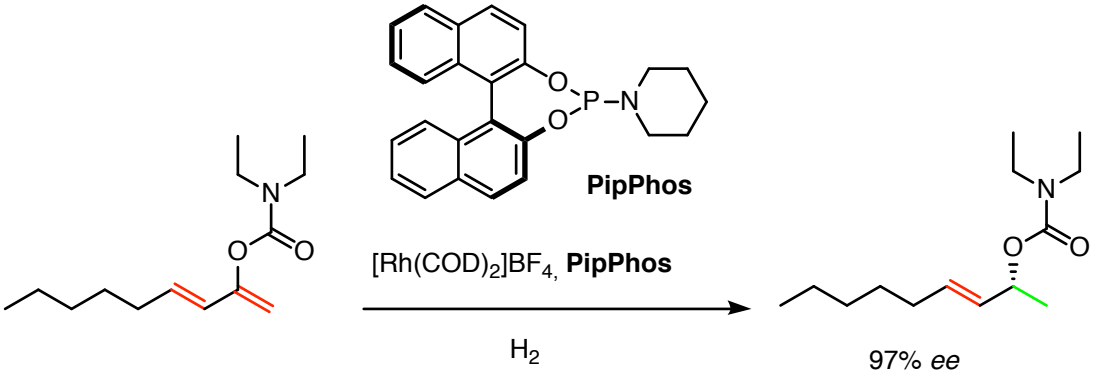
a) Rhodium chiral monophosphine complex (1980)



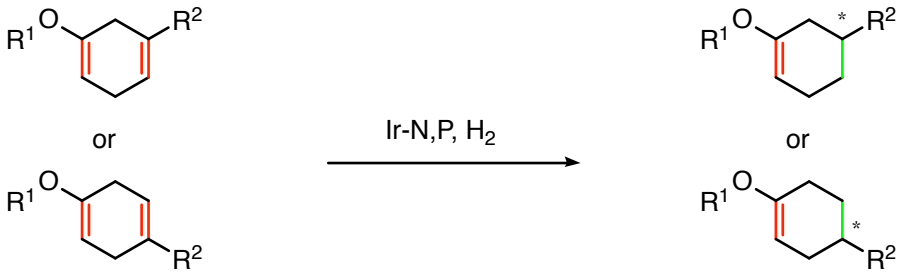
b) BINAP-based Ru dicarboxylate complex (1987)



c) Monodentate phosphoramidites Rh complex (2005)



d) Ir-N,P complex (this work)



Regioselective Iridium-catalyzed Asymmetric Monohydrogenation of 1,4-Dienes

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KEYWORDS Regioselective • asymmetric hydrogenation• iridium catalysis• 1,4 dienes.

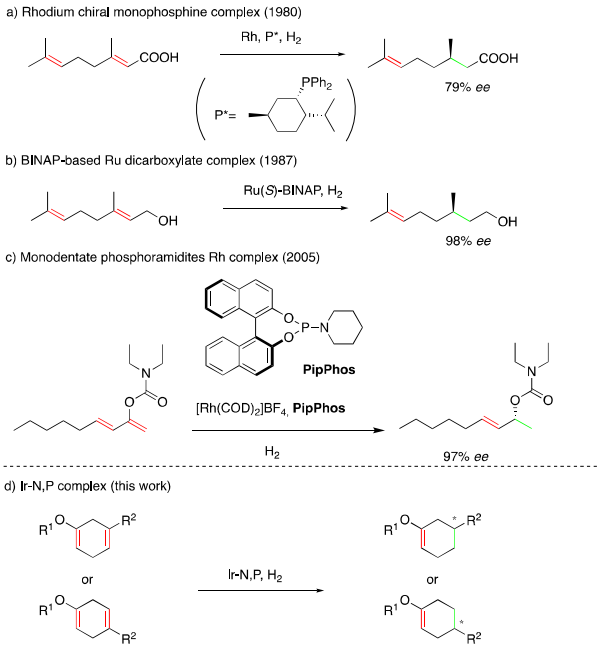
ABSTRACT: A highly efficient regio- and enantioselective monohydrogenation of 1,4-dienes has been realized using an iridium catalyst with a chiral N,P-ligand under mild conditions. The substrate scope was studied and included both unfunctionalized as well as functionalized substituents on the meta- or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

INTRODUCTION

Synthesis of enantiopure products by asymmetric catalysis of organic reactions represents an important area in modern synthetic chemistry. Among many successful examples, asymmetric hydrogenation has been most extensively studied in academia and widely applied in industry,[1,2] as affirmed by the award of the 2001 Nobel Prize in chemistry to Knowles and Noyori.[3] Today, asymmetric hydrogenation is still one of the most widely used, reliable catalytic method for the preparation of optically active compounds.[4] In the last few decades, significant progress has been made towards the asymmetric hydrogenation of C=C,[5] C= N,[6] and C=O[4d,7] utilizing transition-metal chiral-ligand complexes.[4,8] The reduction of olefins containing an adjacent polar group (i.e., dehydro-amino acids) by Rh- and Ru-catalyst precursors modified with phosphorus ligands has a long history. Rhodium and ruthenium catalysts have a strong preference to hydrogenate olefins having a polar functional group next to the C=C bond which can coordinate to the metal center and help in achieving high levels of activity and stereo control.[9]

Asymmetric hydrogenation of unfunctionalized olefins have attracted considerable interest recently[10] and chiral Ir-P,N complexes have been found to be extremely useful catalytic precursors for the asymmetric hydrogenation of minimally functionalized di- and tri-substituted olefins.[11,12] However, despite the development of highly *enantioselective* protocols, *regioselectivity*, or the ability to hydrogenate only one out of several olefins in a certain substrate is still a generally unsolved task.[2a,4c,5e,10e]

A few examples have been reported and consist almost exclusively of Rh- and Ru-catalyzed hydrogenations of an olefin having a polar substituent in preference over an unfunctionalized olefin in the same substrate. An early example of regioselective hydrogenation of (*E*)-3,7-dimethylocta-2,6-dienoic acid was reported in 1980 by Toth using 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 dihydrocitronellol.[14]



Scheme 1. Regioselective asymmetric hydrogenation using transition metals.

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 C=C bond. Ir on the other hand, is believed to operate via a mechanism involving an eta-2 (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 is still rare and limited.

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

RESULTS AND DISCUSSION

Our initial investigation began with the hydrogenation of **1a**. It was found that the regioselectivity between the two olefins was modest when using the standard hydrogenation conditions (entry 1-3). However, the regioselectivity was found to depend on the catalyst and especially on the addition of base. Thus, when using catalyst B (Figure 1) and Poly(4-vinylpyridine) (PVP) as the base, it was possible to run the reaction to completion with a regioselectivity of 97:3. Interestingly, the selectivity observed was opposite to what is normally reported for Rh- and Ru-catalyzed hydrogenations (Scheme 1a,b), with the Ir-catalyst the unfunctionalized olefin was hydrogenated in preference over the enol ether. One possible explanation for the observed selectivity for Ir to preferentially hydrogenate the olefin and not the enol ether could originate from the possibility of the enol ether to form an eta-3 (η^3) coordination, which would compete with the coordination of the dihydrogen molecule to the iridium catalyst.

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

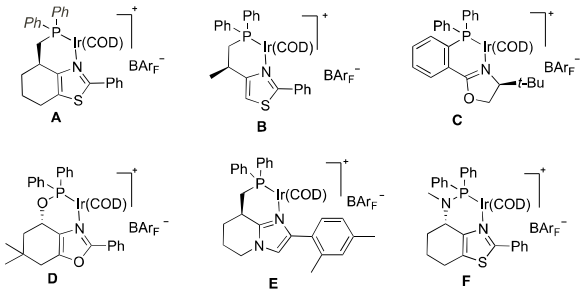
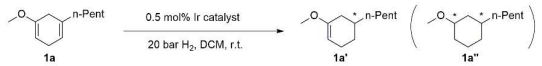


Figure 1. Catalysts used in this study.

Table 1. Optimization of asymmetric hydrogenation conditions[a] using 1a

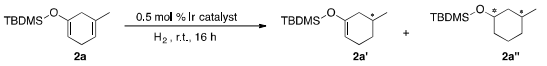


Entry	Cat.	Time	Base	Conv. (%)[b]	(1a") *ee* (%)[c]	1a' / 1a"[c]
1	A	12 min	No	91	83	79/21
2	A	30 min	No	98	81	47/53
3	A	2 h	No	99	N.D.[d]	1/99
4	B	12 min	No	50	83	99/1
5	B	3 h	No	99	N.D.[d]	3/97
6	B	3 h	PVP	98	84	97/3

[a] Reaction conditions: 0.125 mmol of substrate, 0.5 mol % catalyst, 10 mol% base, H_2, and r.t. unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral GC analysis, see Supporting Information for details. [d] N.D. = Not Determined.

A screening of some Ir N,P-ligand catalysts revealed that silyl enol ether **2a** gave full conversion and good to high enantioselectivies (Table 2, entries 1-6). The best enantioselectivity was obtained for catalyst **F**, which gave **2a'** in 95% *ee* (entry 6). Next, the reaction was optimized with regards to solvent effects, base and pressure. The combination of Ph-CF_3 as solvent and K_3PO_4 as base under 10 bar of hydrogen was the most suitable reaction condition for this reaction (entry 11). (See Supporting Information for results of hydrogenations carried out at shorter time intervals.)

Table 2. Optimization of asymmetric hydrogenation conditions[a] using 2a



Entry	Cat.	Pressure (bar)	Solvent	Base	Conv. (%)[b]	2a' / 2a"	(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_3PO_4	99	72/28	91
8	F	20	Benzene	K_3PO_4	99	40/60	91
9	F	20	Toluene	K_3PO_4	99	41/59	94
10	F	20	Ph-CF_3	K_3PO_4	99	85/15	96
11	F	10	Ph-CF_3	K_3PO_4	99	93/7	96

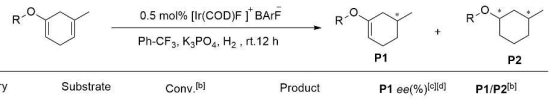
[a] Reaction conditions: 0.125 mmol of substrate, 0.5 mol % catalyst, 10 mol% base, H_2, 16 h, and r.t. unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral GC analysis, see Supporting Information for details.

With the optimized reaction conditions established, the effect of the different protecting groups was evaluated (Table 3). Interestingly, the type of protecting group used had relatively little influence on the regioselectivities and enantioselectivities observed. The EOM (methoxy methyl acetal), EE (ethoxy ethyl acetal) and the silyl protecting groups (entries 1, 2 and 4-6) all resulted in high enantioselectivities. Of all the protecting groups, TES (tri-ethyl silyl ether) and TBDMS (tert-butyl dimethyl silyl ether) showed optimal results and was used to investigate the scope of the reaction.

A number of 1,4-diene substrates were prepared in high yield using the Birch reduction and were selectively hydrogenated to the corresponding protected silyl enol olefins in high yield and good to excellent enantioselectivities. Having the substituent at the *meta* position in the silyl protected enol ethers resulted in all cases in very high enantioselectivities (between 95% to 99%, Table 4, entries 1-7). These are surprisingly high levels of stereoselectivities, given that the olefin being reduced only have aliphatic substituents, something that normally results in lower *ee*'s. Having the substituent at the *para* position was also investigated for both the TBDMS (entry 8) and the TES protected enol ethers (entries 9-10). Although the TBDMS protected **13a** only resulted in an *ee* of 80%, the *ee* TES protected enol gave good enantioselectivities (entry 9-10). The tetrasubstituted enol compounds **16a** and **17a** also resulted in excellent enantioselectivities of 95% and 98%. Also, some substrates having functionalized side-chains were prepared and evaluated: **18a**, **19a**, **20a** were hydrogenated in excellent enantioselectivities. Finally, having a functionalized substituent in the *para* position also resulted in high enantioselectivity (entry 16).

In order to investigate if the observed regioselectivity for some reason was limited to 1,4-cyclohexadienes, a number of acyclic substrates containing two olefins were also prepared and evaluated. The acyclic substrates **22a-24a** were thus tested in this reaction, resulting in similar high regioselectivities for all the substrates. Excellent enantioselectivity were obtained for prochiral substrates and products 24a' and 25a' was isolated in 99% and 98% *ees*, respectively.

Table 3. Asymmetric hydrogenation with different types of protecting groups[a]

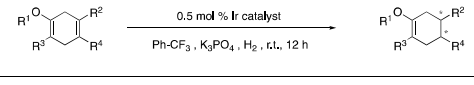


Entry	Substrate	Conv.[b]	Product	P1 *ee*(%)[c][d]	P1/P2[b]
1	EOM	65	EOM	96(*R*)	99/1
2	EE	93	EE	97(*R*)	94/6
3	THP	70	THP	83(*R*)	99/1
4	TIPS	73	TIPS	97(*R*)	99/1
5	TES	99	TES	96(*R*)	86/14
6	TBDMS	99	TBDMS	96(*R*)	93/7

[a] Reaction conditions: 0.125 mmol of substrate, 0.5 mol % catalyst, 10 mol% base, H_2, 12 h, and r.t. unless otherwise stated. [b] Determined by ^{1}H NMR spectroscopy. [c] Determined by chiral GC analysis, see Supporting Information for details. [d] Absolute configuration of the hydrogenated product was assigned on the basis of elution order of hydrolysis product compared with commercially available (*R*)-(+)-3-methylcyclohexanone.

Although the chiral, *meta* or *para* substituted enol ethers constitutes 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]

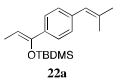
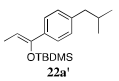
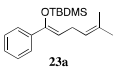
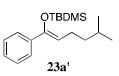
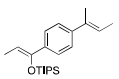
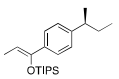
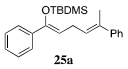
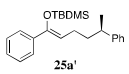
Table 4. Asymmetric hydrogenation of different silyl protected substrates[a]



Entry	Substrate	Catalyst	Product	Yield (%)	*ee* (%)[d]
1	TBDMS **2a**	F	TBDMS **2a'**	58[b]	96(*R*)[e]
2	TES **7a**	F	TES **7a'**	79[c,f]	96(*R*)[e]
3	TES Et **8a**	E	TES Et **8a'**	56[c,f]	99(*S*)
4	TBDMS n-Bu **9a**	F	TBDMS n-Bu **9a'**	54[b]	92(*R*)
5	TES n-Bu **10a**	F	TES n-Bu **10a'**	55[c]	95(*R*)
6	TBDMS n-Pent **11a**	F	TBDMS n-Pent **11a'**	78[b]	96(*R*)
7	TES n-Pent **12a**	F	TES n-Pent **12a'**	70[b]	95(*R*)
8	TBDMS **13a**	F	TBDMS **13a'**	45[b]	80(*R*)
9	TES **14a**	F	TES **14a'**	75[c,f]	95(*R*)
10	TES n-Pr **15a**	F	TES n-Pr **15a'**	56[c,f]	92(*R*)
11	TBDMS **16a**	E	TBDMS **16a'**	81[c]	95(*S*)
12	TES **17a**	E	TES **17a'**	79[c]	98(*S*)
13[h]	TBDMSO OTBDMS **18a**	F	TBDMSO OTBDMS **18a'**	89[g]	97(*R*)
14	TBDMSO O O **19a**	F	TBDMSO O O **19a'**	89[c]	95(*R*)
15	TBDMSO O O **20a**	F	TBDMSO O O **20a'**	82[c]	98(*R*)
16[h]	TBDMSO OTBDMS **21a**	F	TBDMSO OTBDMS **21a'**	94[g]	94(*R*)

[a] Reaction conditions: 0.25 mmol of substrate, 0.5 mol % catalyst, 2 mL of Ph-CF_3, 10 bar H_2. 12 h, and r.t. unless otherwise stated. [b] NMR yield using internal standard 1,3,5-trimethoxybenzene. [c] Isolated yield. [d] Determined by chiral GC or SFC analysis, see Supporting Information for details. [e] Absolute configuration of the hydrogenated product was assigned on the basis of elution order of hydrolysis product compared with commercially available (*R*)-(+)-3-methylcyclohexanone. [f] Observed 5-10% over reduction product, see Supporting Information for details. [g] Conversion determined by ^{1}H NMR spectroscopy. [h] Reaction conditions: 0.25 mmol of substrate, 0.5 mol % catalyst, 2 mL of Ph-CF_3, 20 bar H_2. 24 h, and r.t.

Table 5. Asymmetric hydrogenation of different silyl protected substrates[a, f]

Entry	Substrate	Catalyst	Product	Isolated Yield (%)	*ee* (%)[e]
17	 22a	B	 22a'	81	- -
18	 23a	B	 23a'	78[b]	- -
19	 24a	F	 24a'	82[c]	99 (*R*)
20	 25a	Ent-A	 25a'	93[d]	98 (*R*)

[a] Reaction conditions: 0.178 mmol of substrate, 0.5 mol % catalyst, 2 mL of Ph-CF_3, 5 bar H_2. 14 h, and r.t. unless otherwise stated. [b] Reaction time, 3 h [c] 0.120 mmol of substrate. [d] 0.089 mmol of substrate. [e] Determined by chiral GC or SFC analysis, see Supporting Information for details. [f] Observed 2-5% over reduction product, see Supporting Information for details.

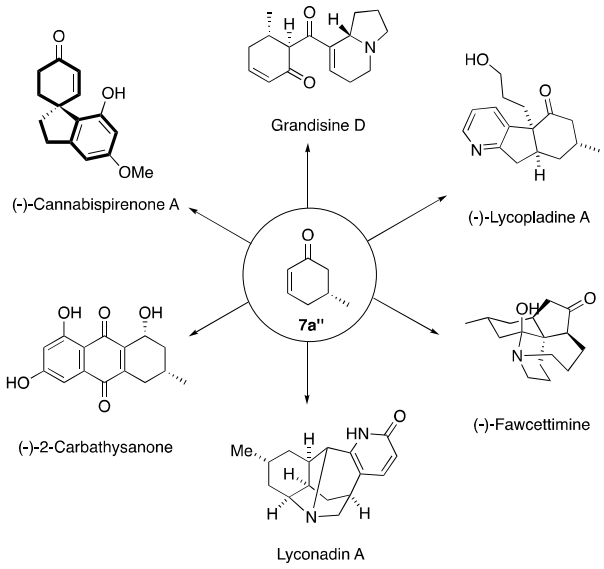
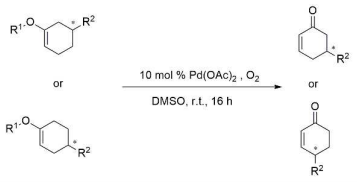
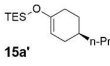
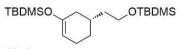
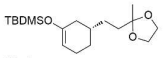
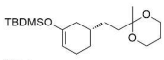
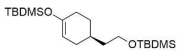


Figure 2. Examples of total syntheses of biologically active compounds originating from chiral 7a''

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 Herzon[20] using 10% Pd and O_2 as 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 centres (Table 5).

Table 6. Synthesis of α,β–unsaturated ketones[a]



Entry	Substrate	Product	Yield (%)	*ee* (%)[d]
1	 7a'	 7a''	86[b]	95(*R*)
2	 14a'	 14a''	68[b]	95(*R*)
3	 15a'	 15a''	78[b]	92(*R*)
4[f]	 18a'	 18a''	59[c]	97(*R*)[e,21]
5[g]	 19a'	 19a''	56[c]	95(*R*)
6[g]	 20a'	 20a''	51[c]	98(*R*)
7[f]	 21a'	 21a''	62[c]	94(*S*)

[a] Reaction conditions: 0.25 mmol of substrate, 10 mol % $Pd(OAc)_2$, 5 mL of DMSO, balloon O_2. 16 h, and r.t. [b] NMR yield using internal standard 1,3,5-trimethoxybenzene. [c] Isolated yield. [d] Determined by chiral GC or SFC analysis, see Supporting Information for details. [e] Absolute configuration of the hydrogenated product was tentatively assigned based on specific optical rotation compared with literature. [f] 0.25 mmol of substrate, 20 mol % $Pd(OAc)_2$, 5 mL of DMSO, balloon O_2. 24 h, and r.t. [g] 0.25 mmol of substrate, 30 mol % $Pd(OAc)_2$, 5 mL of DMSO, balloon O_2. 48 h, and r.t.

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 and with preserved enantiomeric purity.

Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge *via* the Internet at http://pubs.acs.org

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Author Contributions

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ACKNOWLEDGMENT

The Swedish Research Council (VR), Stiftelsen Olle Engkvist Byggmästare and The Swedish Energy Agency supported this work. Jianguo Liu thanks the Guangzhou Elite Scholarship Council for the PhD fellowship. Thishana Singh acknowledges

the NRF and the College of Agriculture, Engineering and Science, University of KwaZulu-Natal, South Africa for a postdoctoral research fellowship. Napasawan Chumnanvej thanks VR/SIDA for the three-month exchange fellowship to Stockholm University. Giulia De Seriis thanks the University of Bologna for an Erasmus scholarship. Many thanks to Prof. David Tanner from the Technical University of Denmark for helpful suggestions and discussions in the early stages of this work.

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ABBREVIATIONS

COD 1,5-cyclooctadiene; EE, Ethoxy ethyl acetal; EOM, Methoxy methyl acetal; GC/MS Gas Chromatography Mass Spectroscopy; HPLC High Performance Liquid Chromatography; PVP, Poly(4-vinylpyridine); TBDMS, Tert-butyl dimethyl silyl ether; TES, Tri-ethyl silyl ether; TESCl, Chlorotriethylsilane; THP, Tetra-hydro pyranyl acetal; TIPS, Triisopropyl silyl ether.

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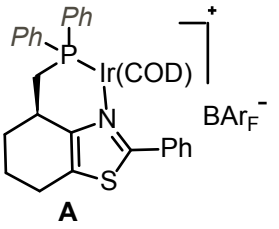
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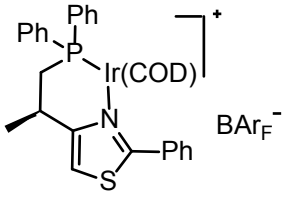
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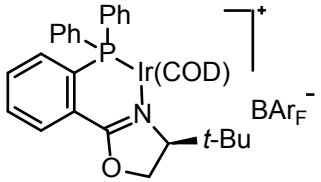
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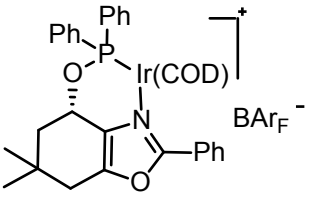
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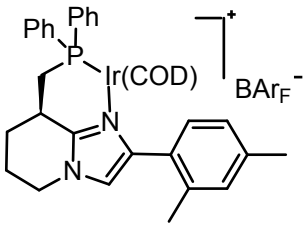
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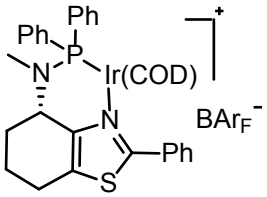
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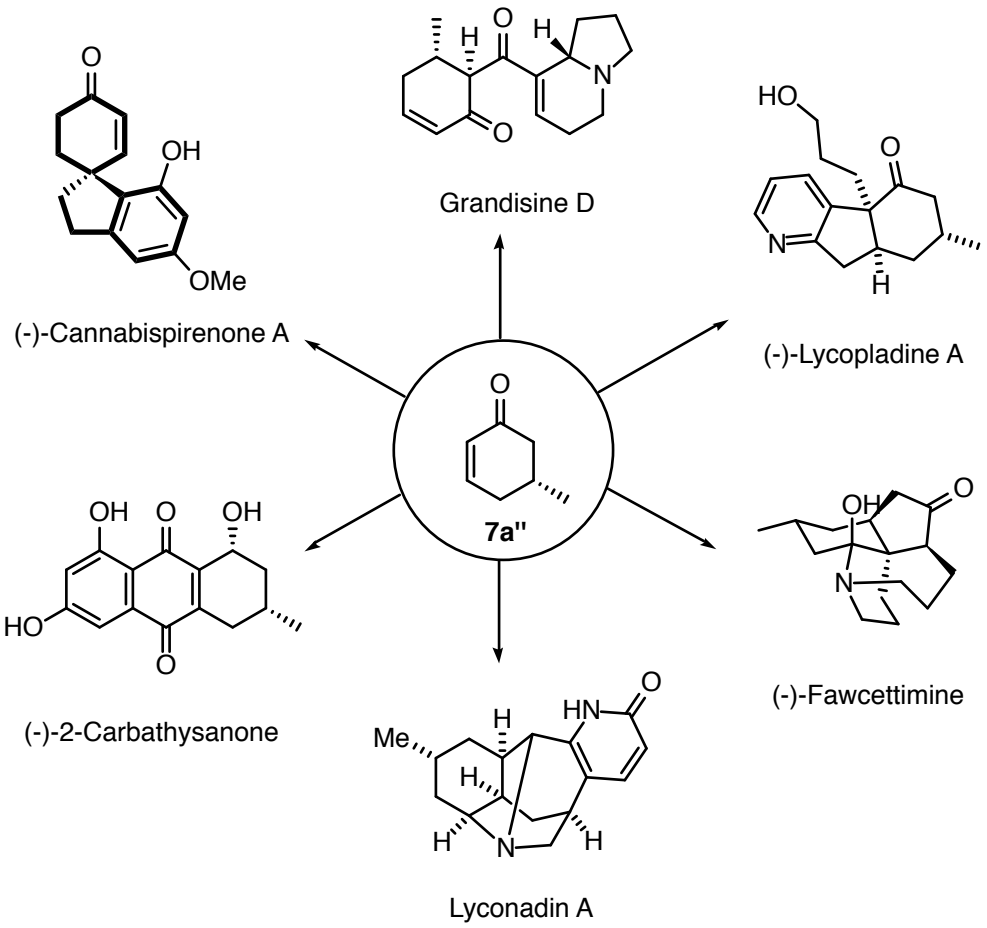
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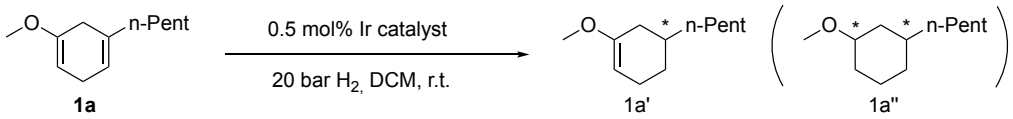

1a 1a' 1a''

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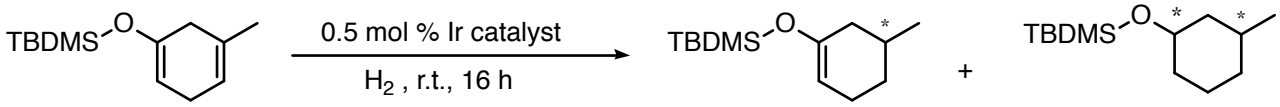
2	A	30 min	No	98	81	47/53
3	A	2 h	No	99	N.D.[d]	1/99
4	B	12 min	No	50	83	99/1
5	B	3 h	No	99	N.D.[d]	3/97
6	B	3 h	PVP	98	84	97/3



2a **2a'** **2a''**

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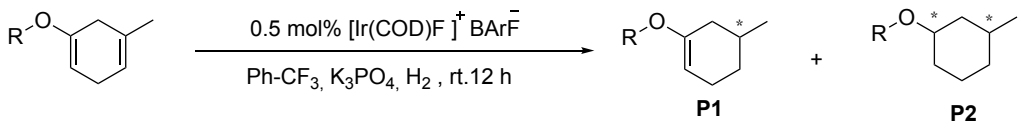
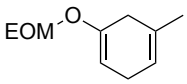
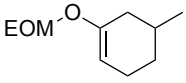
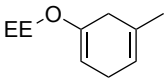
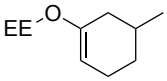
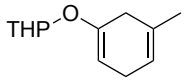
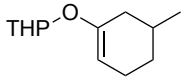
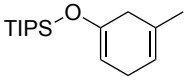
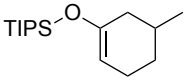
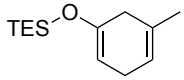
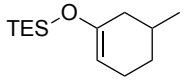
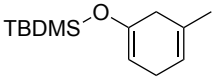
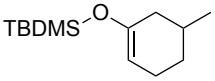
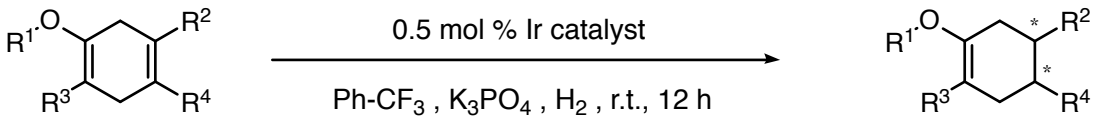
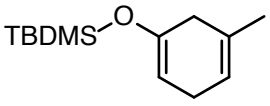
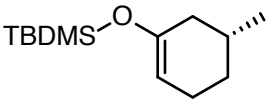
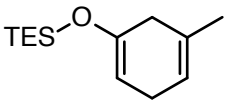
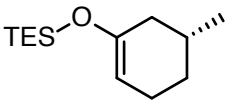
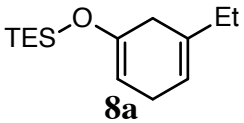
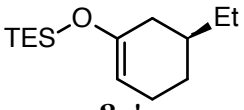
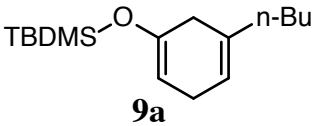
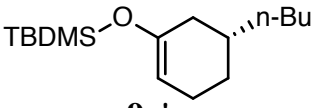
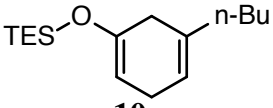
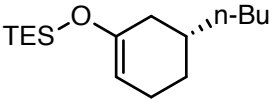
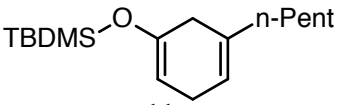
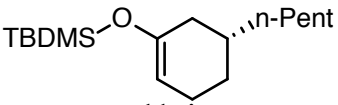
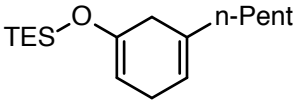
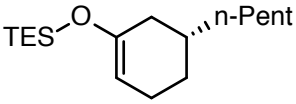
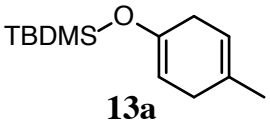
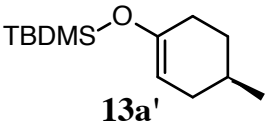
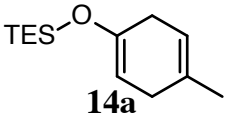
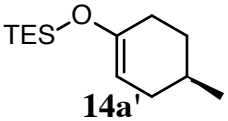
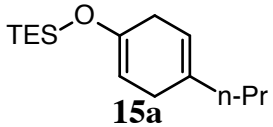
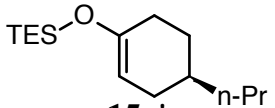
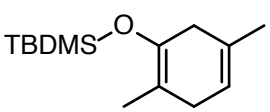
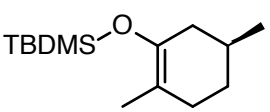
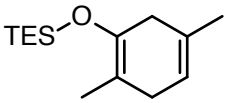
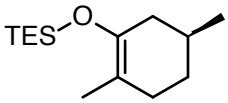
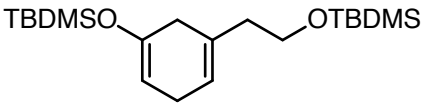
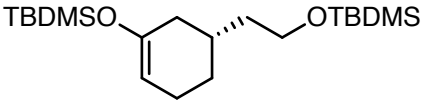
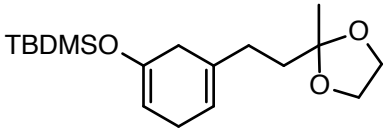
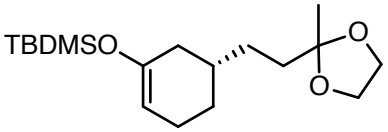
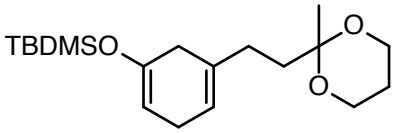
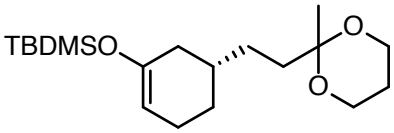
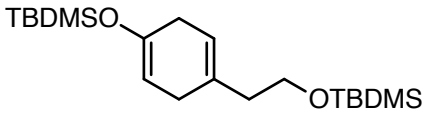
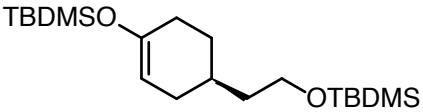
2	B	20	DCM	PVP	99	93/7	78
3	C	20	DCM	PVP	99	67/33	82
4	D	20	DCM	PVP	99	81/19	90
5	E	20	DCM	PVP	99	27/73	94
6	F	20	DCM	PVP	99	78/22	95
7	F	20	DCM	K_3PO_4	99	72/28	91
8	F	20	Benzene	K_3PO_4	99	40/60	91
9	F	20	Toluene	K_3PO_4	99	41/59	94
10	F	20	Ph-CF_3	K_3PO_4	99	85/15	96
11	F	10	Ph-CF_3	K_3PO_4	99	93/7	96

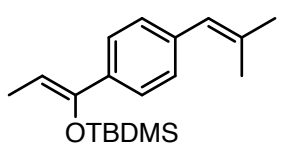
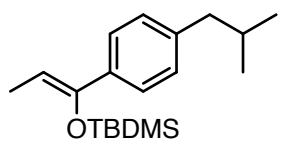
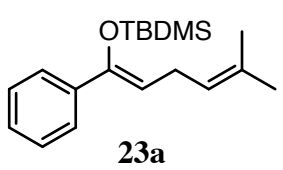
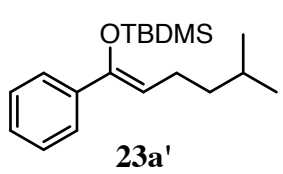
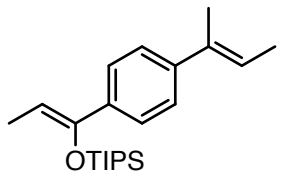
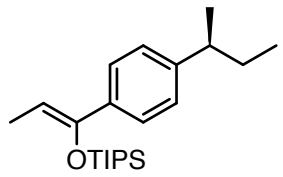
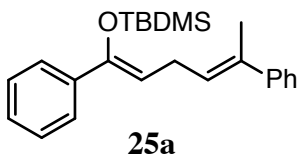
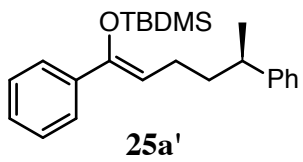


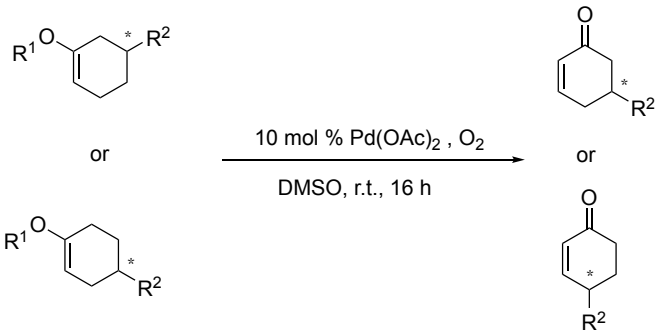
Entry	Substrate	Conv.[b]	Product	**P1** *ee*(%)[c][d]	**P1**/**P2**[b]
1		65		96(*R*)	99/1
2		93		97(*R*)	94/6
3		70		83(*R*)	99/1
4		73		97(*R*)	99/1
5		99		96(*R*)	86/14
6		99		96(*R*)	93/7

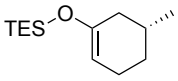
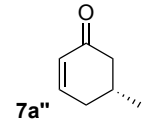
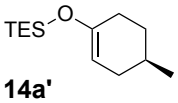
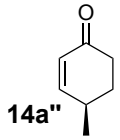
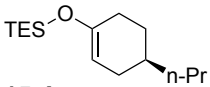
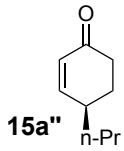
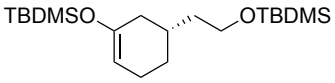
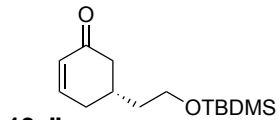
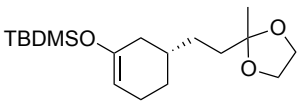
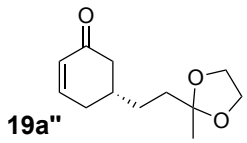
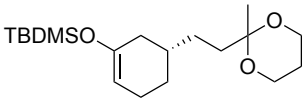
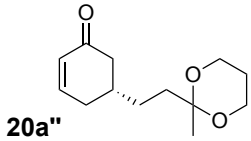
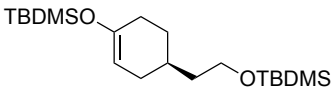
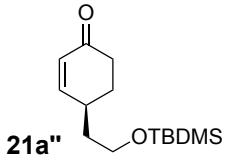


Entry	Substrate	Catalyst	Product	Yield (%)	*ee* (%)[d]
1	 **2a**	F	 **2a'**	58[b]	96(*R*)[e]
2	 **7a**	F	 **7a'**	79[c,f]	96(*R*)[e]
3	 **8a**	E	 **8a'**	56[c,f]	99(*S*)
4	 **9a**	F	 **9a'**	54[b]	92(*R*)
5	 **10a**	F	 **10a'**	55[c]	95(*R*)
6	 **11a**	F	 **11a'**	78[b]	96(*R*)
7	 **12a**	F	 **12a'**	70[b]	95(*R*)
8	 **13a**	F	 **13a'**	45[b]	80(*R*)
9	 **14a**	F	 **14a'**	75[c,f]	95(*R*)
10	 **15a**	F	 **15a'**	56[c,f]	92(*R*)
11	 **16a**	E	 **16a'**	81[c]	95(*S*)

12	 **17a**	E	 **17a'**	79[c]	98(*S*)
13[h]	 **18a**	F	 **18a'**	89[g]	97(*R*)
14	 **19a**	F	 **19a'**	89[c]	95(*R*)
15	 **20a**	F	 **20a'**	82[c]	98(*R*)
16[h]	 **21a**	F	 **21a'**	94[g]	94(*R*)

Entry	Substrate	Catalyst	Product	Isolated Yield (%)	*ee* (%)[e]
17	 **22a**	**B**	 **22a'**	81	- -
18	 **23a**	**B**	 **23a'**	78[b]	- -
19	 **24a**	**F**	 **24a'**	82[c]	99 (*R*)
20	 **25a**	**Ent-A**	 **25a'**	93[d]	98 (*R*)



Entry	Substrate	Product	Yield (%)	*ee* (%)[d]
1	 **7a'**	 **7a''**	86[b]	95(*R*)
2	 **14a'**	 **14a''**	68[b]	95(*R*)
3	 **15a'**	 **15a''**	78[b]	92(*R*)
4[f]	 **18a'**	 **18a''**	59[c]	97(*R*)[e,21]
5[g]	 **19a'**	 **19a''**	56[c]	95(*R*)
6[g]	 **20a'**	 **20a''**	51[c]	98(*R*)
7[f]	 **21a'**	 **21a''**	62[c]	94(*S*)