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Metathesis For Catalyst Design: *Metacatalysis*

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Metathesis For Catalyst Design: *Metacatalysis*

Supporting Information

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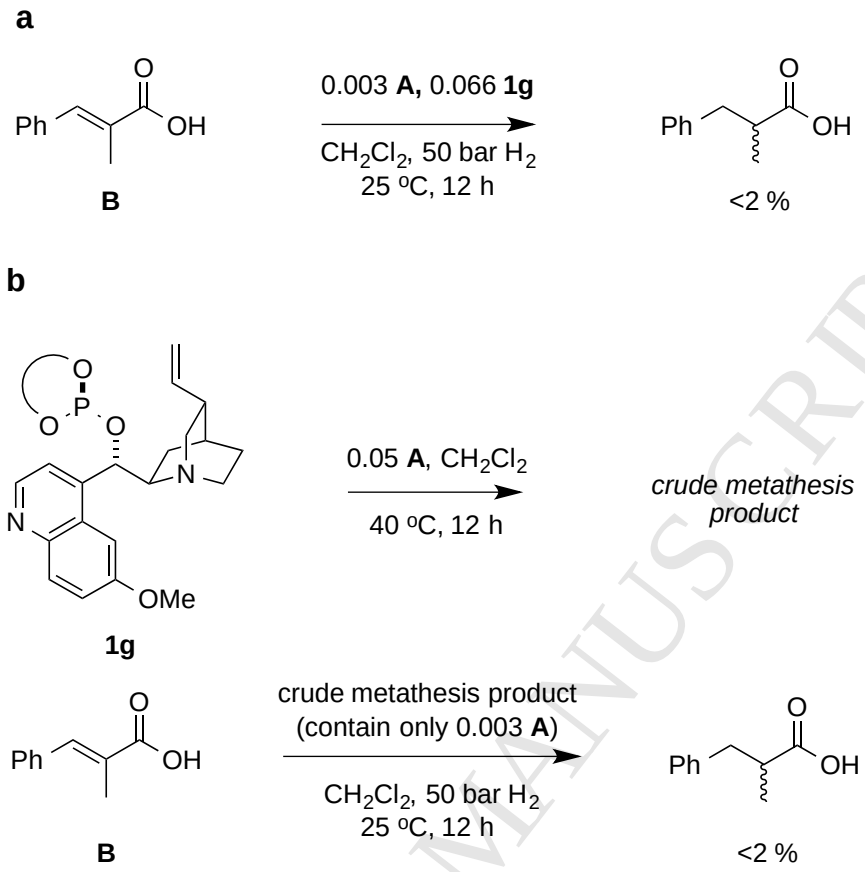


Figure S1. Hydrogenation of α-methylcinnamic acid **B** using 2nd Generation Hoveyda-Grubb's catalyst with **1g**.

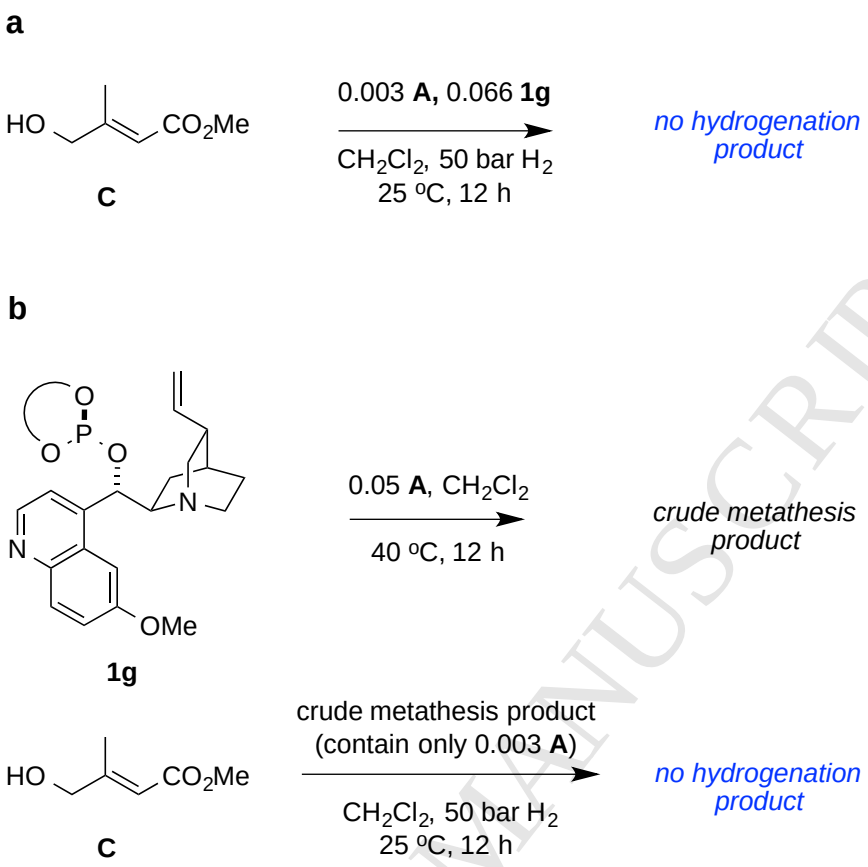


Figure S2. Hydrogenation of hydroxyl-ester **C** using 2nd Generation Hoveyda-Grubb's catalyst with **1g**.

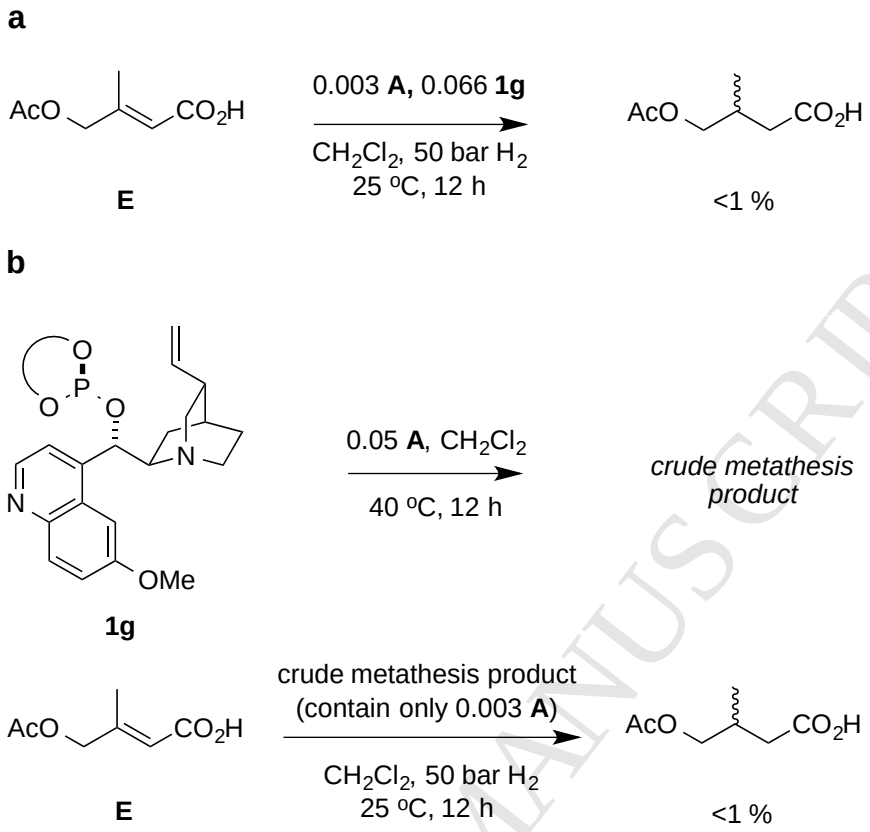


Figure S3. Hydrogenation of acetoxy-acid **E** using 2nd Generation Hoveyda-Grubb's catalyst with **1g**.

Catalytic Hydrogenation Using Chiral Ligand 1g with PPh_3

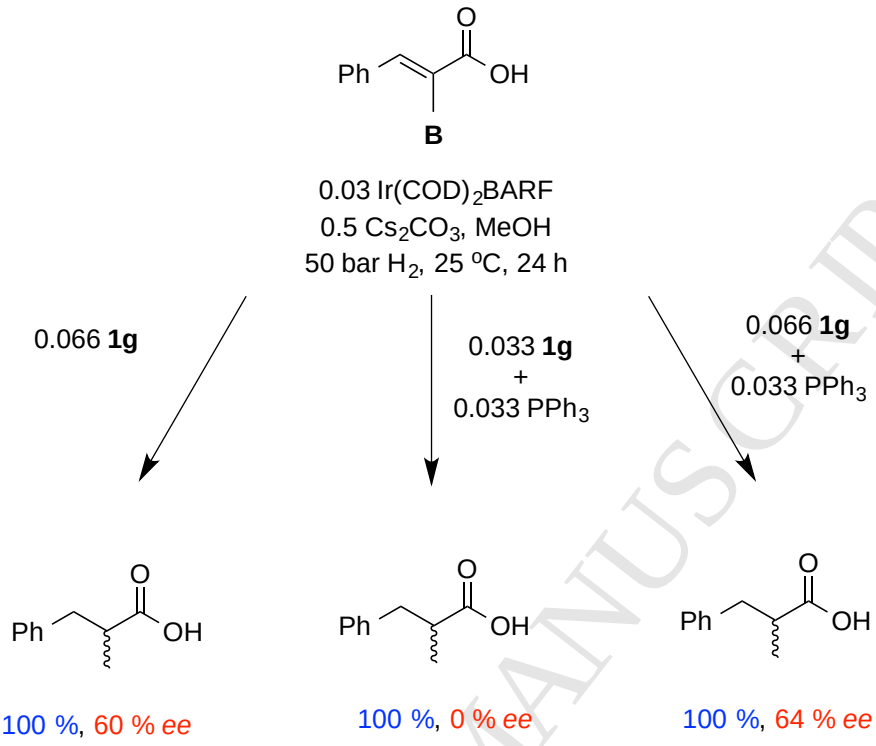


Figure S4. Hydrogenation of α-methylcinnamic acid **B** using catalysts formed from **1g** with and without PPh_3.

Catalytic Hydrogenation of Acetoxy Acid E Using Rh

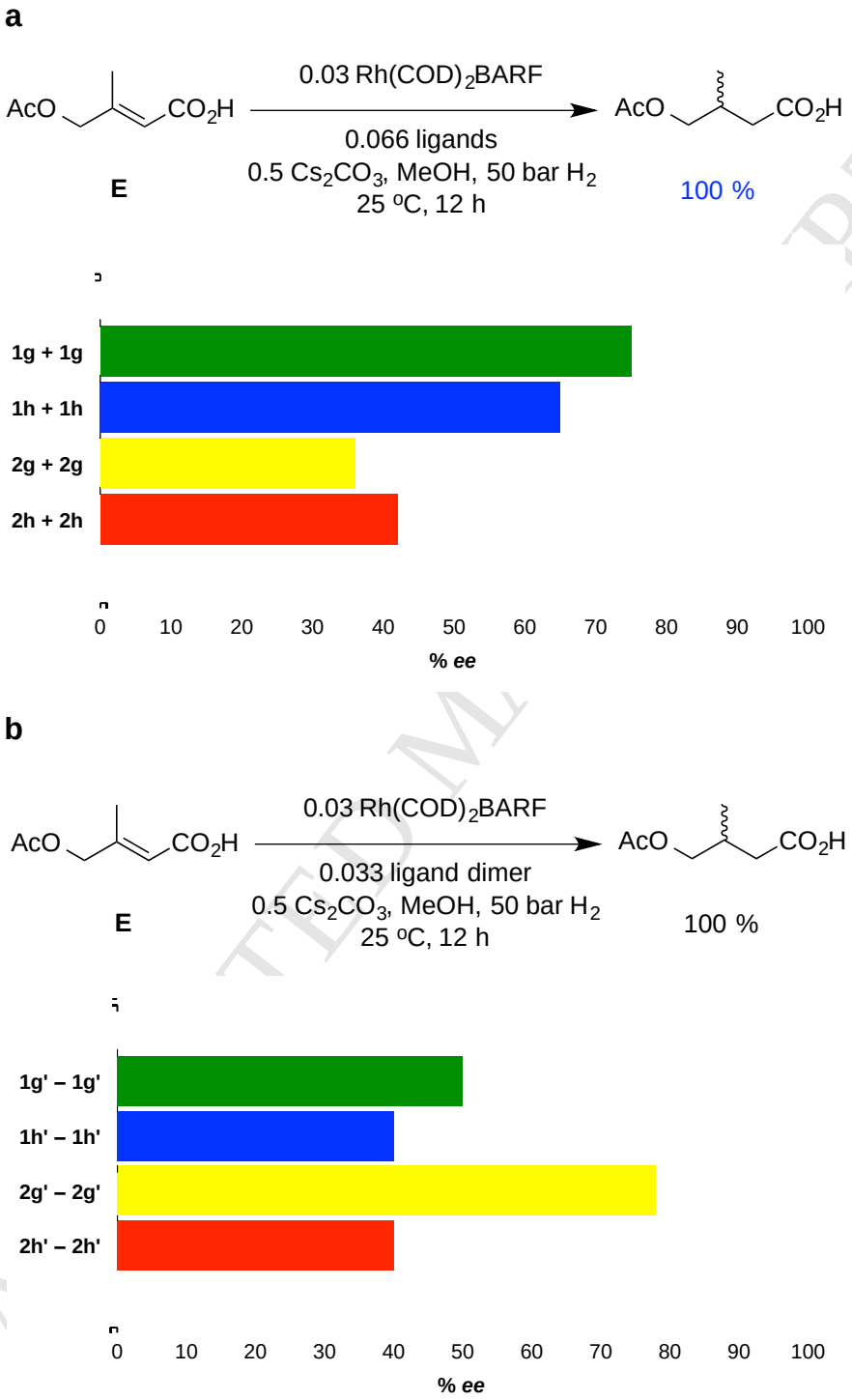
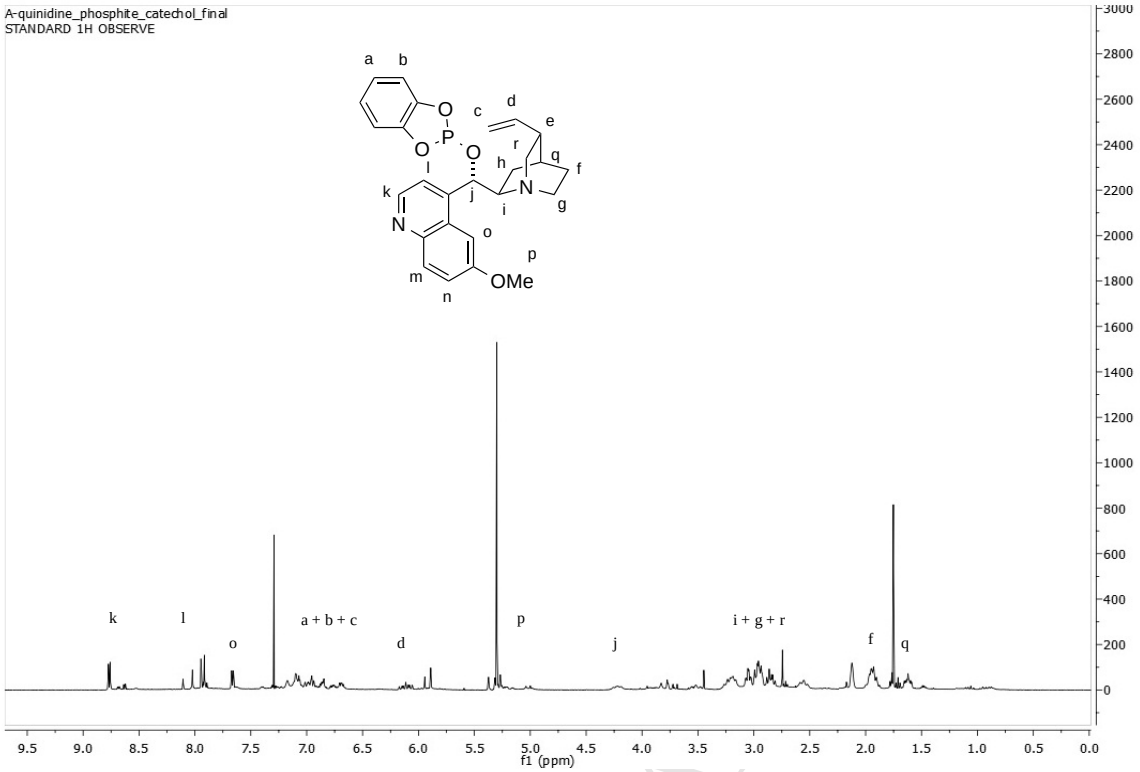


Figure S5. Hydrogenation of the acetoxy acid **E** using: **a** Rh catalysts from the monodentate ligands **1g**, **1h**, **2g**, and **2h**; and **b** from the same ligands after metathesis (as in Figure 3).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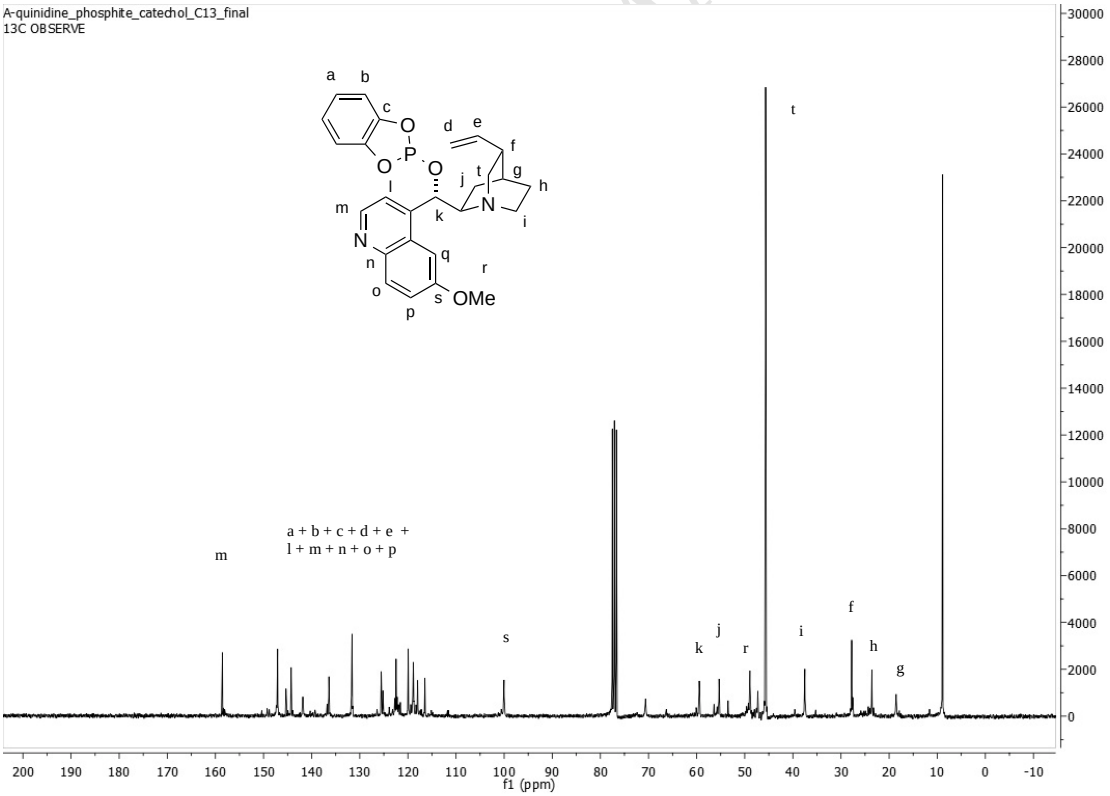
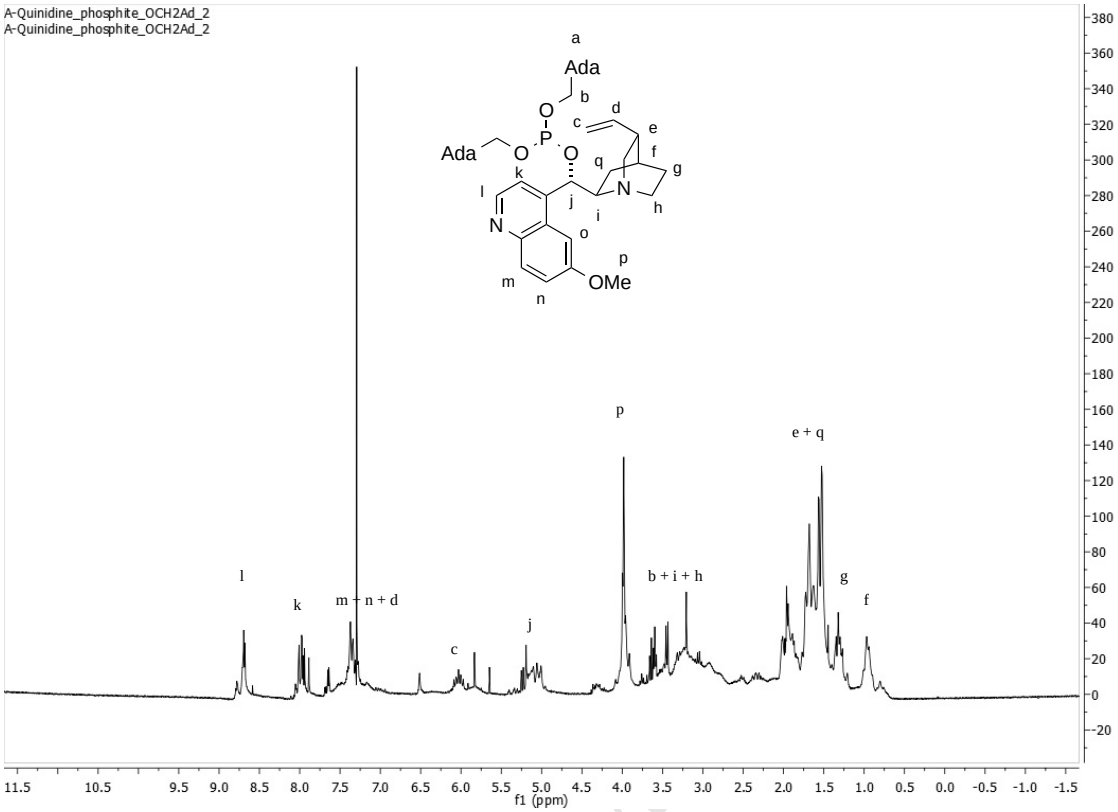
STANDARD 1H OBSERVE
OMe
k
l
o
a + b + c
d
p
j
i + g + r
f
q
f1 (ppm)


A-quinidine_phosphite_catechol_C13_final
13C OBSERVE
OMe
m
a + b + c + d + e +
l + m + n + o + p
s
t
k
j
r
i
f
h
g
f1 (ppm)


A-Quinidine_phosphite_OCH2Ad_2
A-Quinidine_phosphite_OCH2Ad_2
Ada
Ada
OMe
l
k
m + n + d
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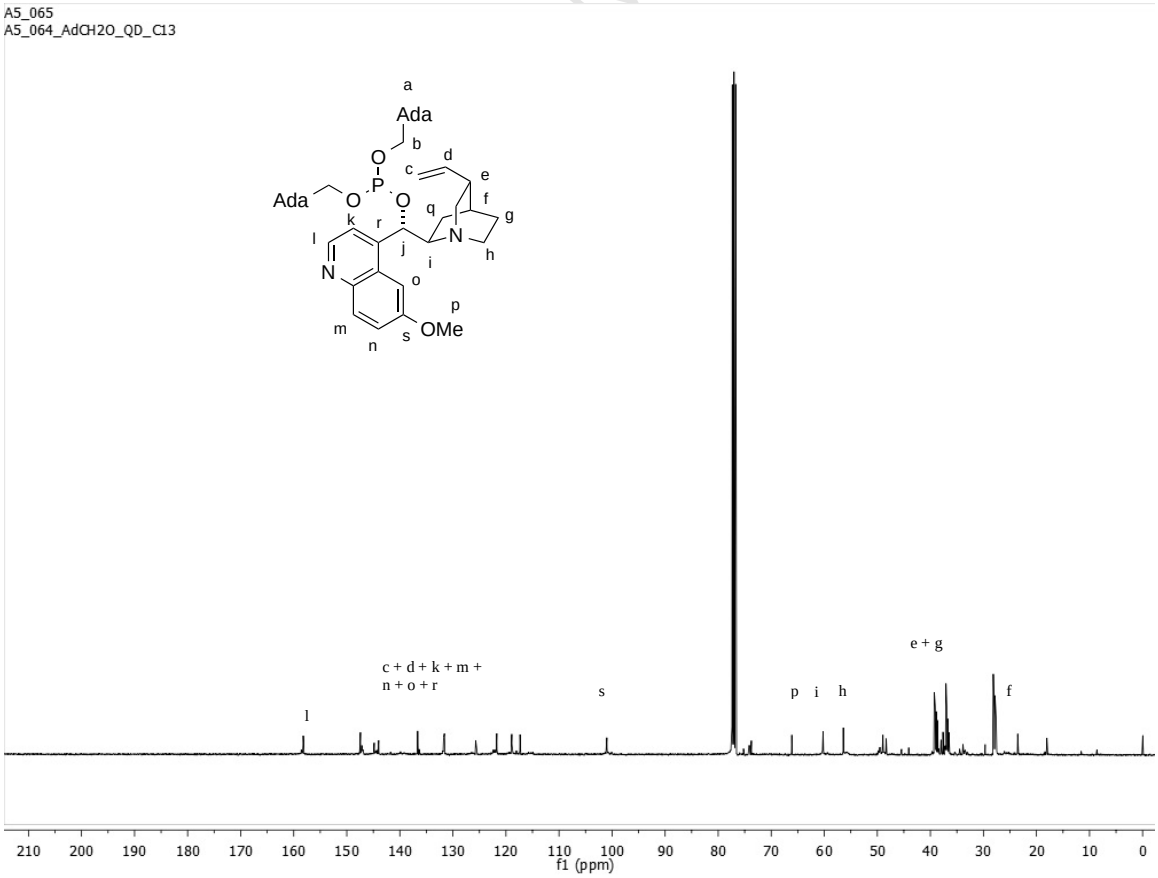
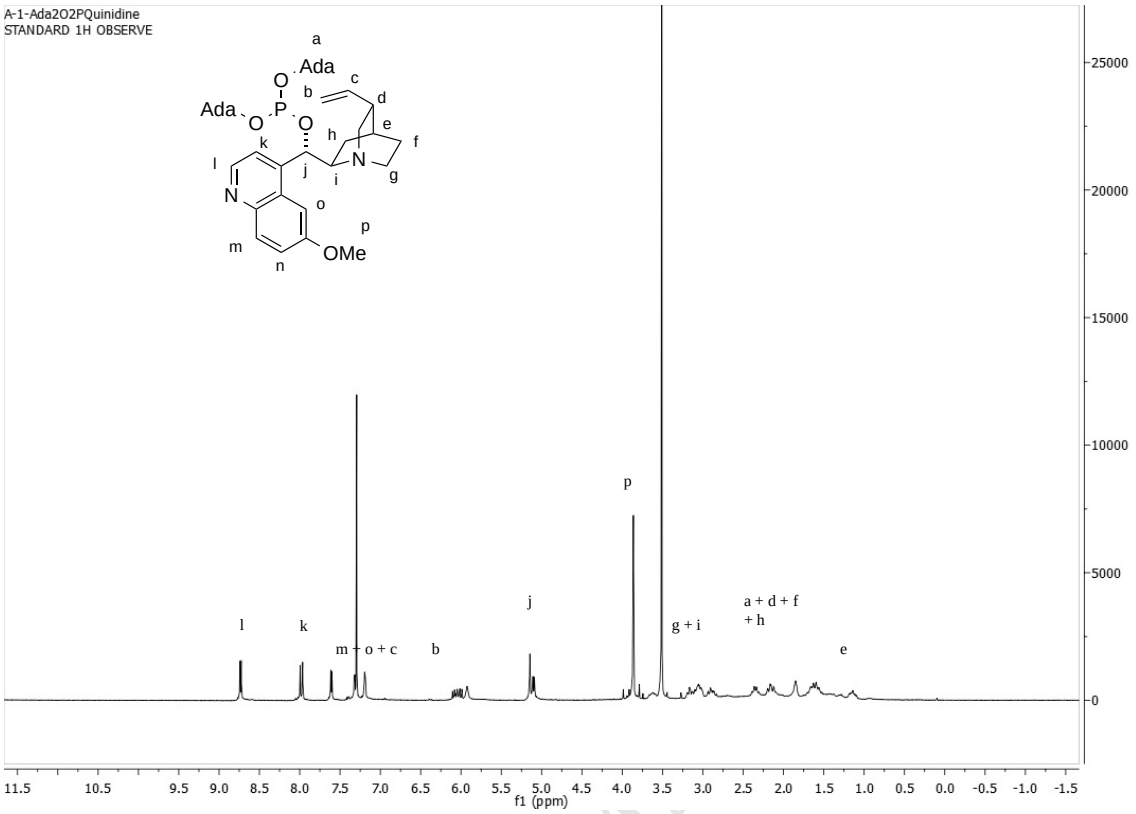
p
b + i + h
e + q
g
f
f1 (ppm)


A5_065
A5_064_AdCH2O_QD_C13
Ada
Ada
OMe
l
c + d + k + m + n + o + r
s
p i h
e + g
f
f1 (ppm)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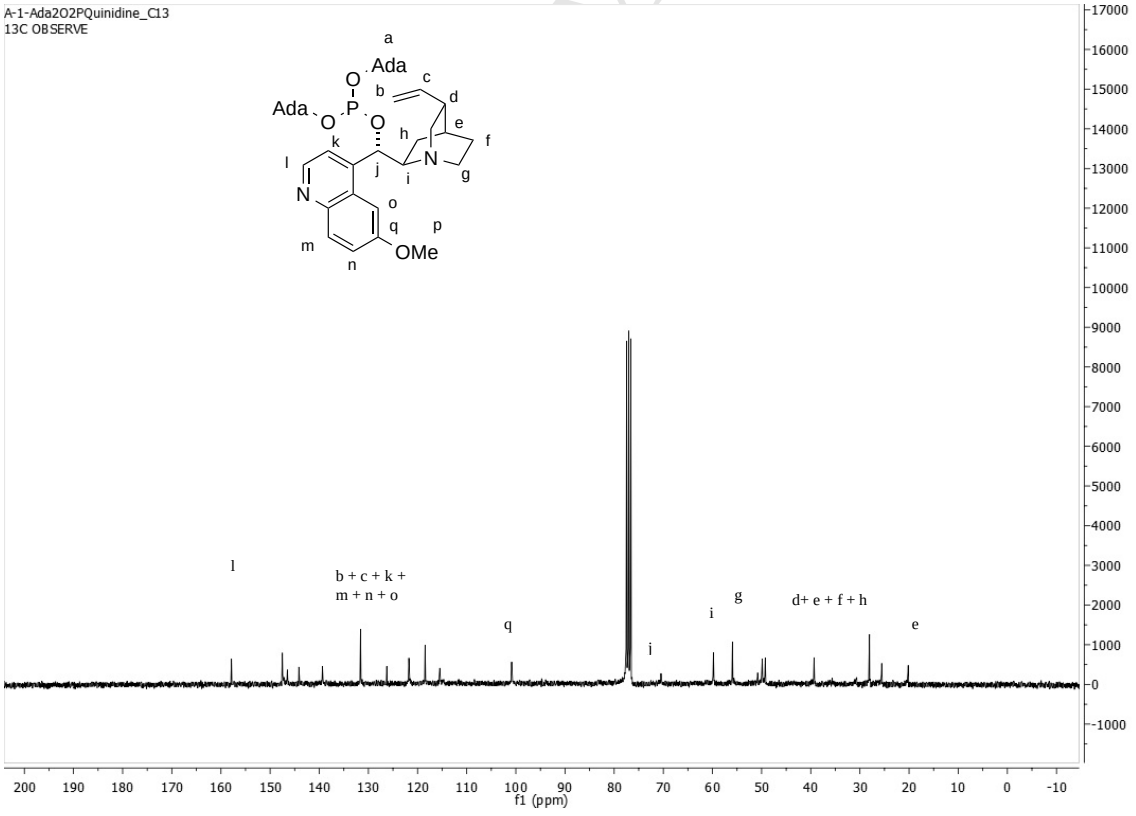
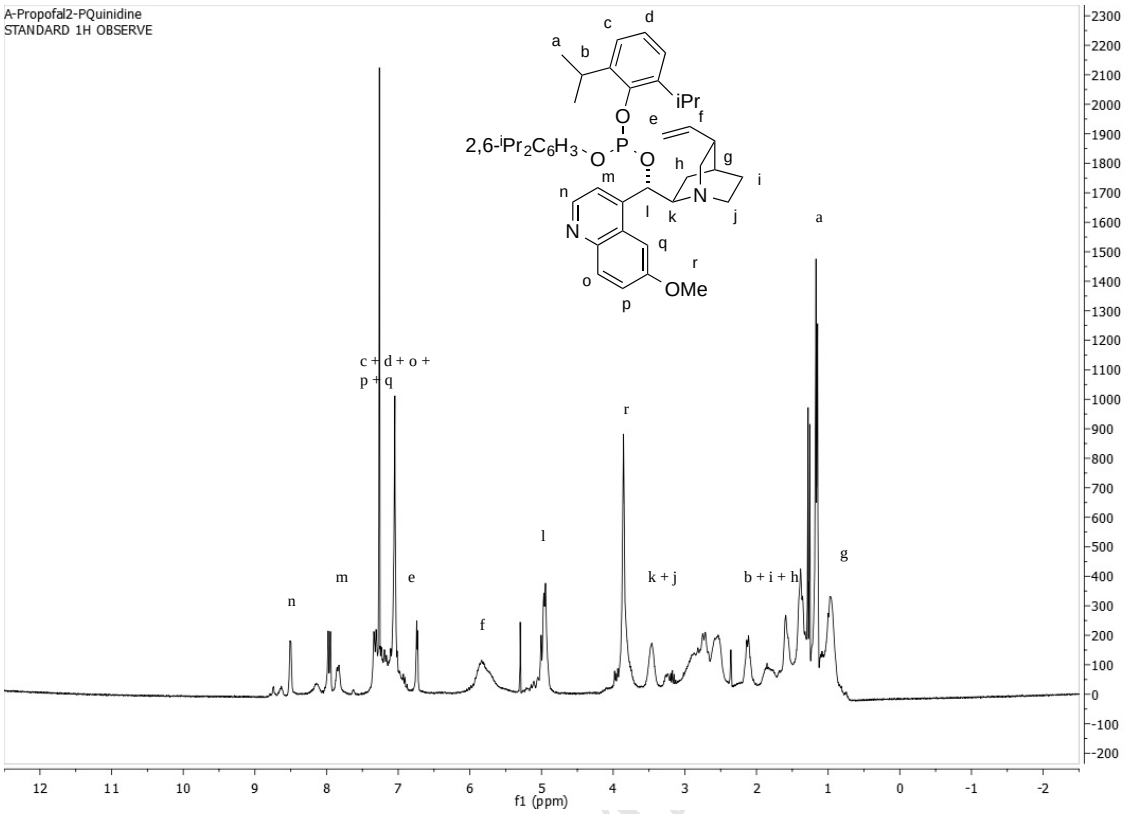
STANDARD 1H OBSERVE
Ada
OMe
l
k
m + o + c
b
j
p
g + i
a + d + f
+ h
e
f1 (ppm)


A-1-Ada2O2PQuinidine_C13
13C OBSERVE
Ada
OMe
l
b + c + k +
m + n + o
q
i
g
d+ e + f + h
e
f1 (ppm)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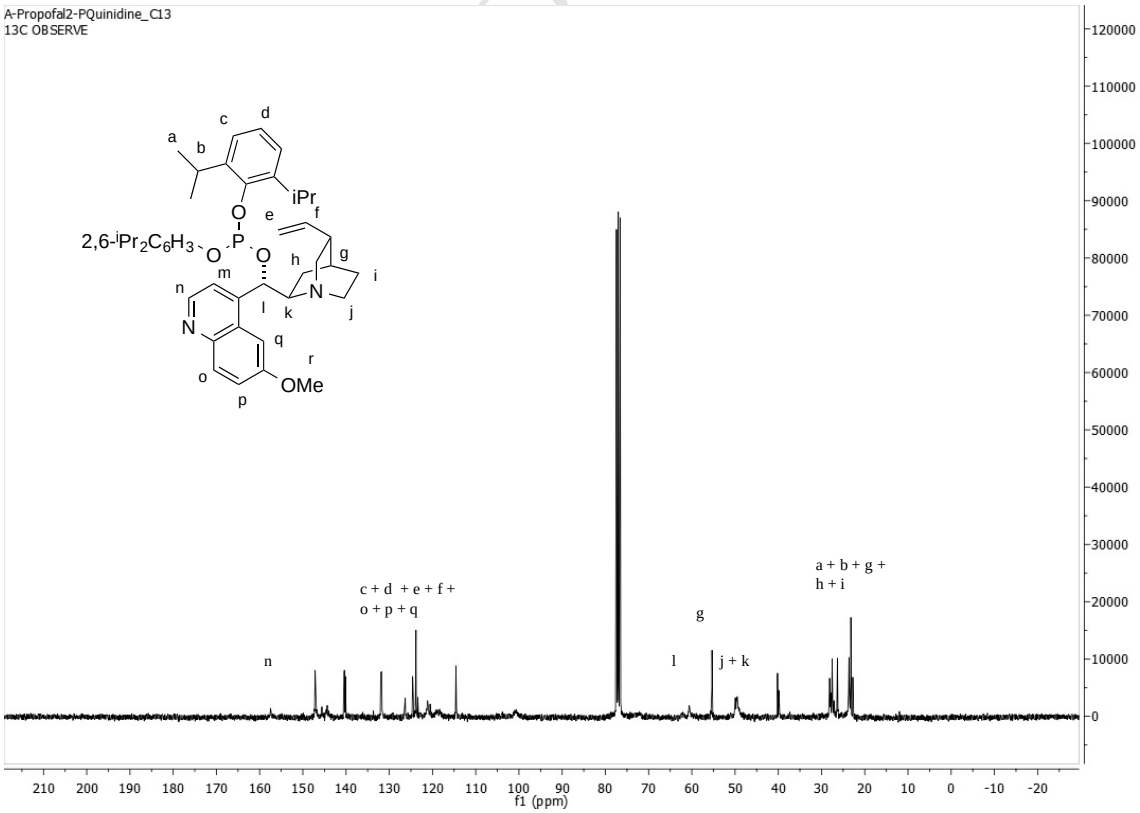
STANDARD 1H OBSERVE
2,6-iPr2C6H3
iPr
OMe
c + d + o + p + q
r
l
a
g
m
e
n
f
k + j
b + i + h
f1 (ppm)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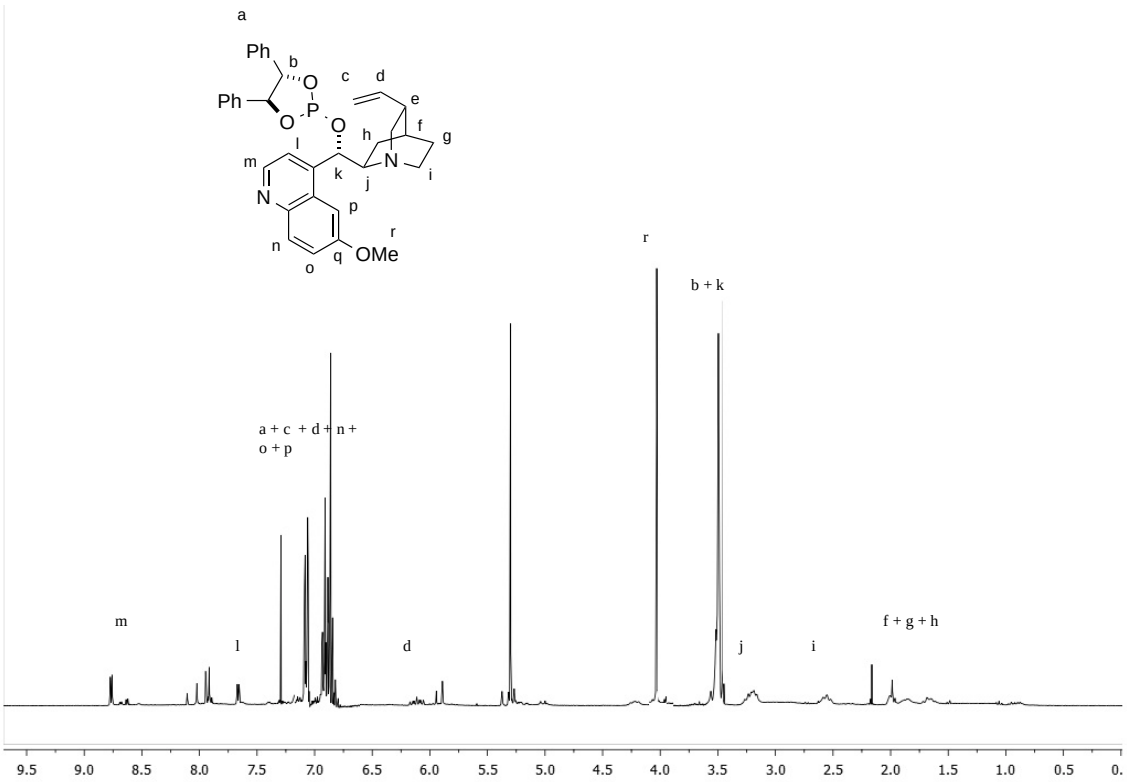
13C OBSERVE
2,6-iPr2C6H3
iPr
OMe
c + d + e + f + o + p + q
a + b + g + h + i
g
n
l
j + k
f1 (ppm)


a
Ph
Ph
O
P
O
O
N
OMe
r
b + k
a + c + d + n + o + p
m
l
d
j
i
f + g + h
9.5
9.0
8.5
8.0
7.5
7.0
6.5
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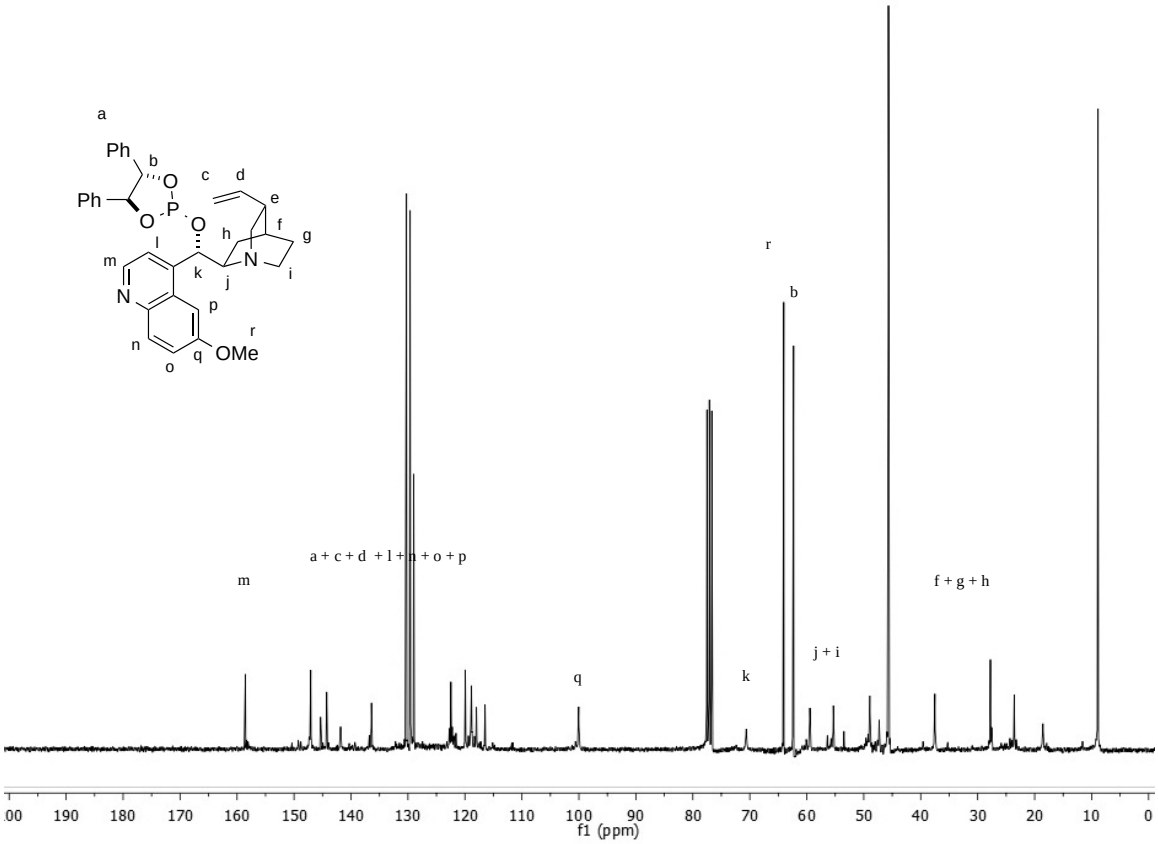
1.0
0.5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Ph
Ph
O
P
O
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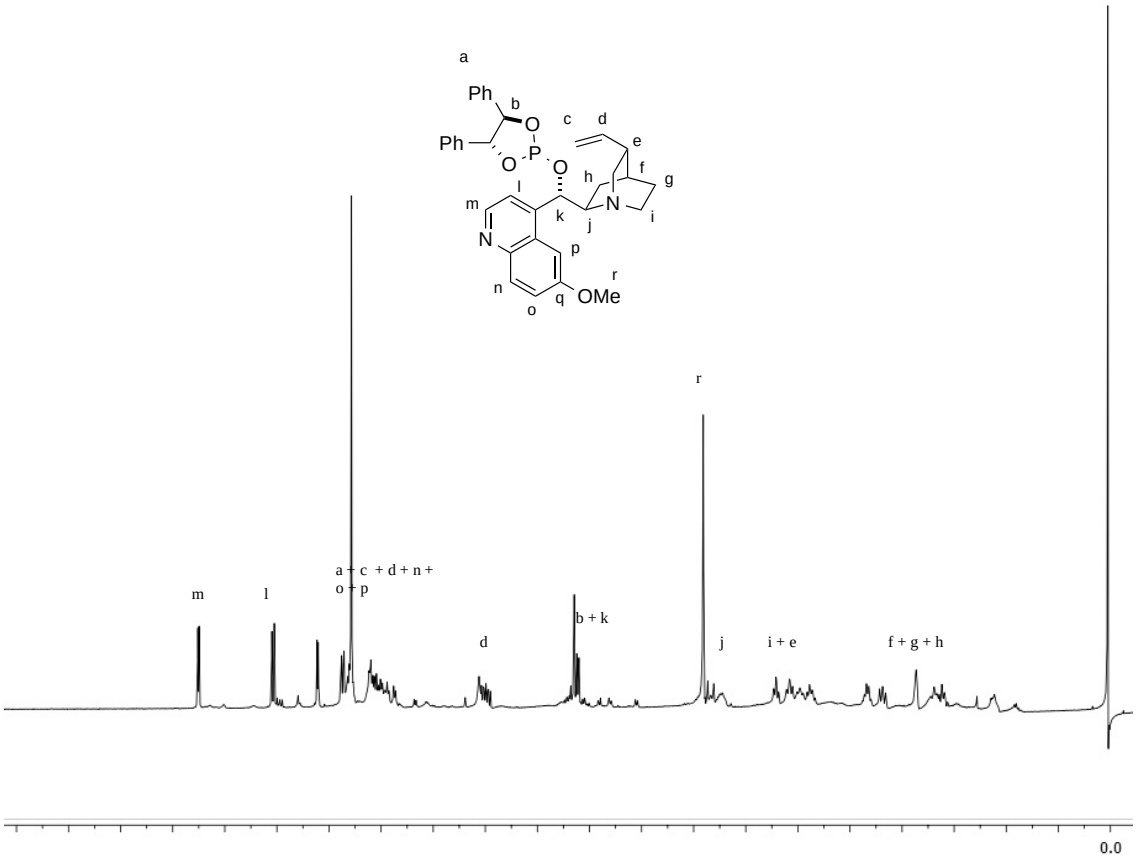
N
OMe
r
b
a + c + d + l + n + o + p
m
q
k
j + i
f + g + h
f1 (ppm)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d
Ph
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P
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f
g
h
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m
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N
j
i
N
p
r
n
q
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l
a + c + d + n +
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b + k
j
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f + g + h
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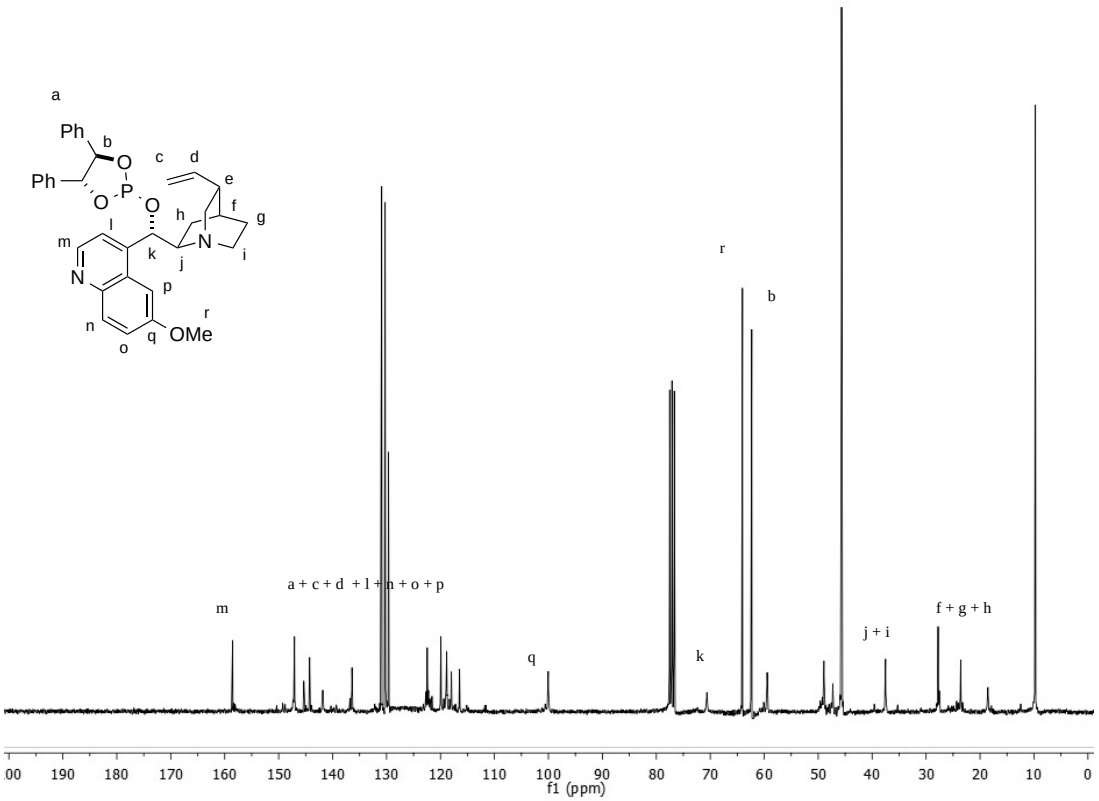
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p
r
n
q
OMe
o
r
b
m
a + c + d + l + n + o + p
q
k
j + i
f + g + h
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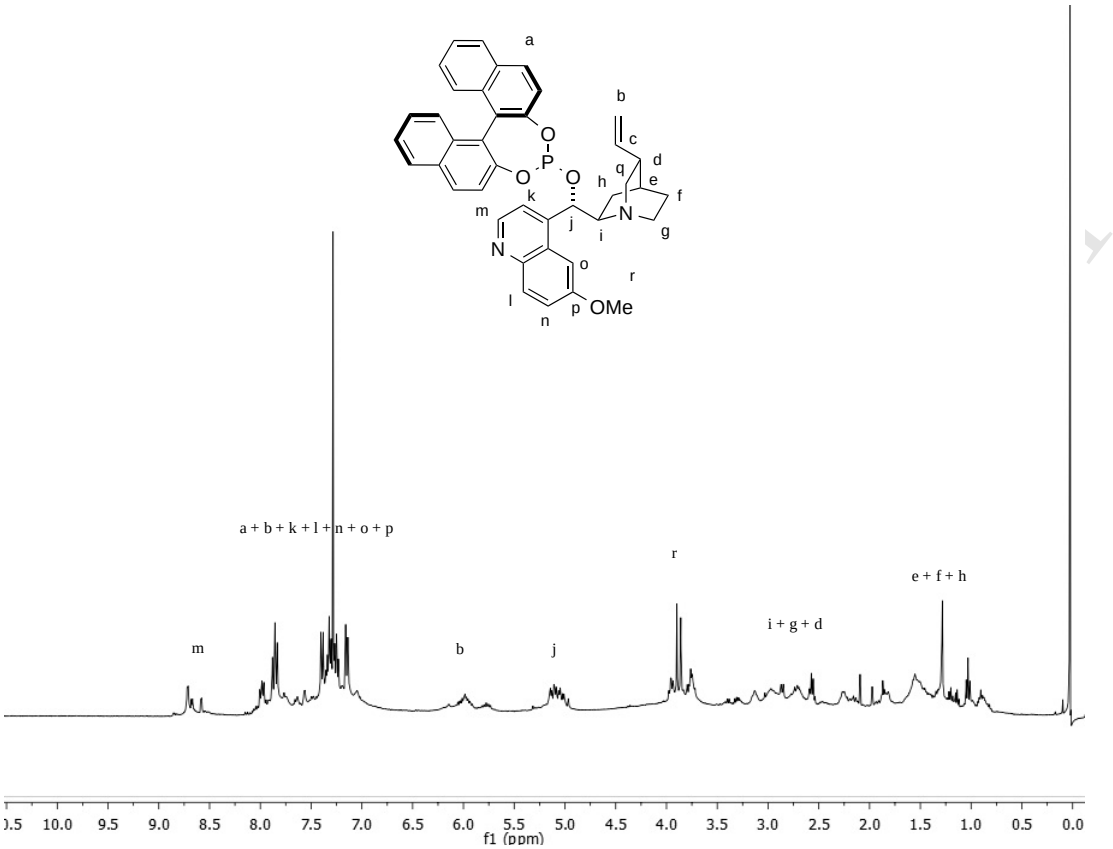
a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
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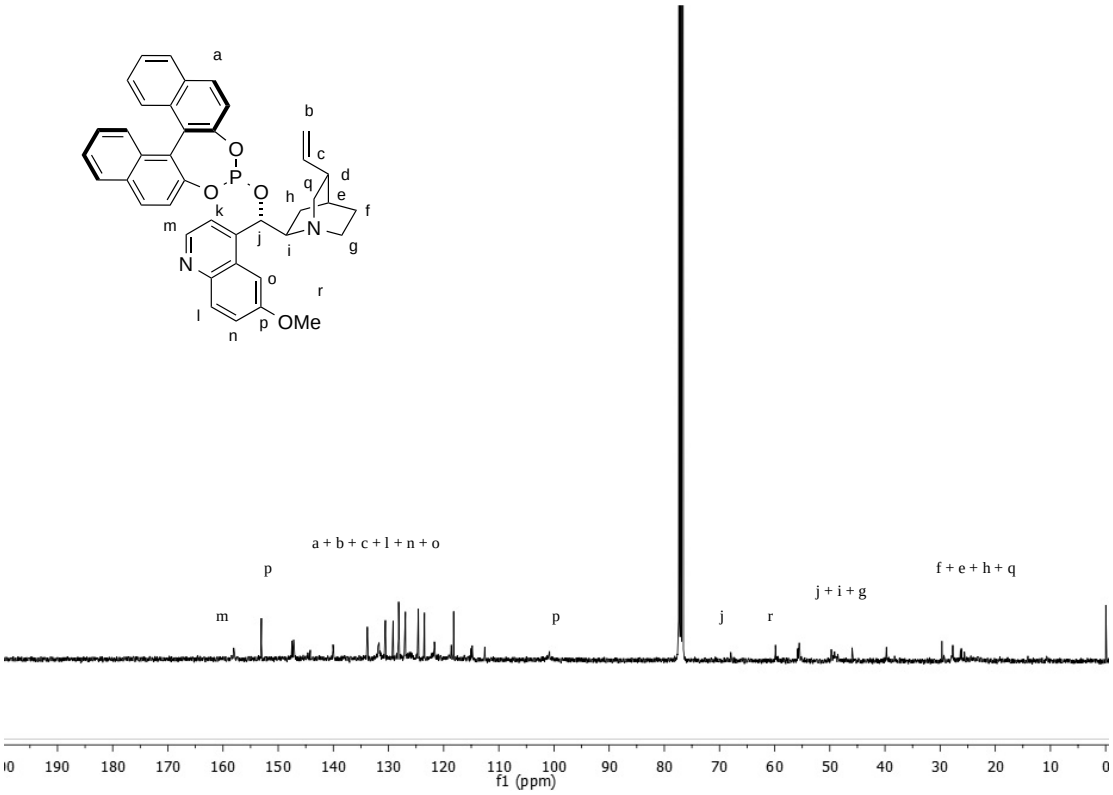
q
r
OMe
a + b + k + l + n + o + p
m
b
j
r
i + g + d
e + f + h
f1 (ppm)


a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
p
q
r
OMe
a + b + c + l + n + o
p
m
p
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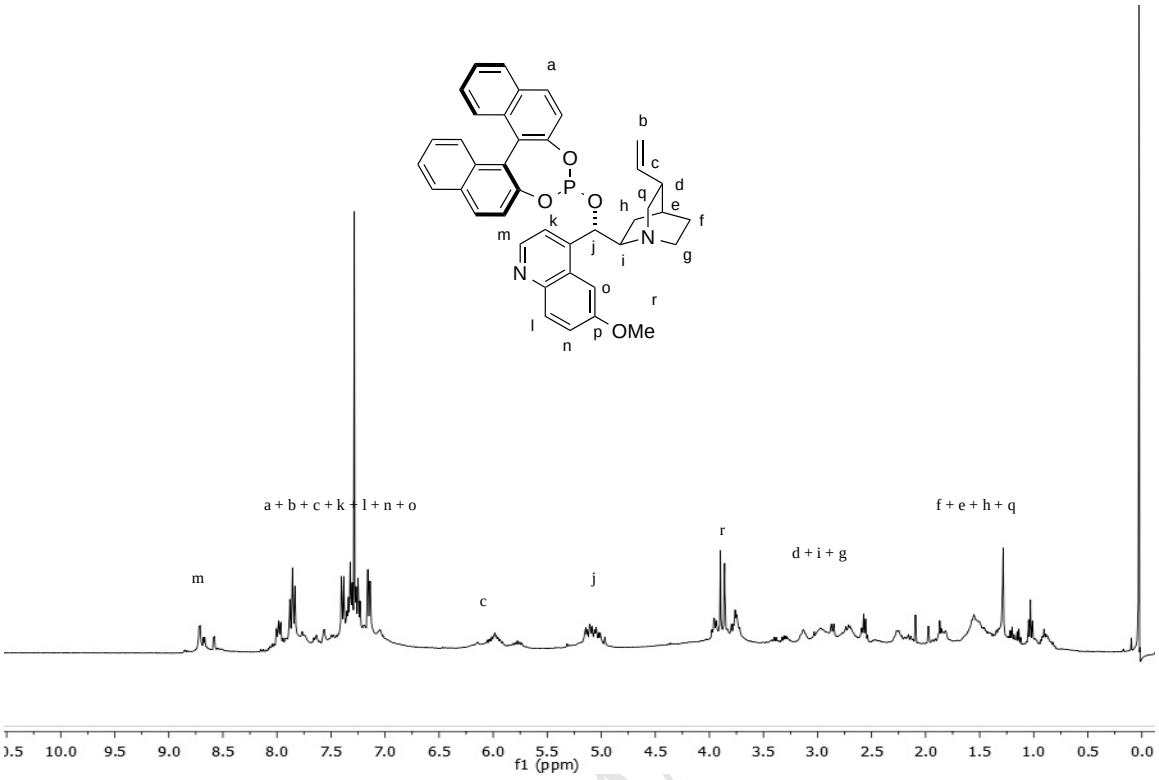
r
j + i + g
f + e + h + q
f1 (ppm)


a
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k
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o
r
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OMe
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a + b + c + k + l + n + o
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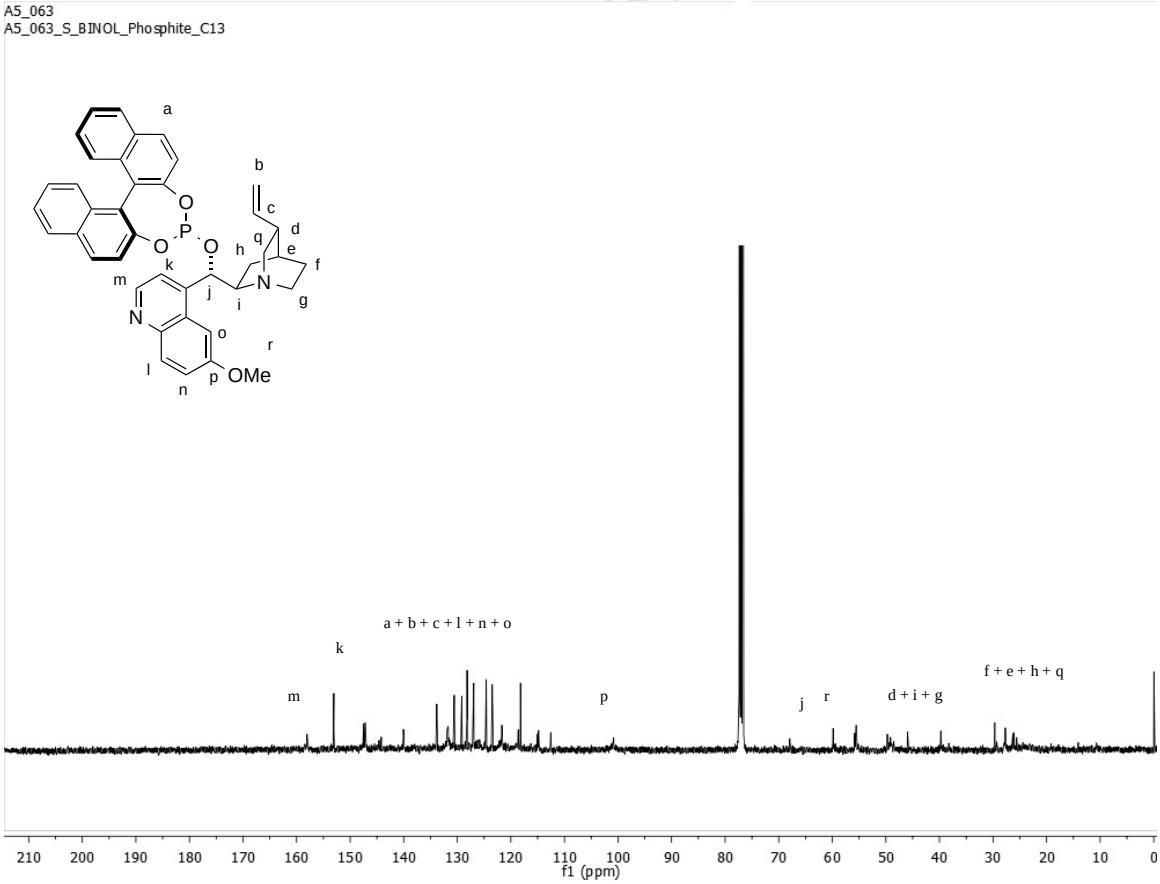
r
d + i + g
f + e + h + q
f1 (ppm)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A5_063_S_BINOL_Phosphite_C13
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m
j
i
N
N
o
r
l
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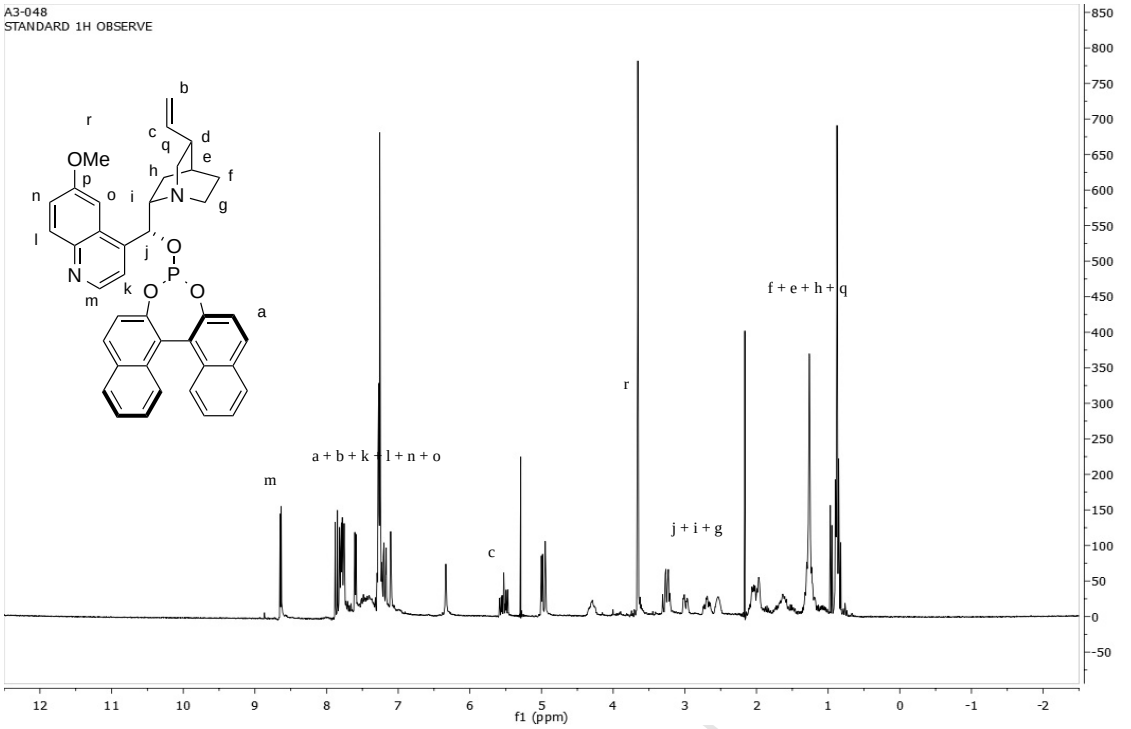
f1 (ppm)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P
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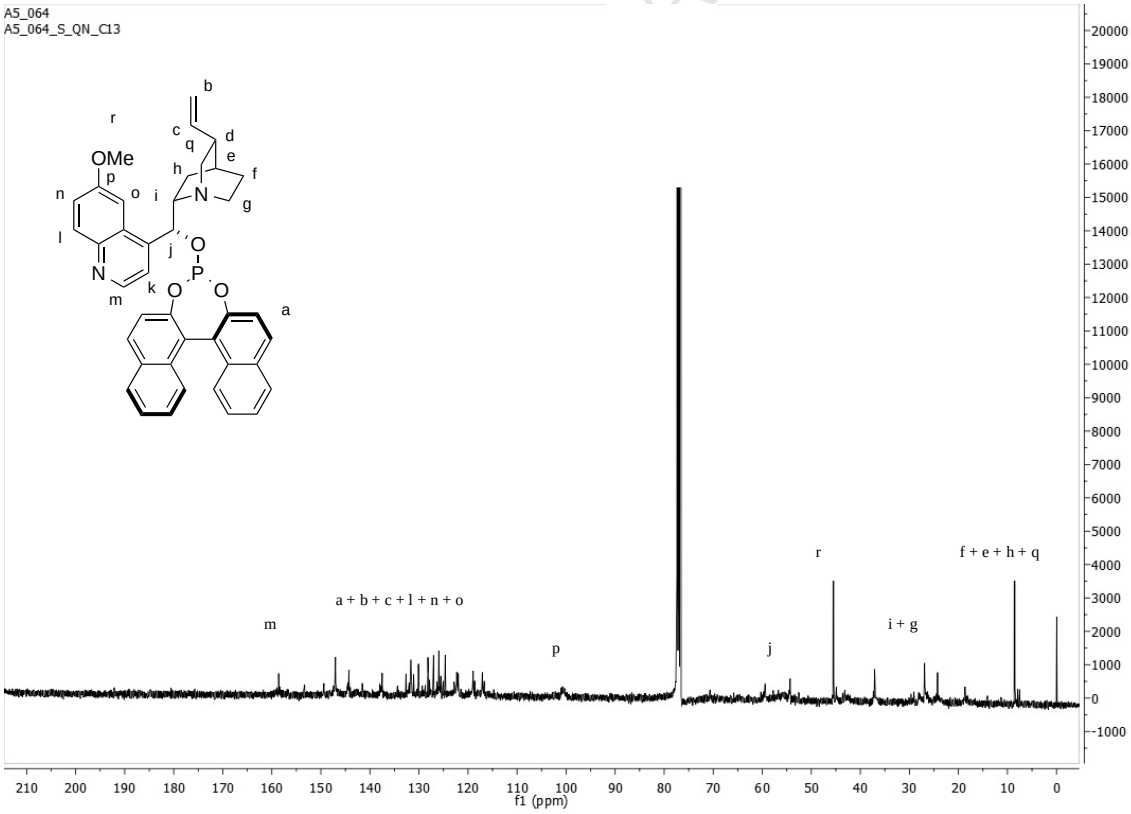
f1 (ppm)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A5_064_S_QN_C13
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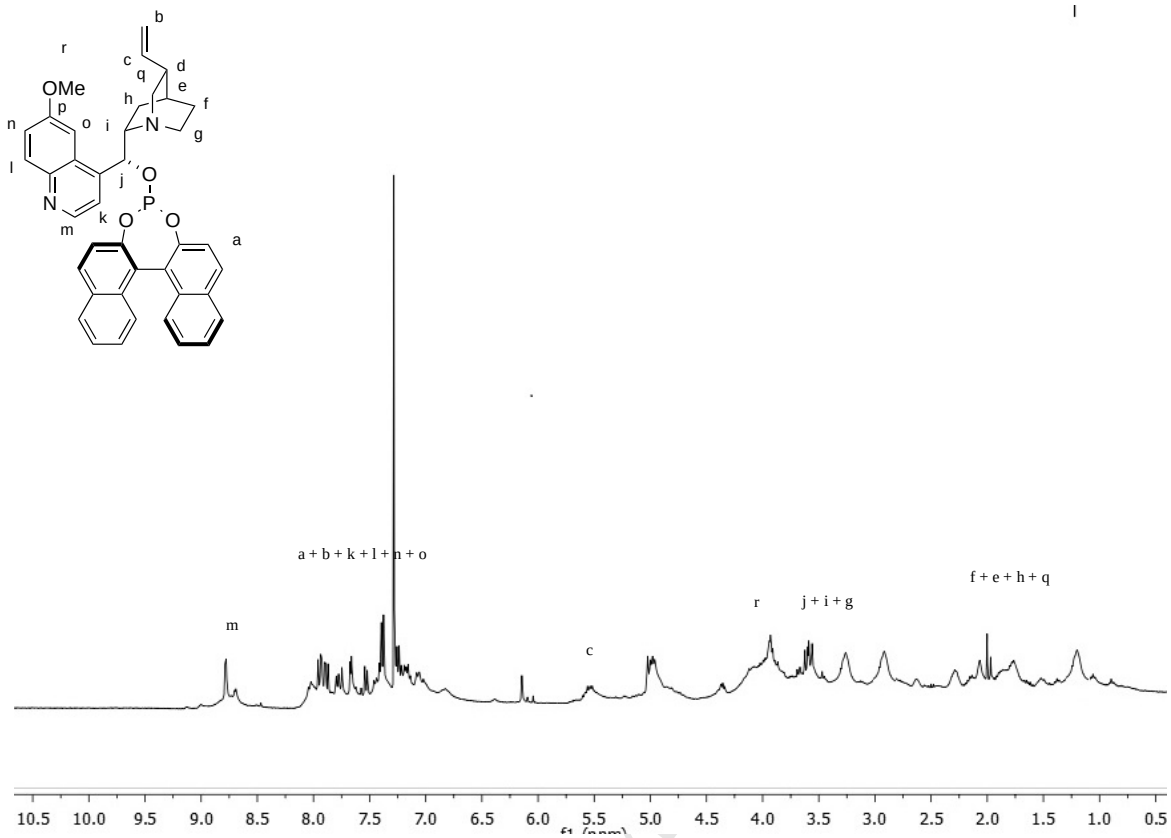
OMe
a + b + k + l + n + o
m
c
r
j + i + g
f + e + h + q
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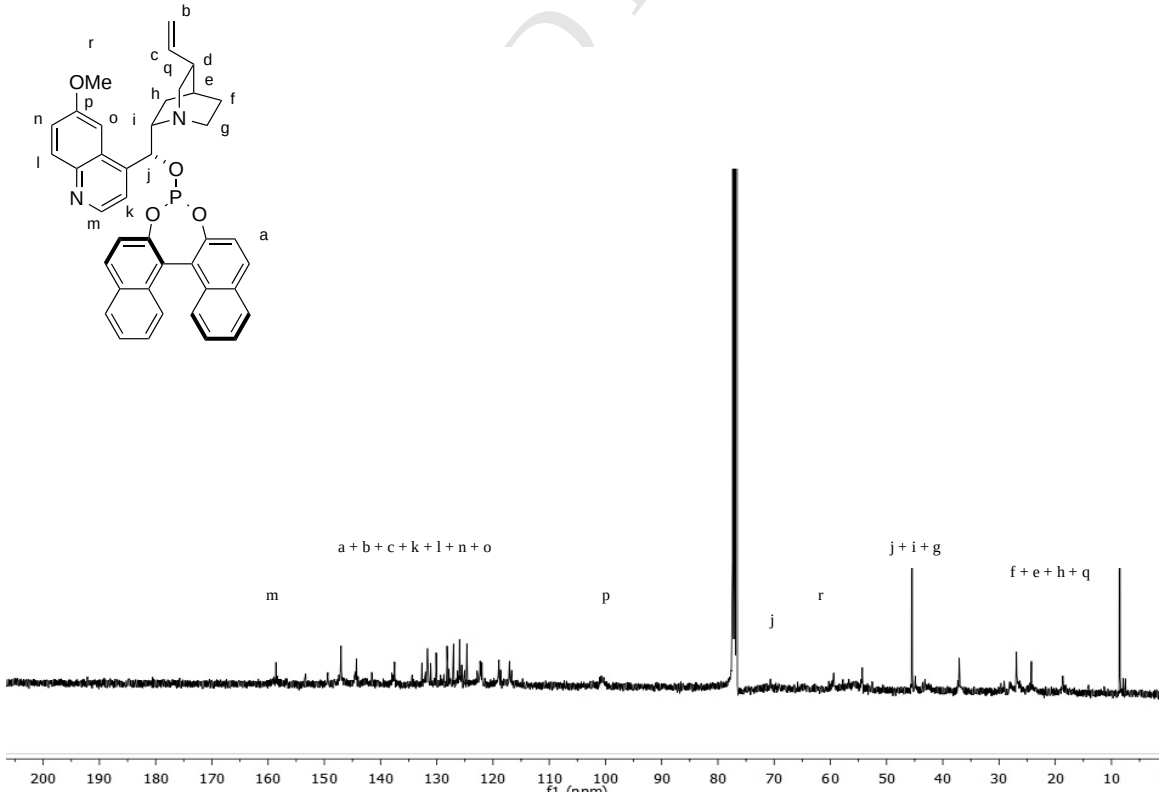
OMe
a + b + c + k + l + n + o
m
p
j
r
j + i + g
f + e + h + q
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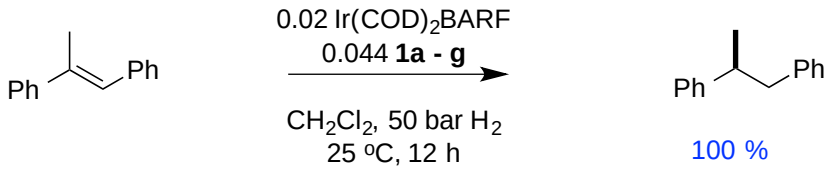
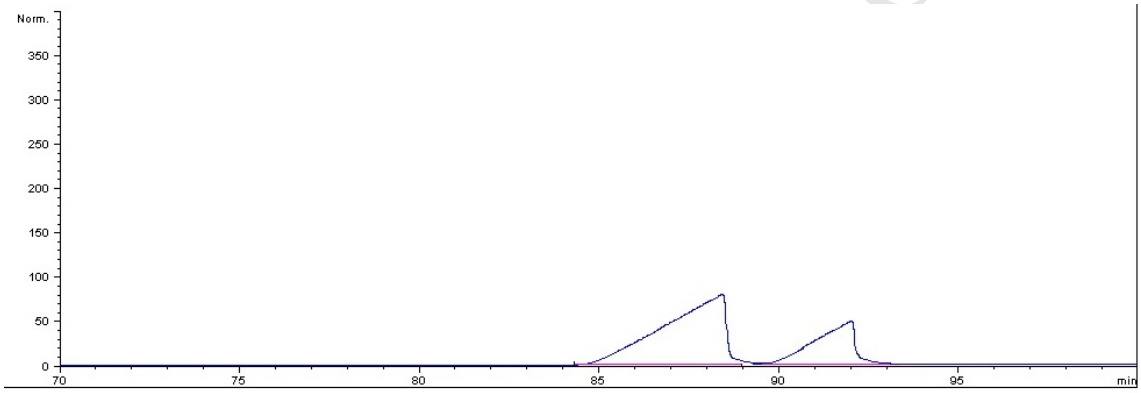
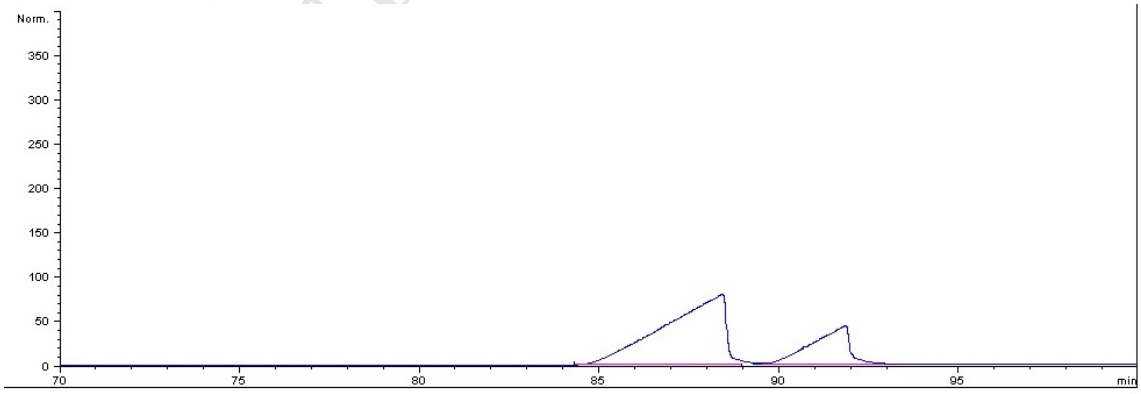
GC Data

Determination of enantiomer using known structure.

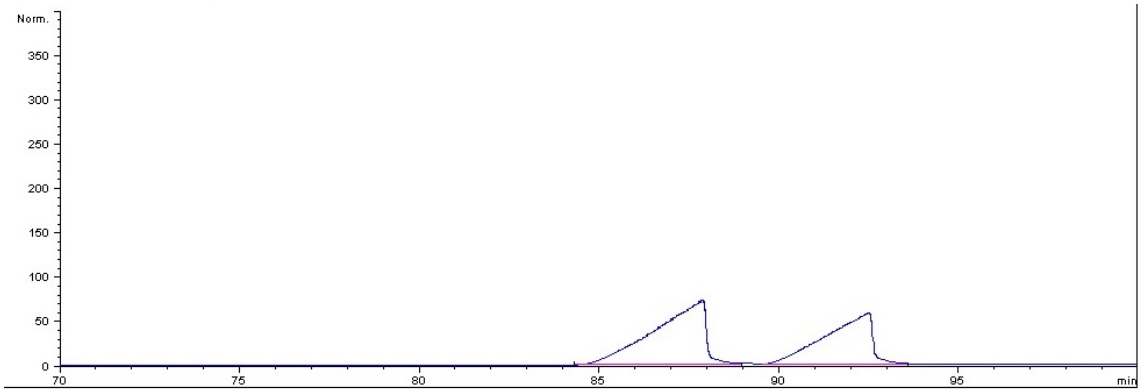




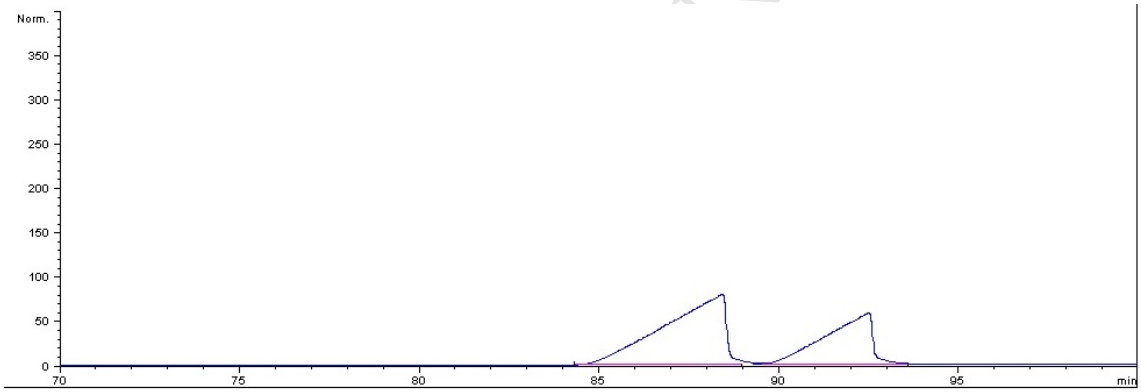
Hydrogenation using **1a**



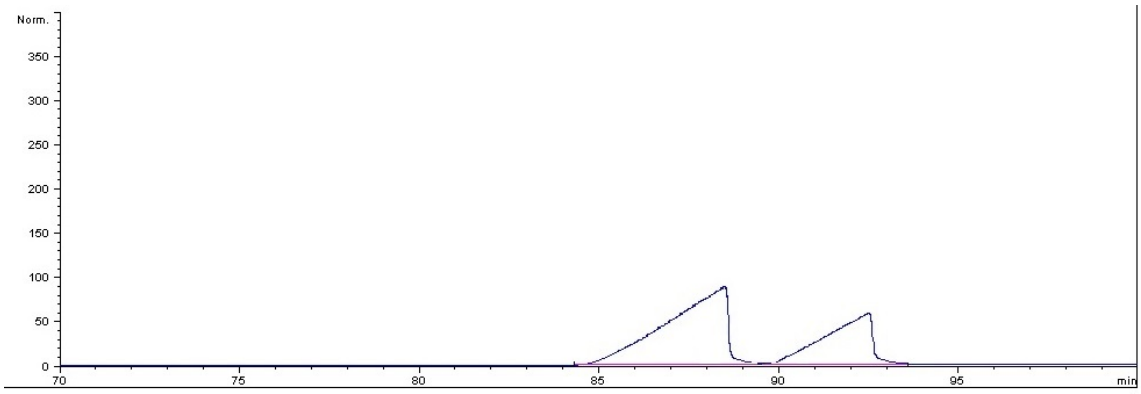
Hydrogenation using **1b**



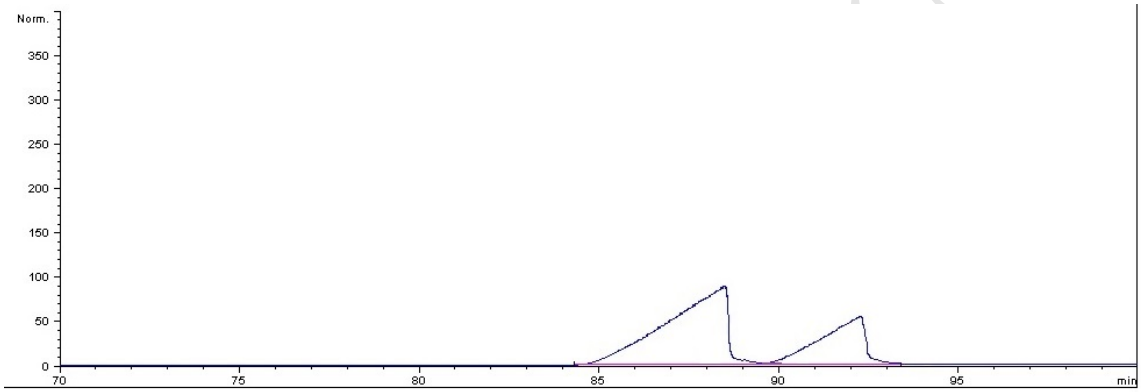
Hydrogenation using **1c**



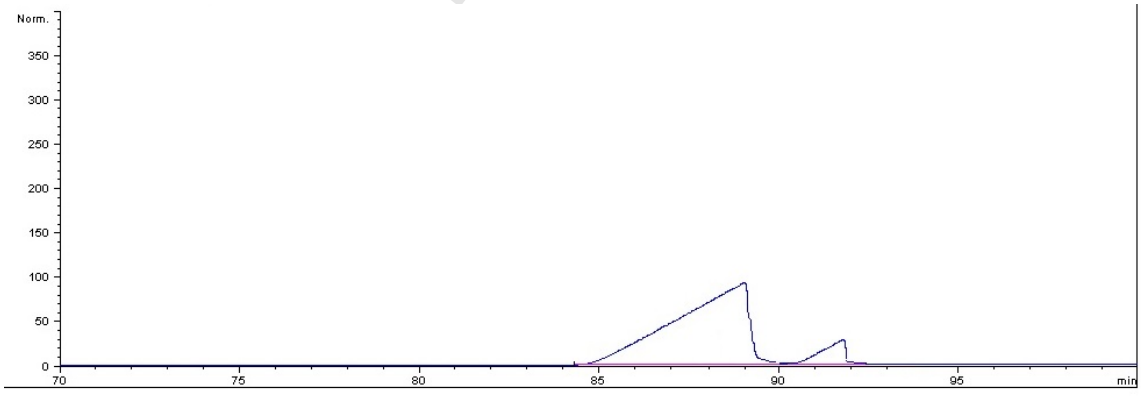
Hydrogenation using **1d**



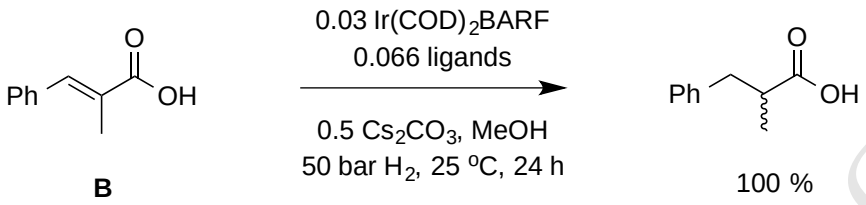
Hydrogenation using **1e**



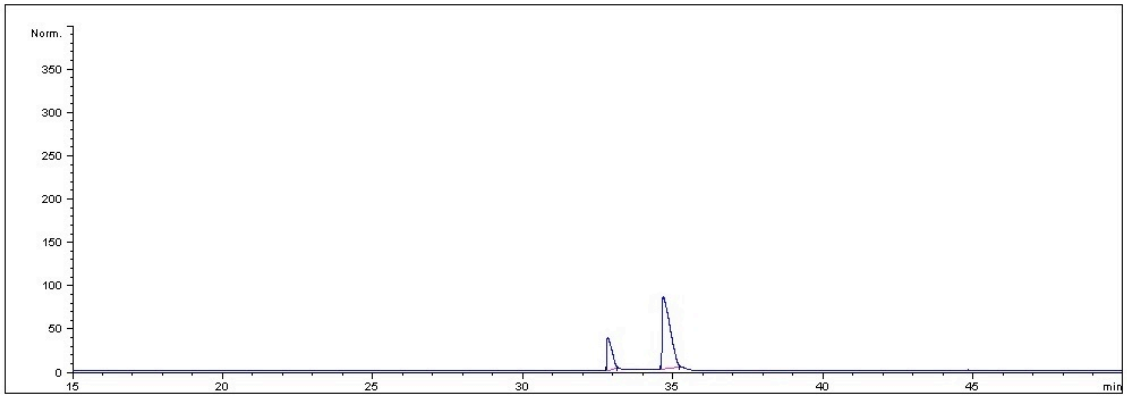
Hydrogenation using **1f**



Hydrogenation using **1g**



B 100 %



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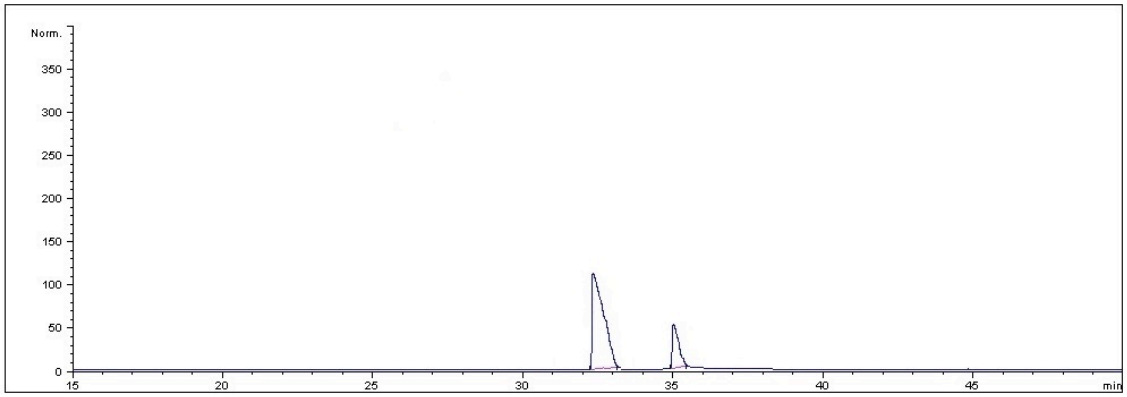
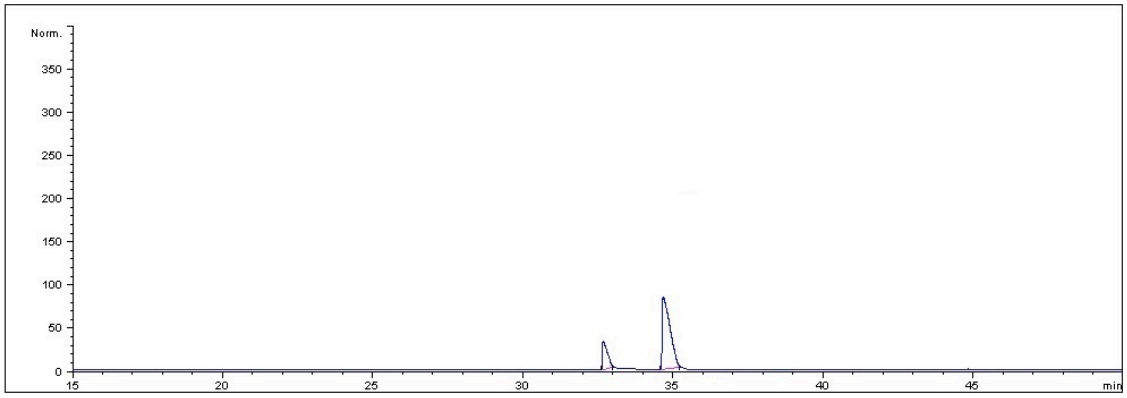
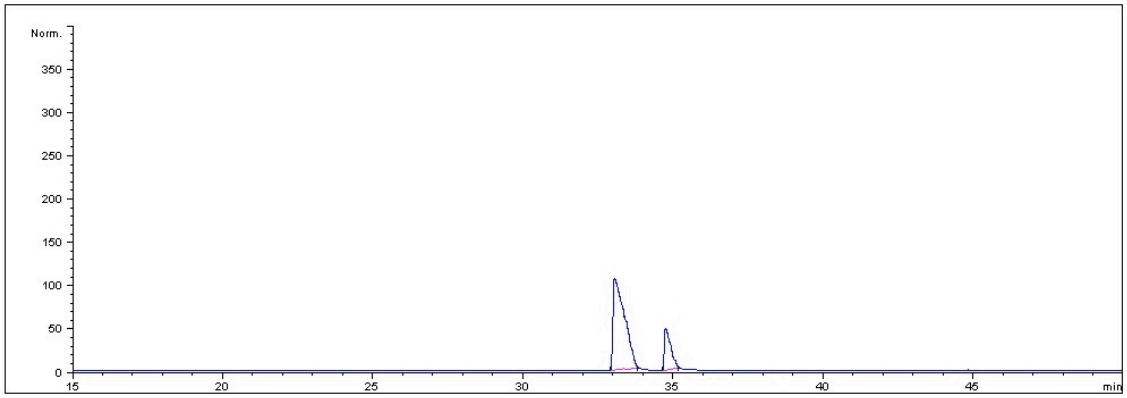


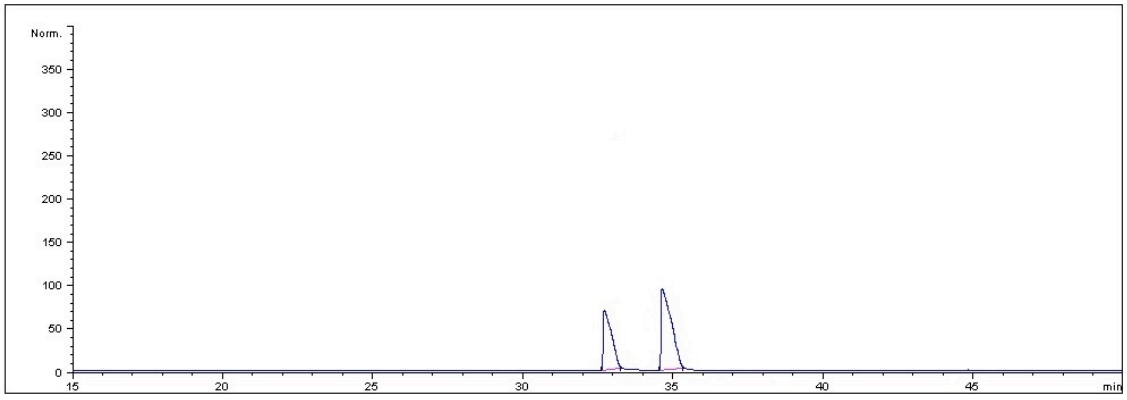
Hydrogenation using **1h**



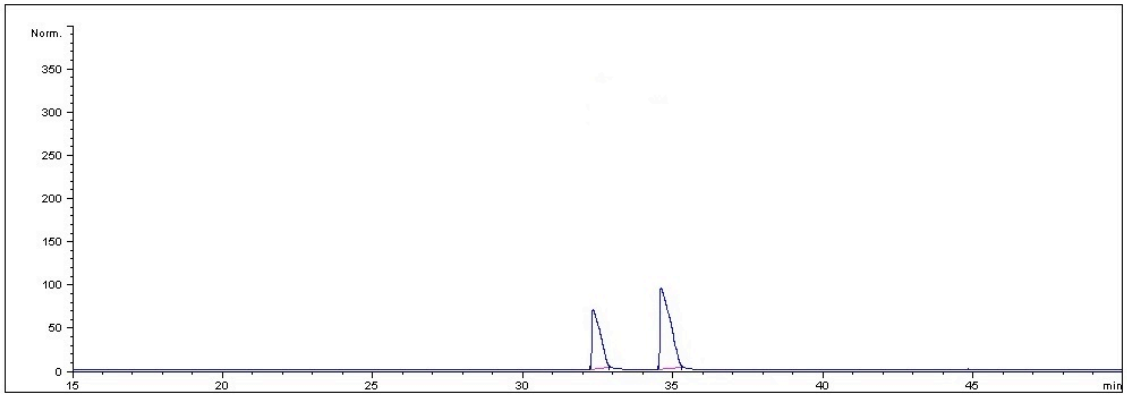
Hydrogenation using **2g**



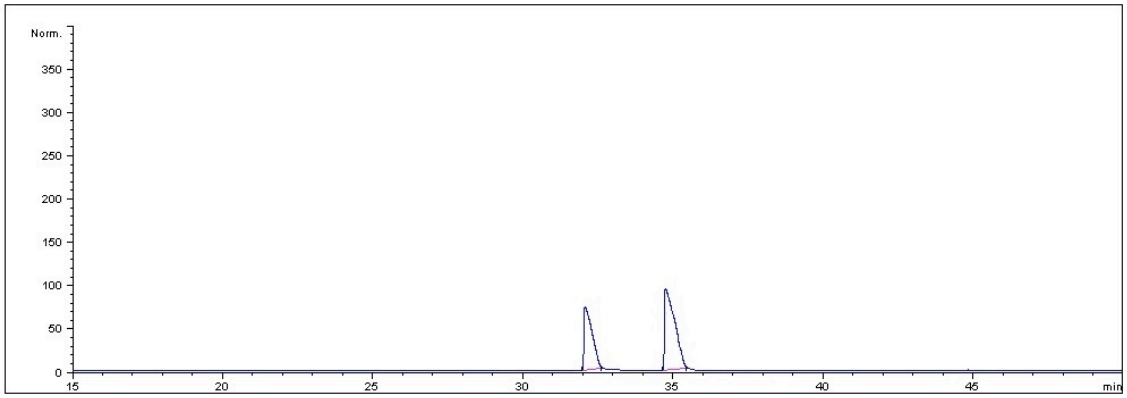
Hydrogenation using **2h**



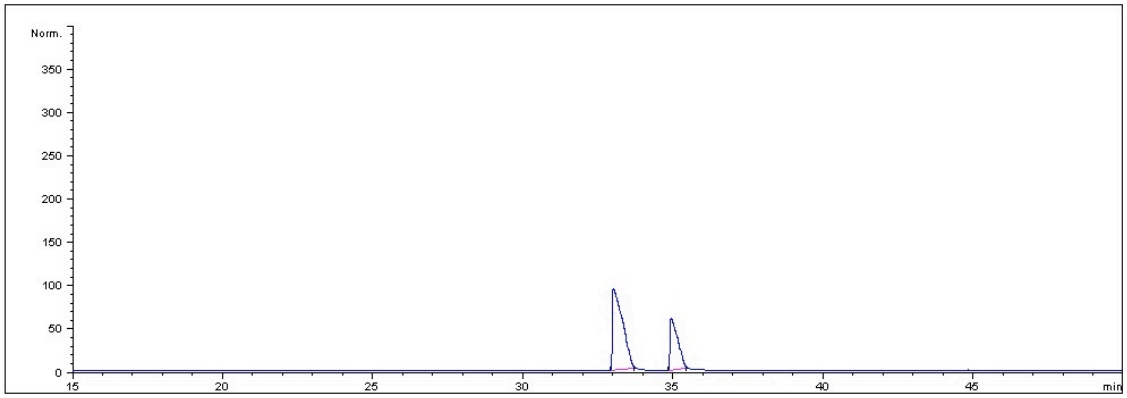
Hydrogenation using **1g + 1h**



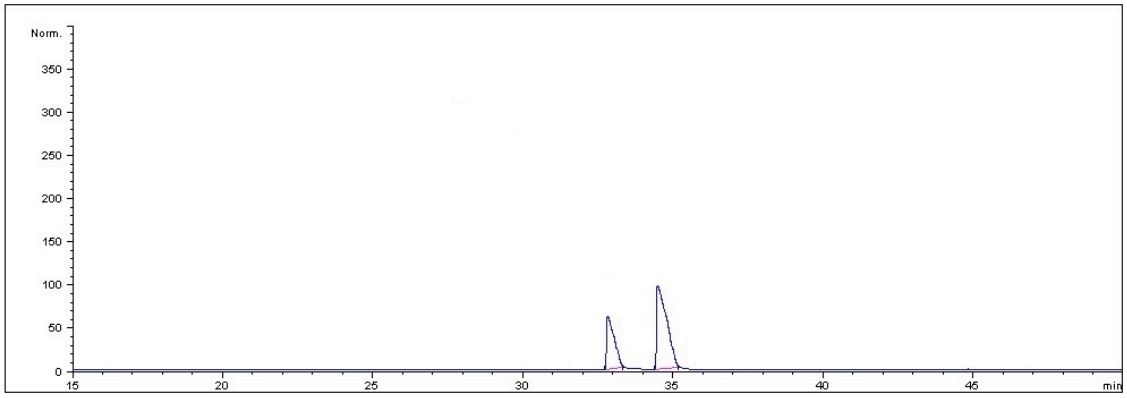
Hydrogenation using **1g + 2h**



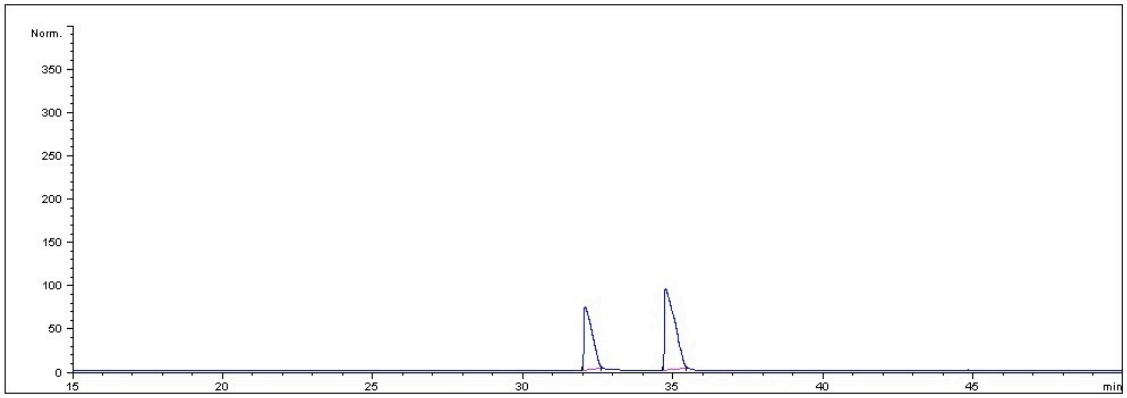
Hydrogenation using **1h + 2g**



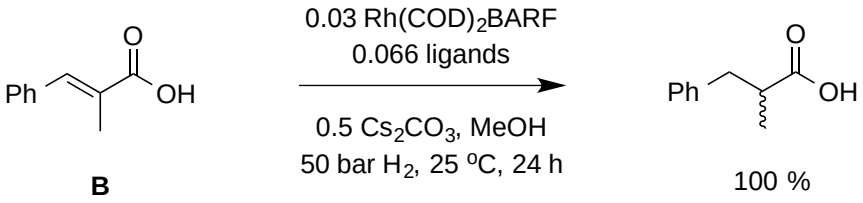
Hydrogenation using **1h + 2h**



Hydrogenation using **2g + 2h**

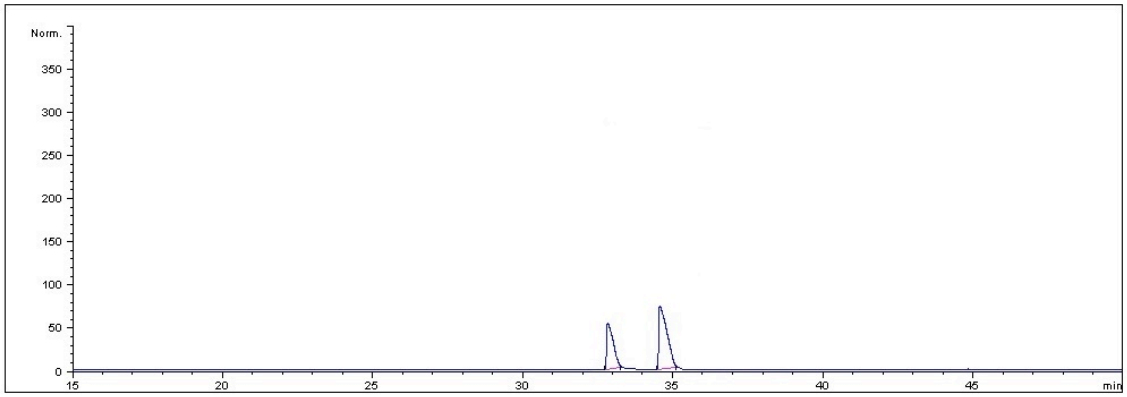


Hydrogenation using **1g + 2g**

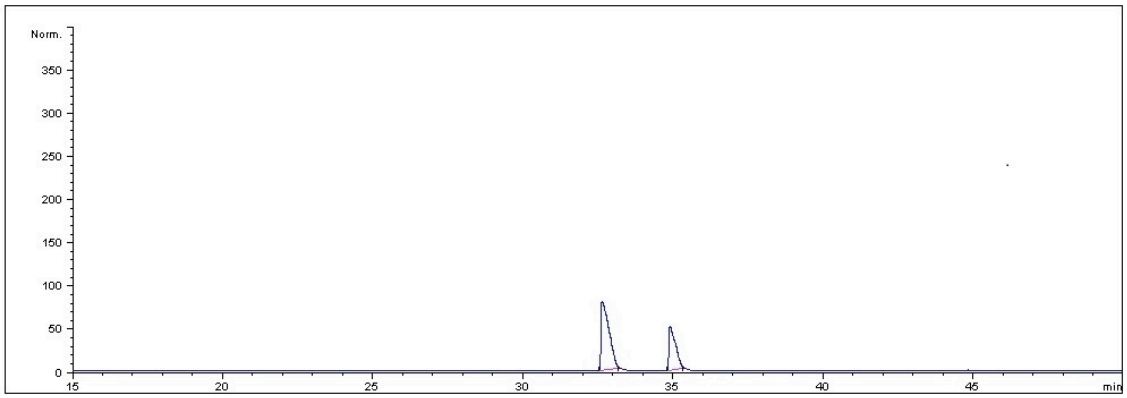


B

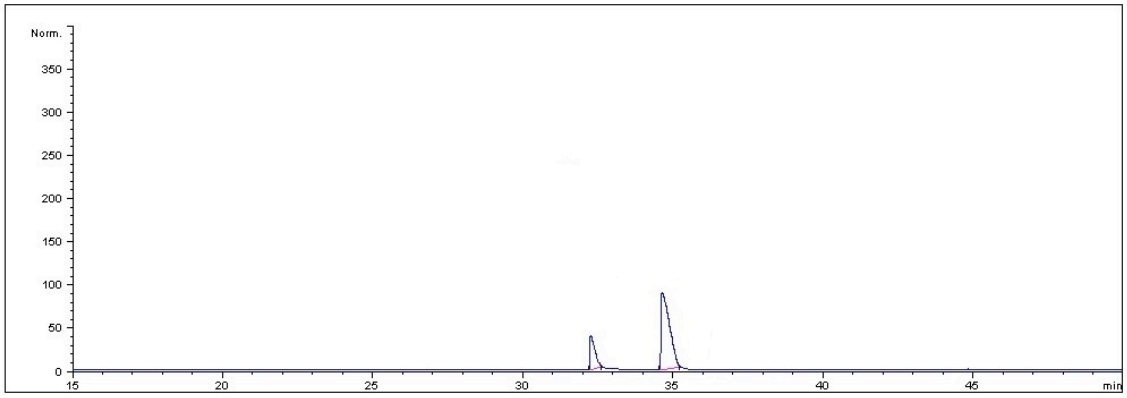
100 %



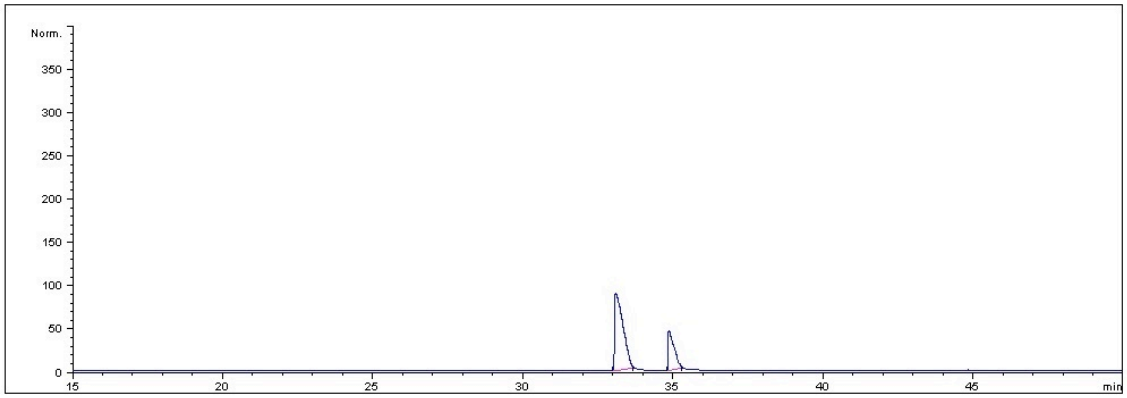
Hydrogenation using **1g**



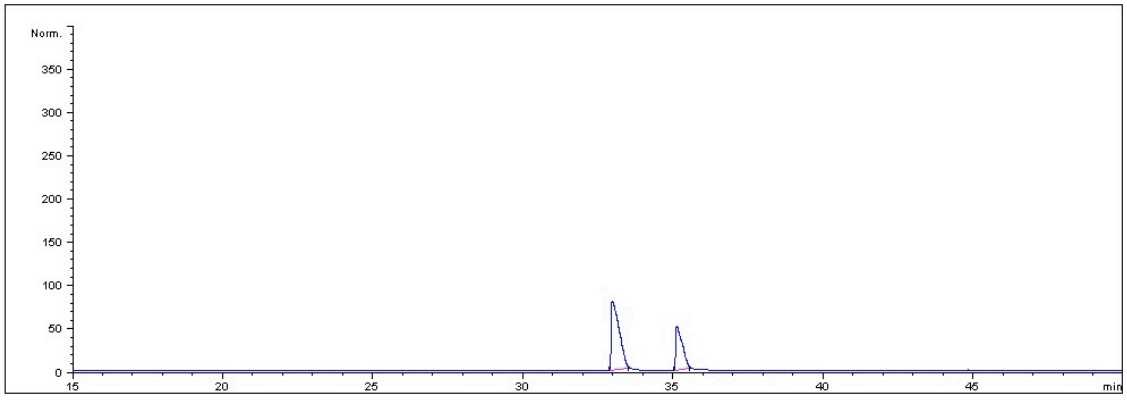
Hydrogenation using **1h**



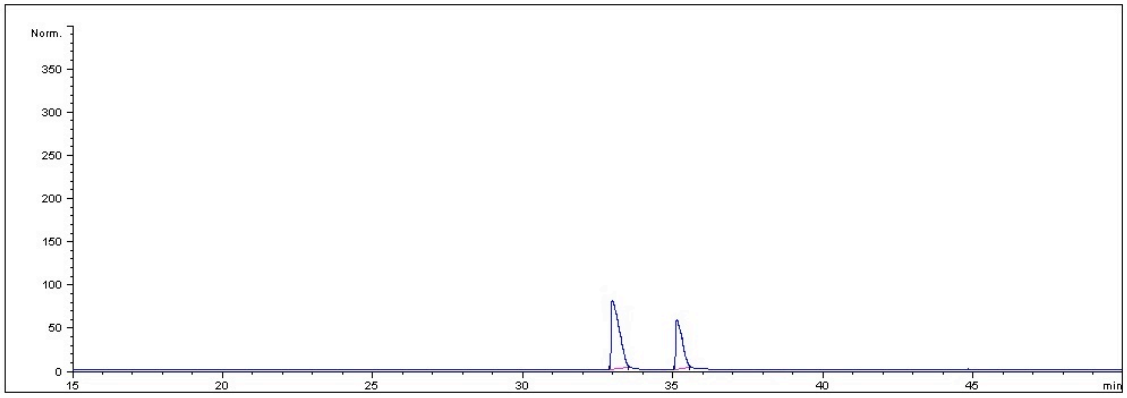
Hydrogenation using **2g**



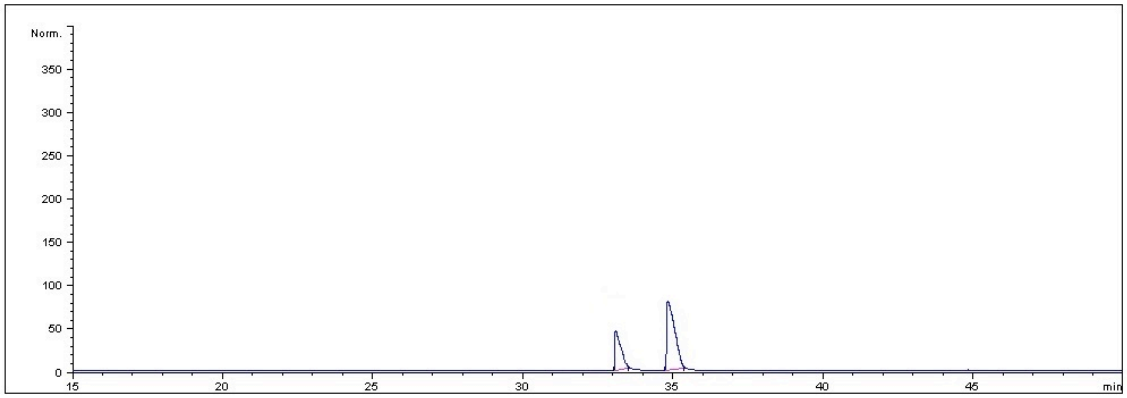
Hydrogenation using **2h**



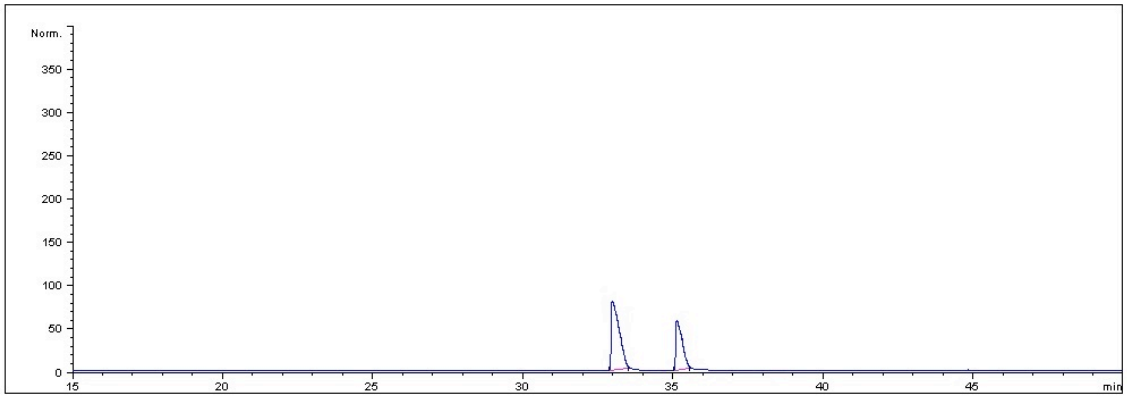
Hydrogenation using **1g + 1h**



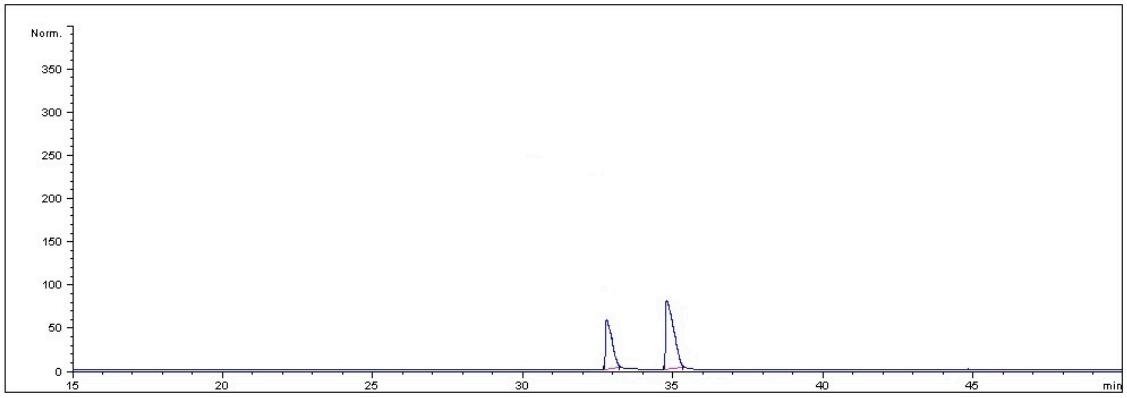
Hydrogenation using **1g + 2h**



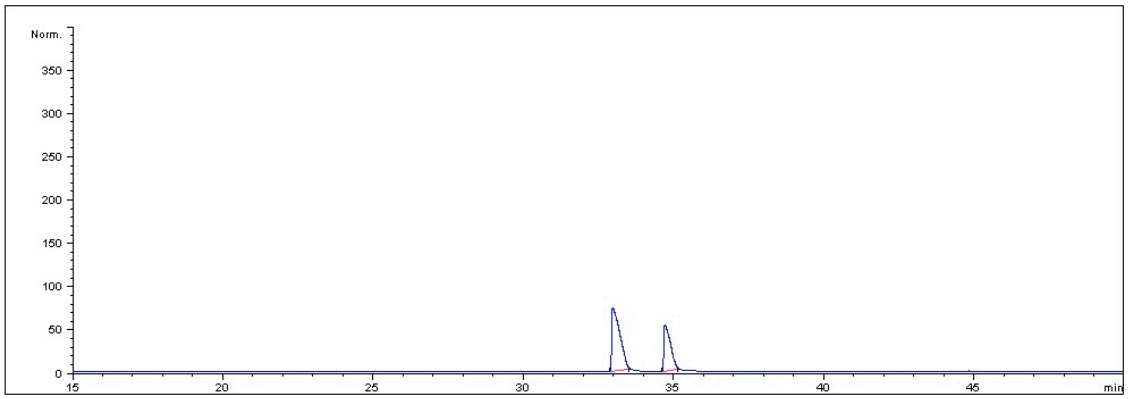
Hydrogenation using **1h + 2g**



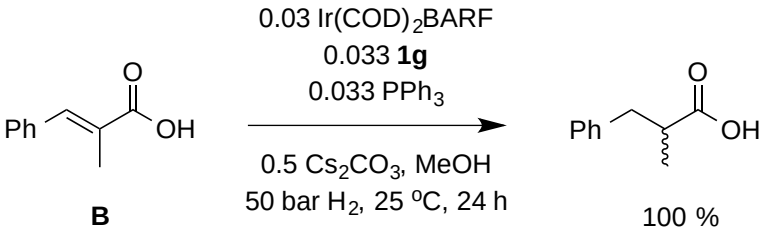
Hydrogenation using **1h + 2h**



Hydrogenation using **2g + 2h**

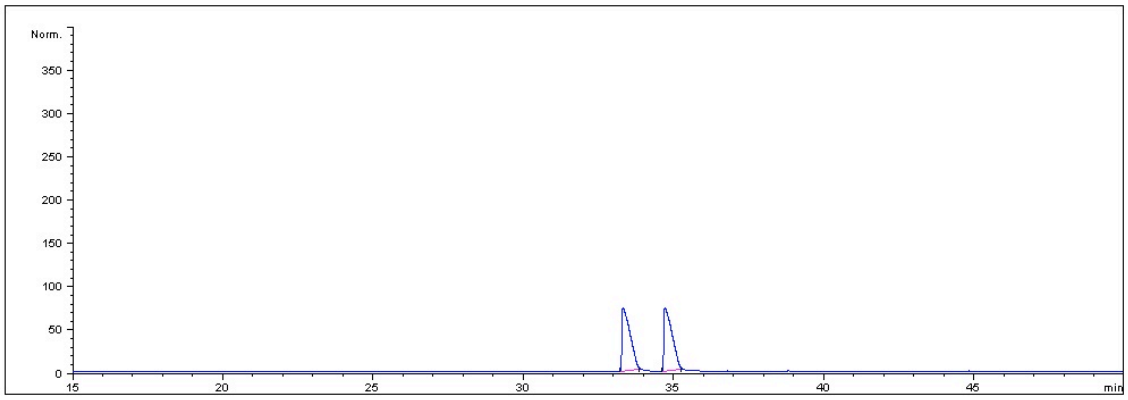


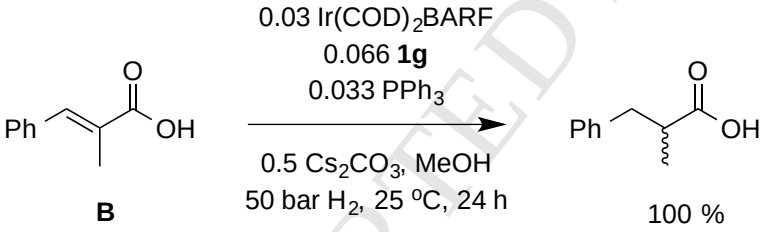
Hydrogenation using **1g + 2g**


0.03 Ir(COD)2BARF
0.033 1g
0.033 PPh3
0.5 Cs2CO3, MeOH
50 bar H2, 25 °C, 24 h
Ph
OH
O

B

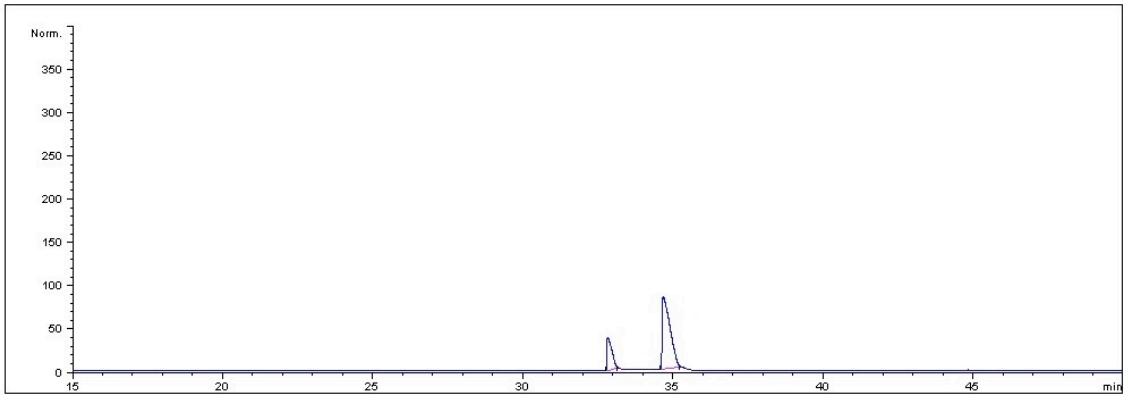
100 %


Norm.
350
300
250
200
150
100
50
0
15
20
25
30
35
40
45
min

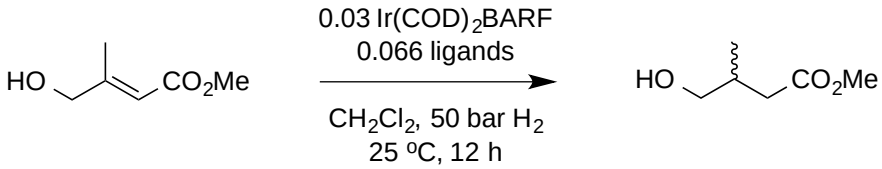

0.03 Ir(COD)2BARF
0.066 1g
0.033 PPh3
0.5 Cs2CO3, MeOH
50 bar H2, 25 °C, 24 h
Ph
OH
O

B

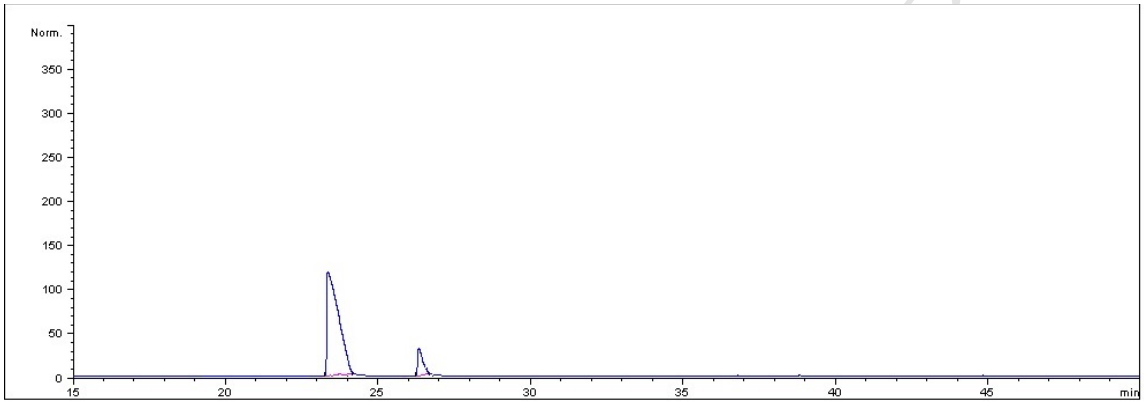
100 %


Norm.
350
300
250
200
150
100
50
0
15
20
25
30
35
40
45
min

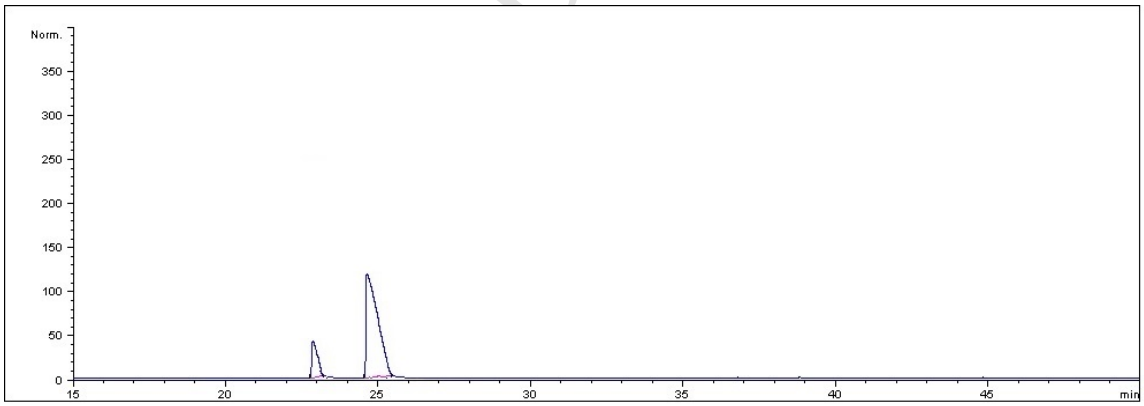
Stereoselectivities were determined using known structure.[2]



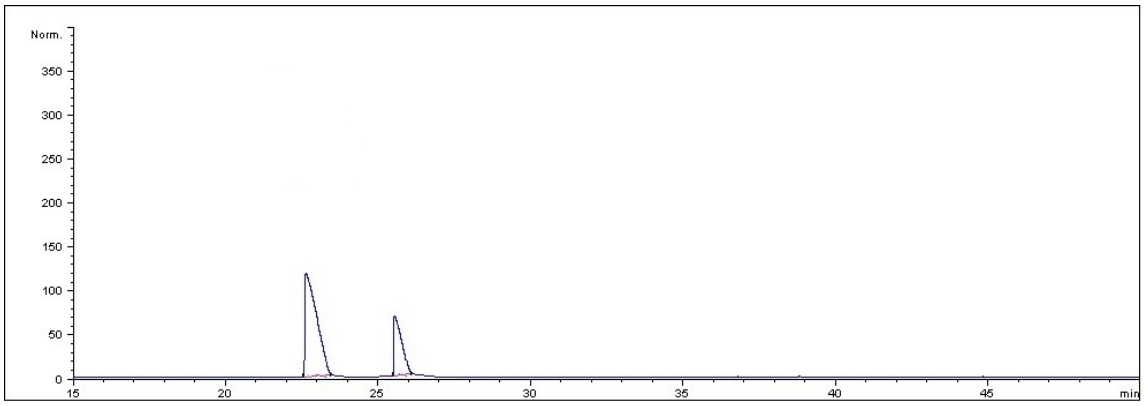
C 100 %



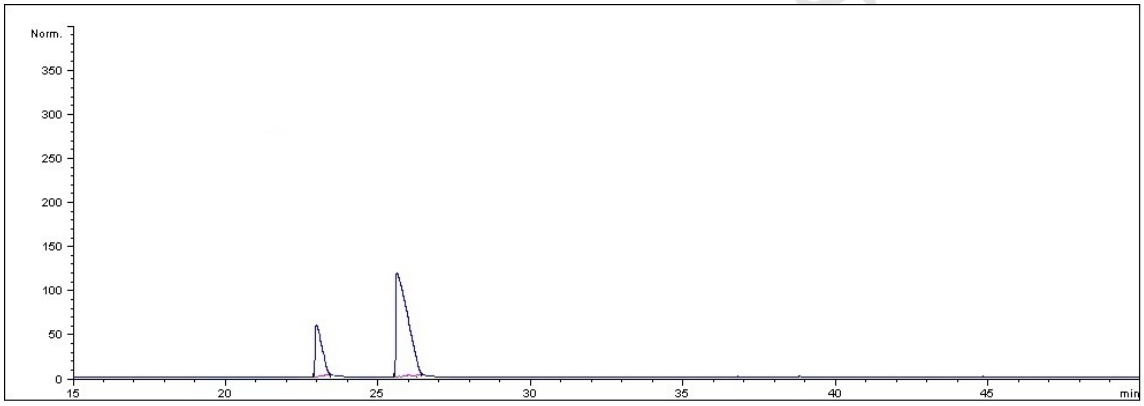
Hydrogenation using **1g**



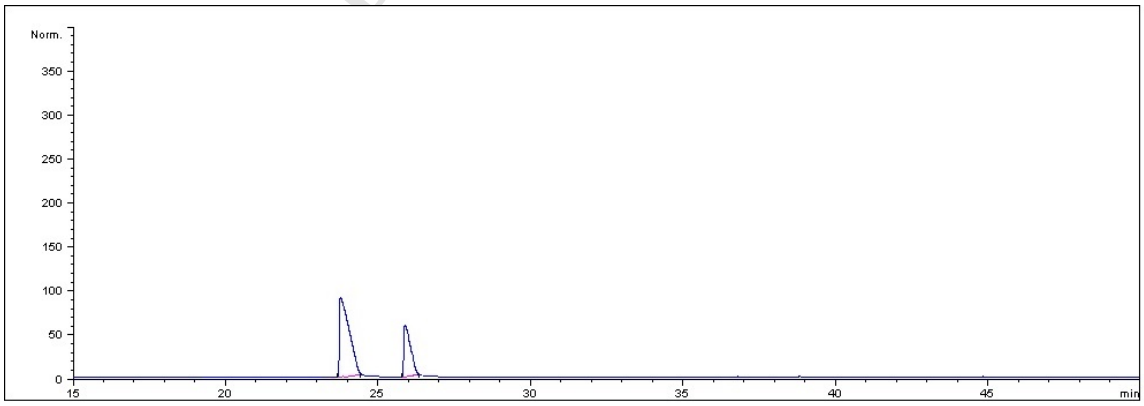
Hydrogenation using **1h**



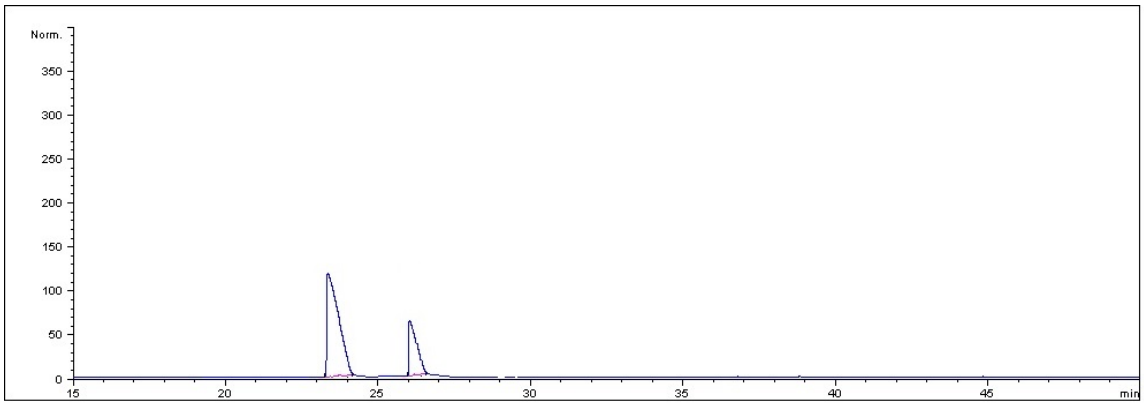
Hydrogenation using **2g**



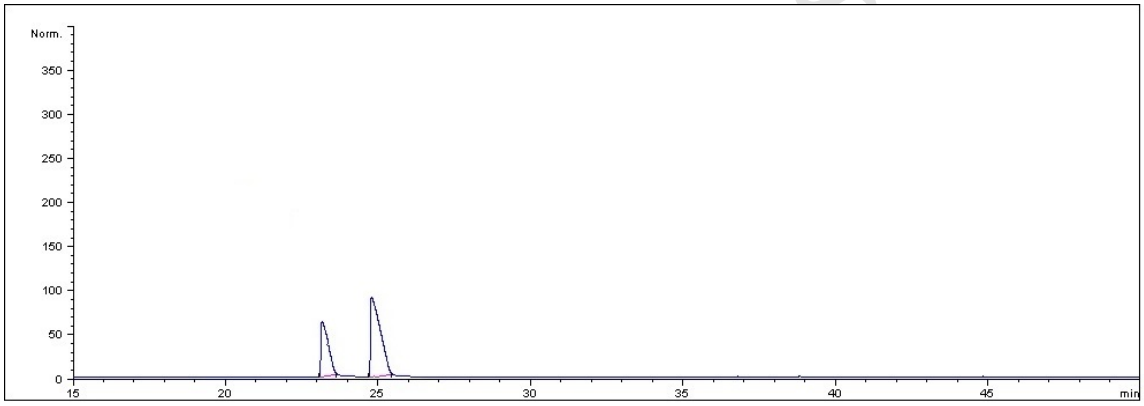
Hydrogenation using **2h**



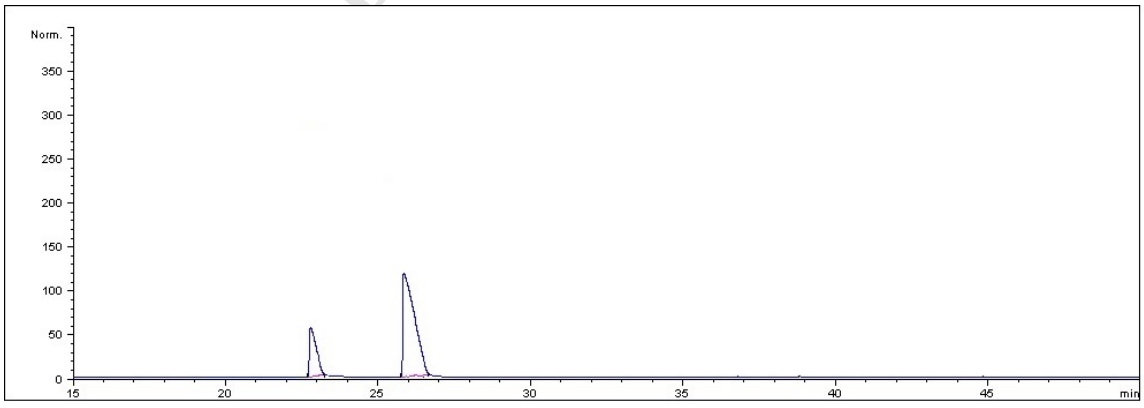
Hydrogenation using **1g + 1h**



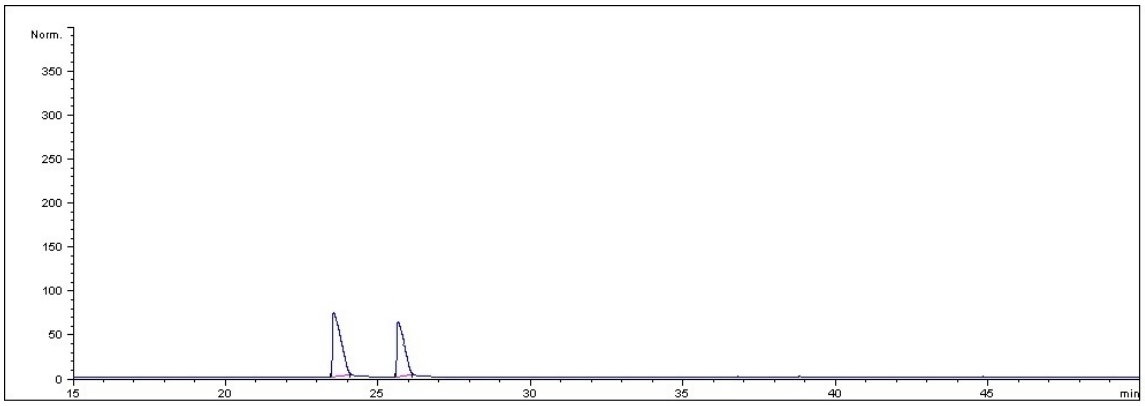
Hydrogenation using **1g + 2h**



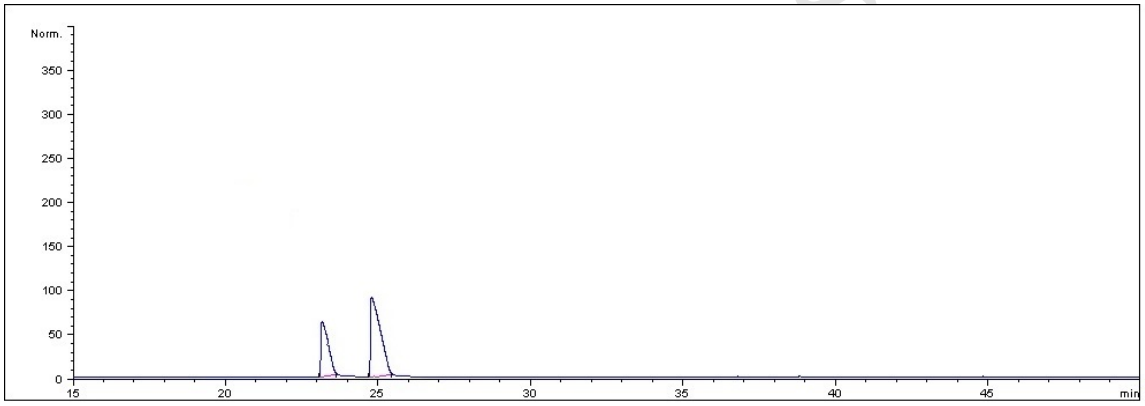
Hydrogenation using **1h + 2g**



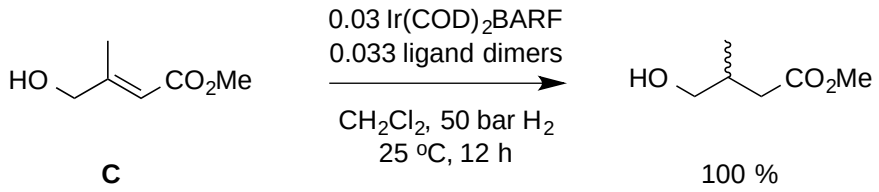
Hydrogenation using **1h + 2h**



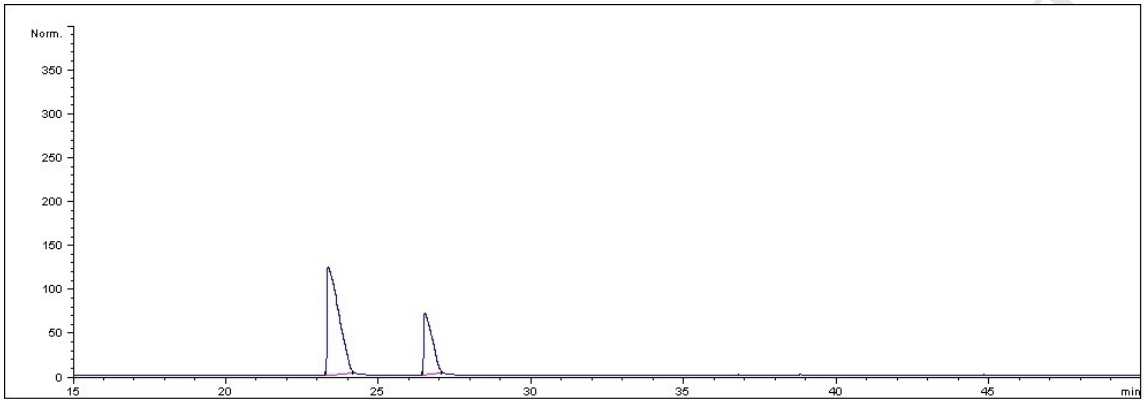
Hydrogenation using **2g + 2h**



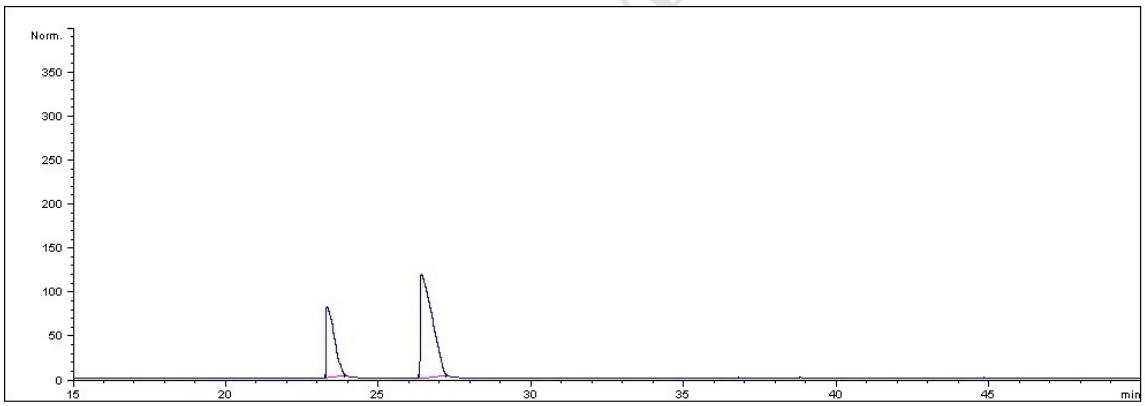
Hydrogenation using **1g + 2g**



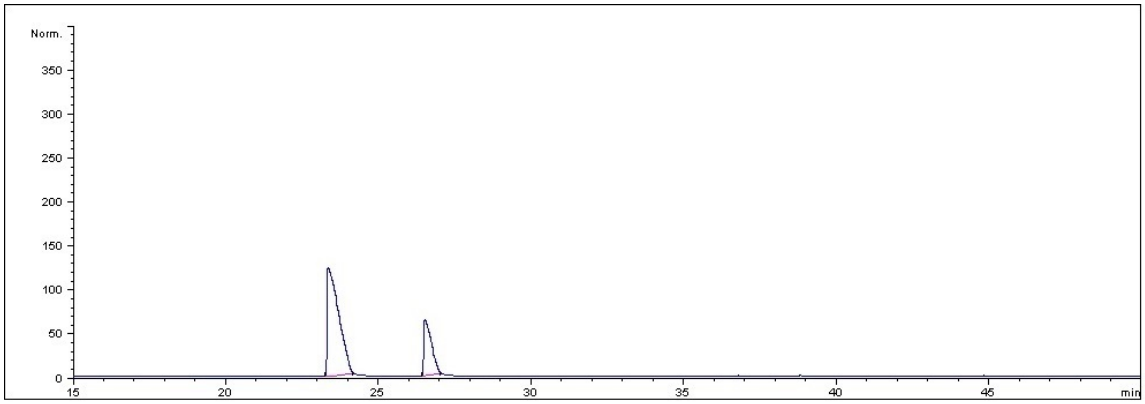
C 100 %



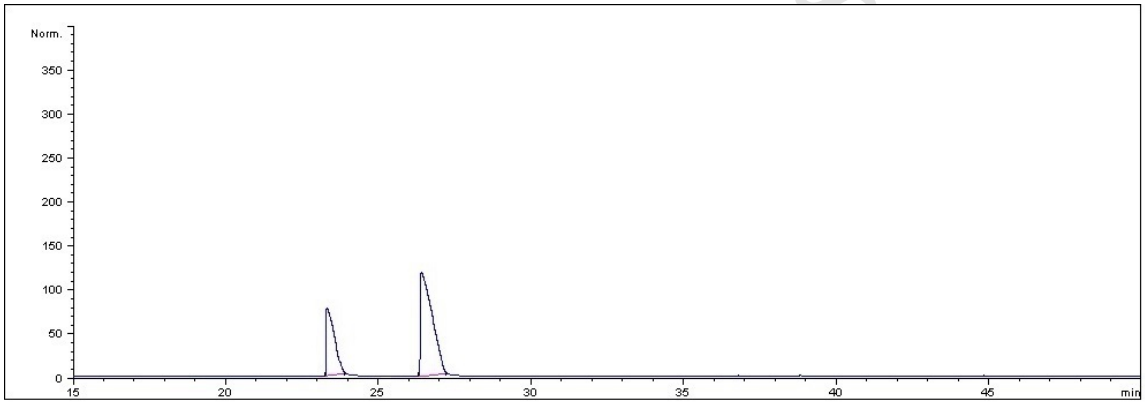
Hydrogenation using **1g' – 1g'**



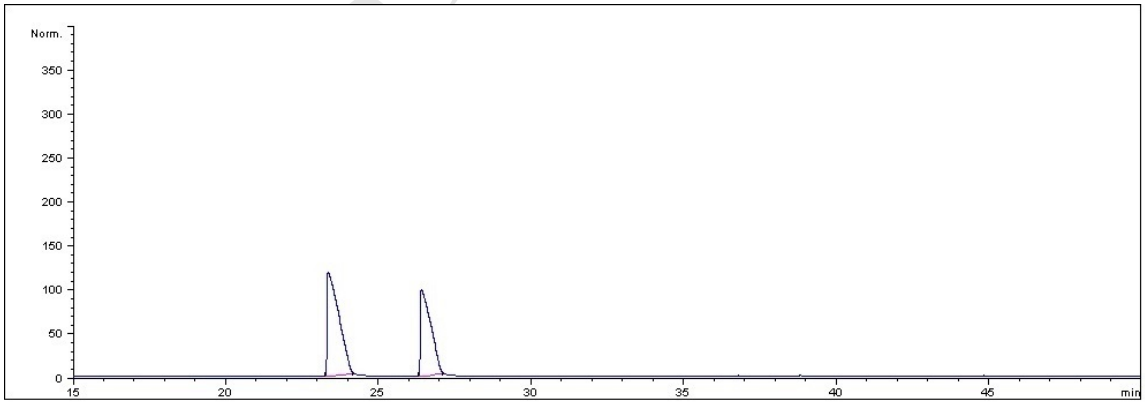
Hydrogenation using **1h' – 1h'**



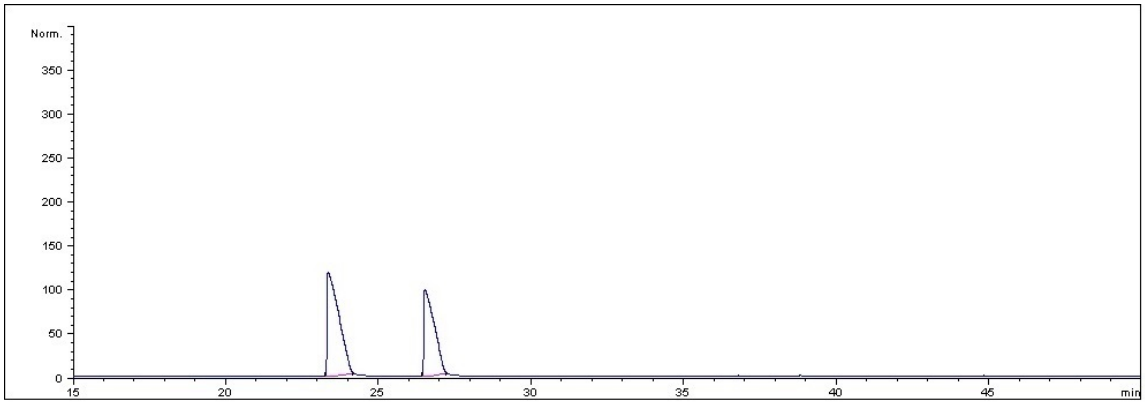
Hydrogenation using **2g' – 2g'**



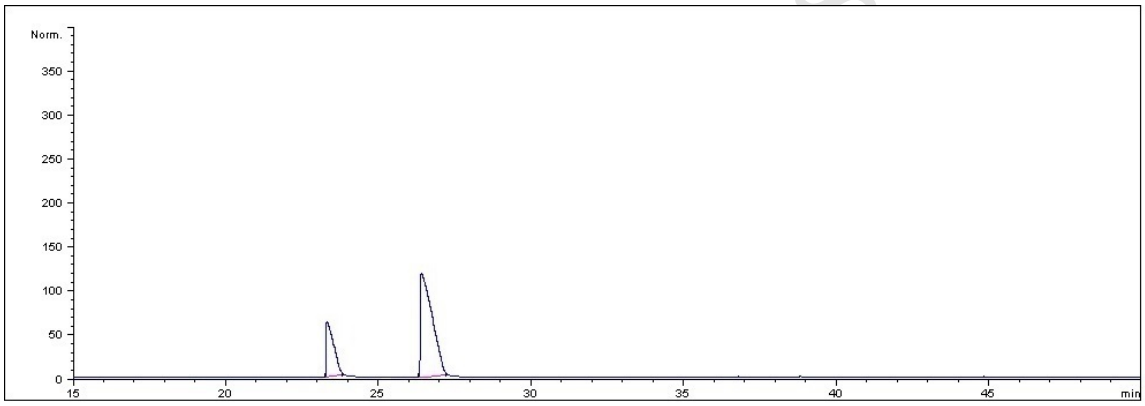
Hydrogenation using **2h' – 2h'**



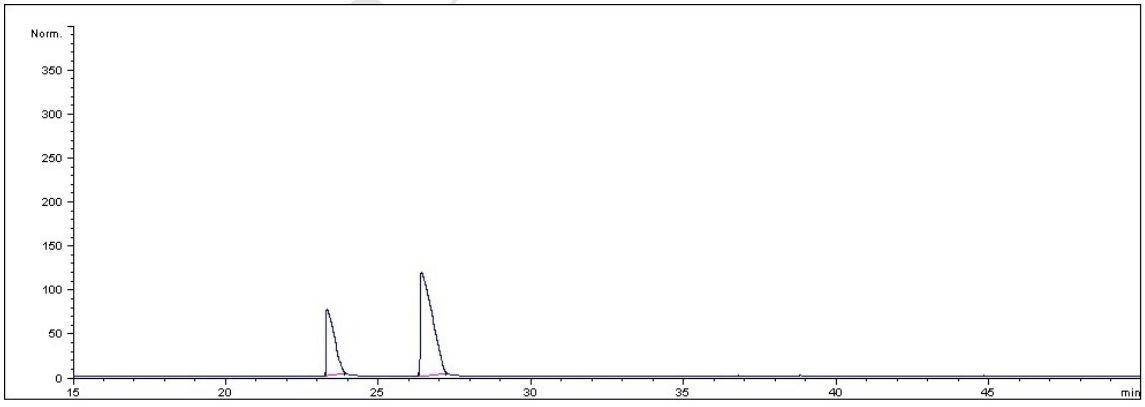
Hydrogenation using **1g' – 1h'**



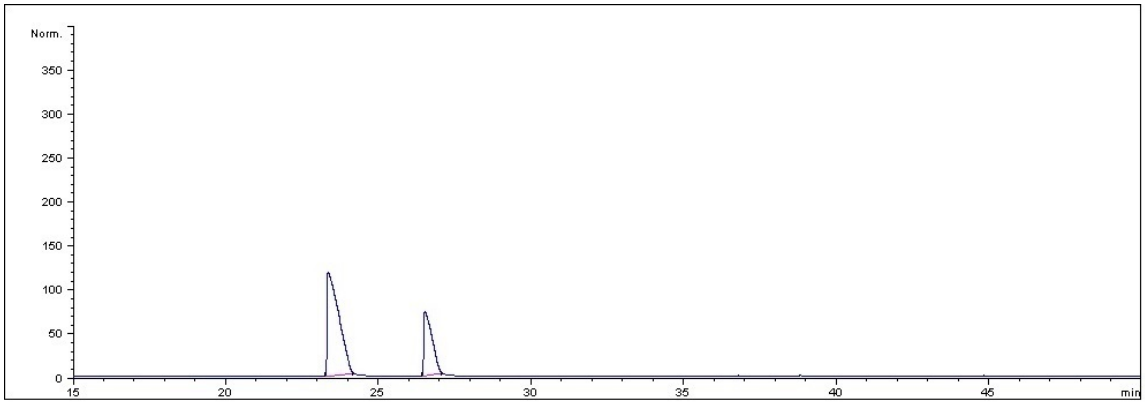
Hydrogenation using **1g' – 2h'**



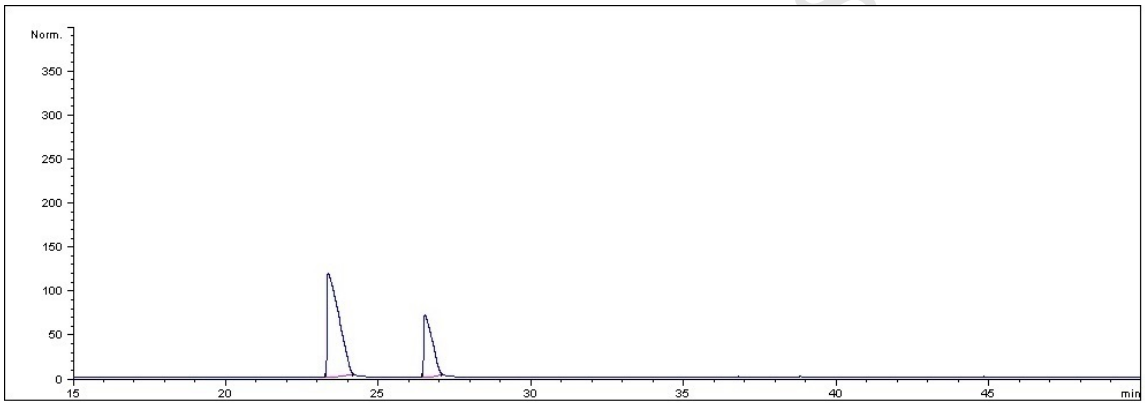
Hydrogenation using **1h' – 2g'**



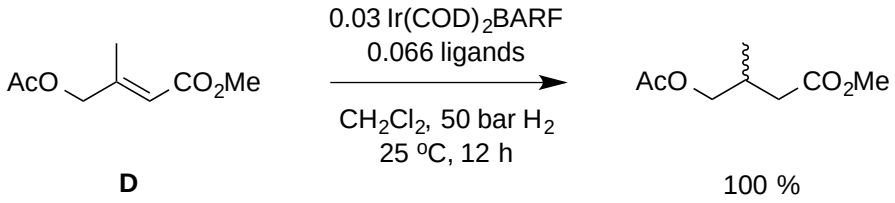
Hydrogenation using **1h' – 2h'**



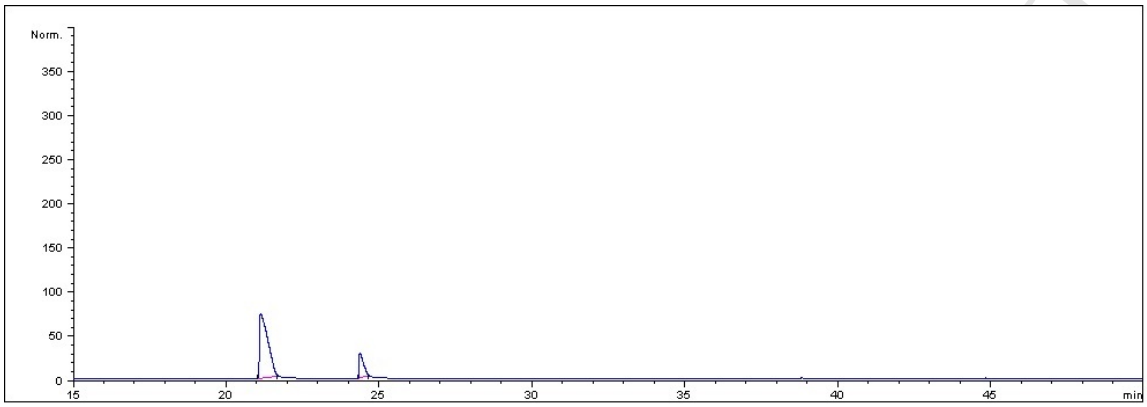
Hydrogenation using **2g' – 2h'**



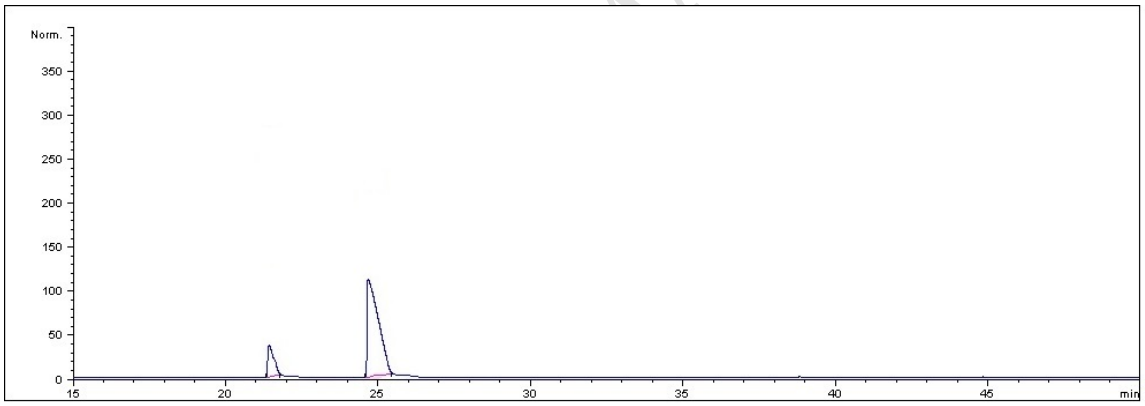
Hydrogenation using **1g' – 2g'**



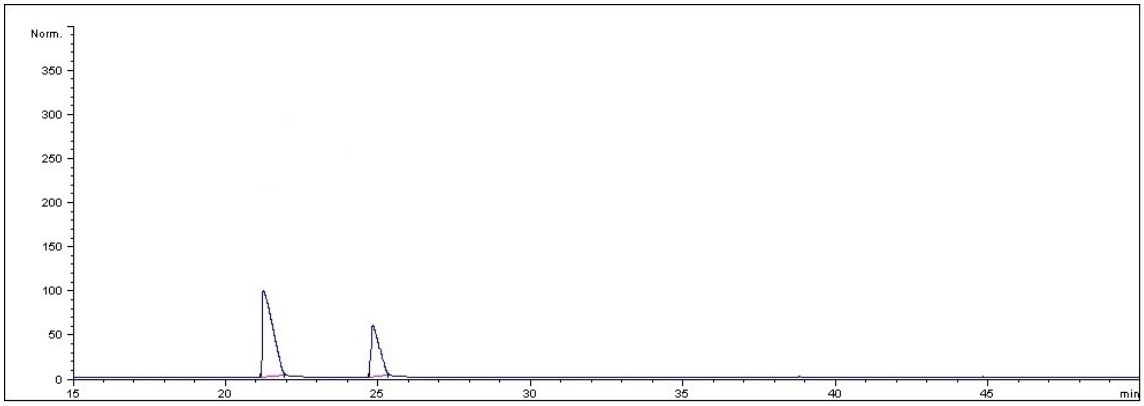
D 100 %



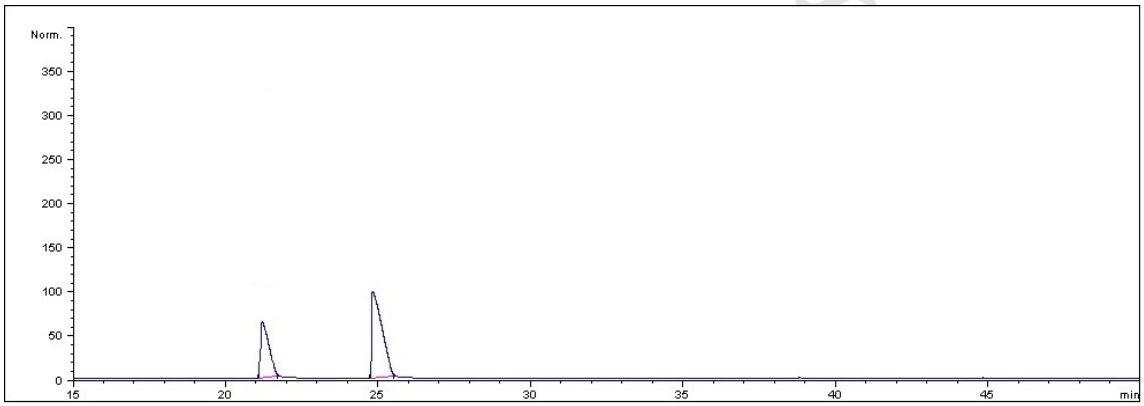
Hydrogenation using **1g**



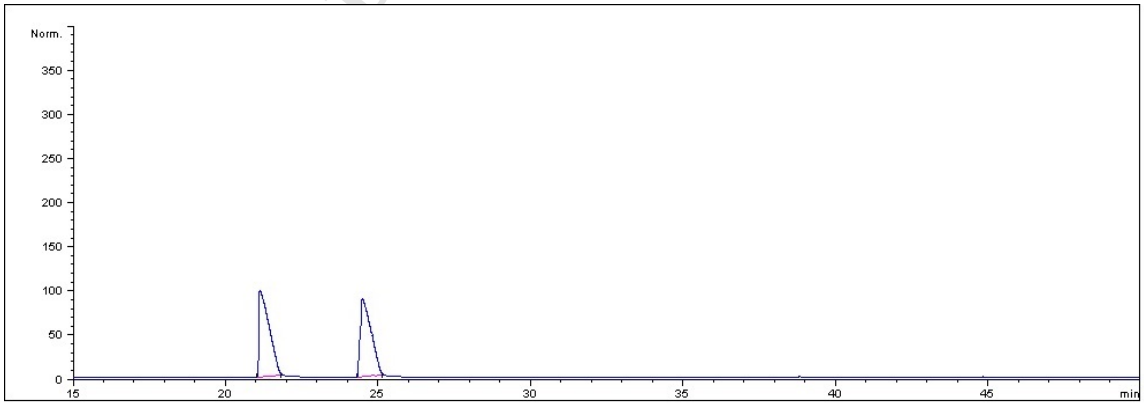
Hydrogenation using **1h**



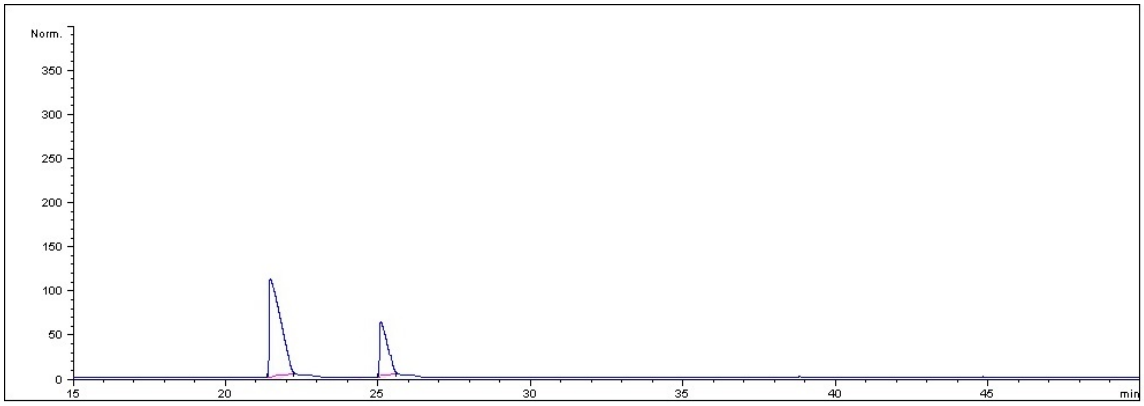
Hydrogenation using **2g**



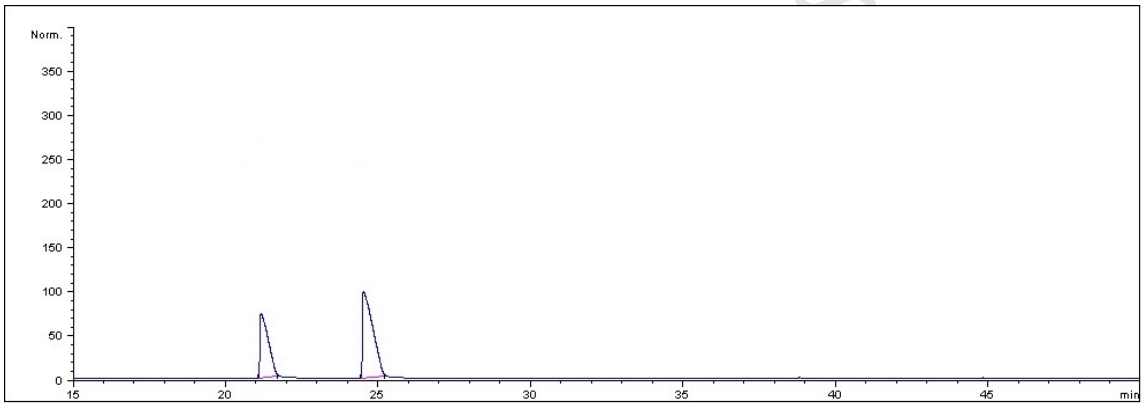
Hydrogenation using **2h**



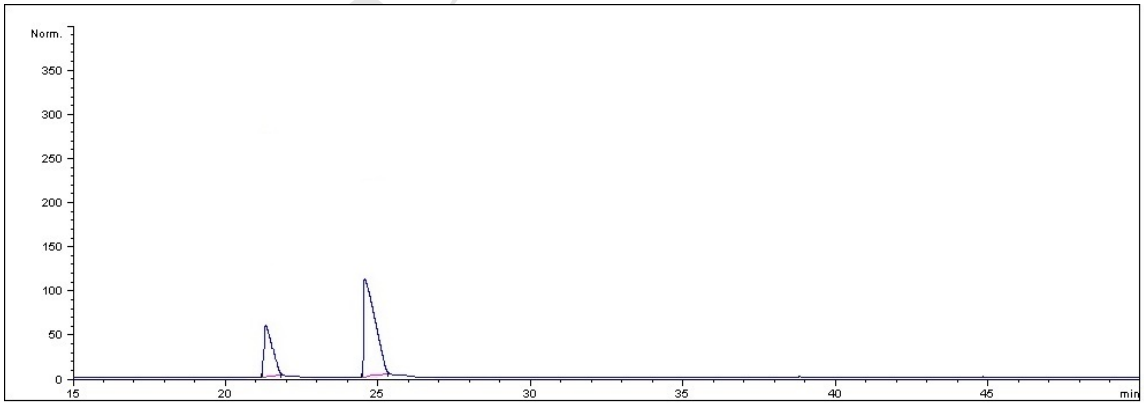
Hydrogenation using **1g + 1h**



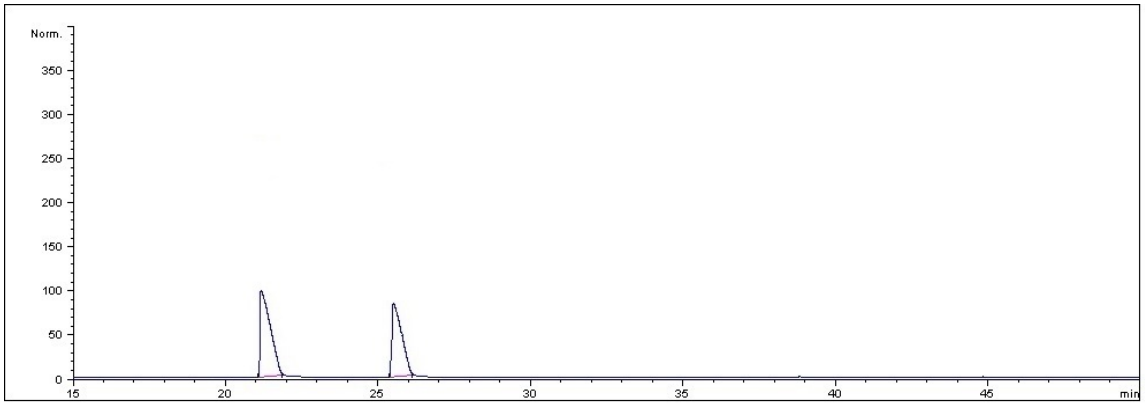
Hydrogenation using **1g + 2h**



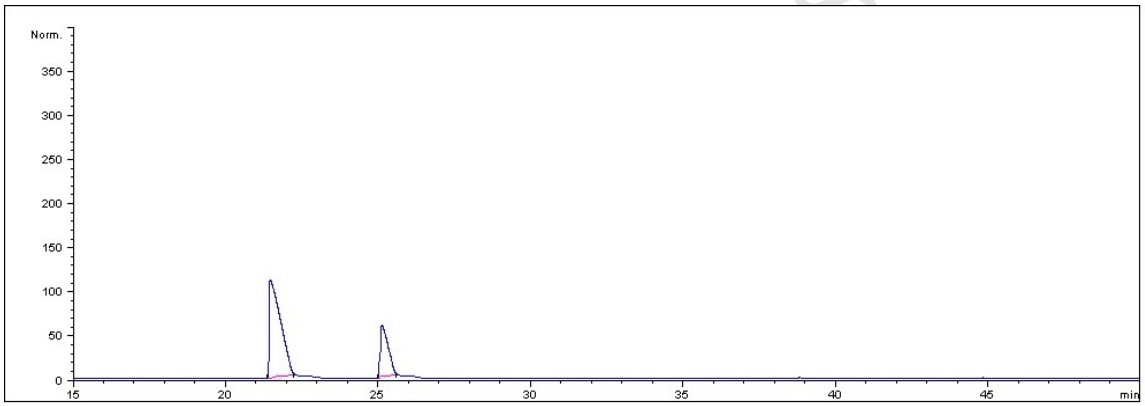
Hydrogenation using **1h + 2g**



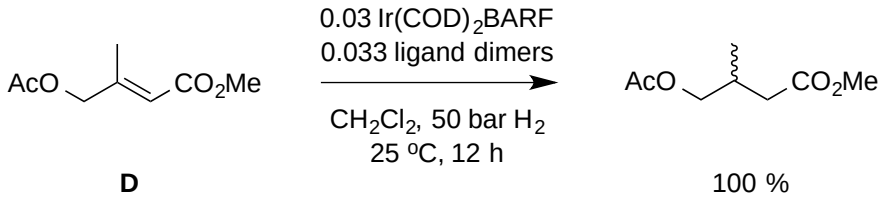
Hydrogenation using **1h + 2h**



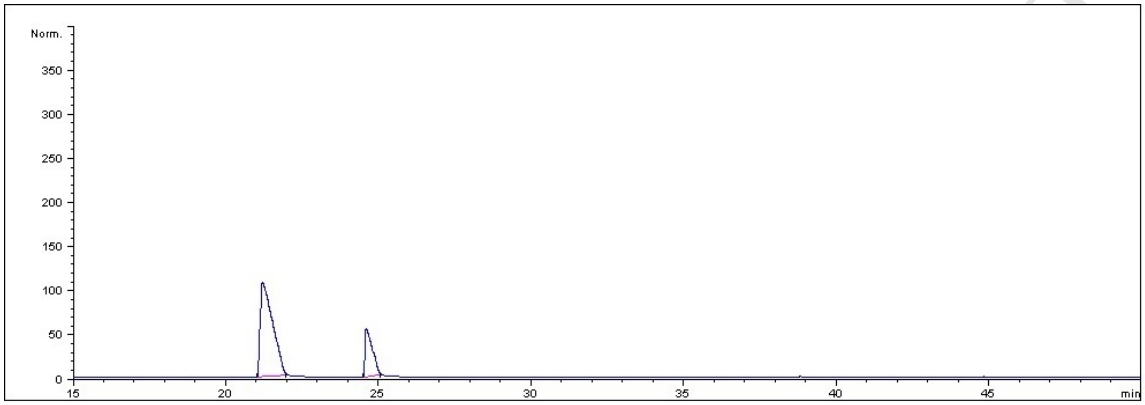
Hydrogenation using **2g + 2h**



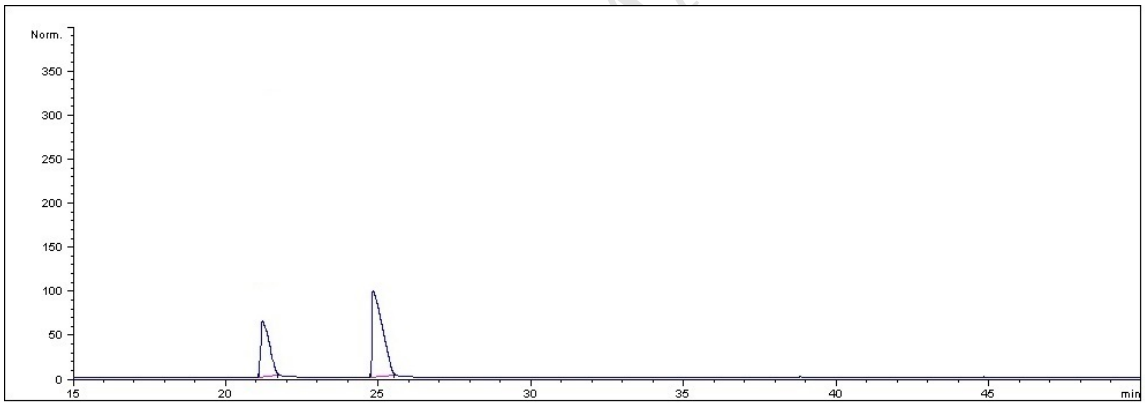
Hydrogenation using **1g + 2g**



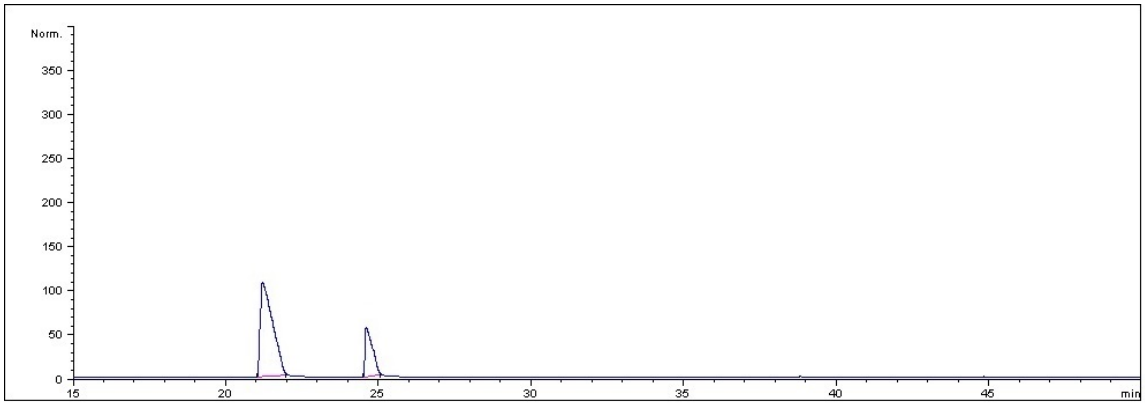
D 100 %



Hydrogenation using **1g' – 1g'**



Hydrogenation using **1h' – 1h'**



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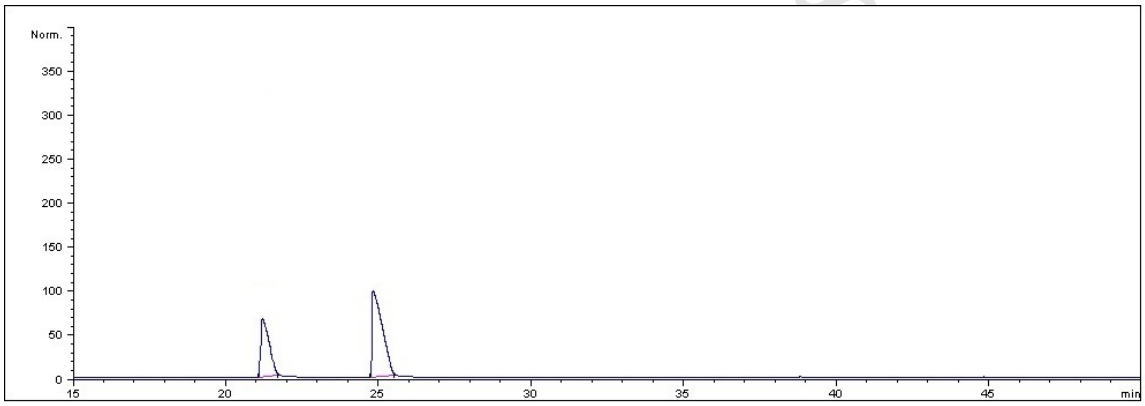

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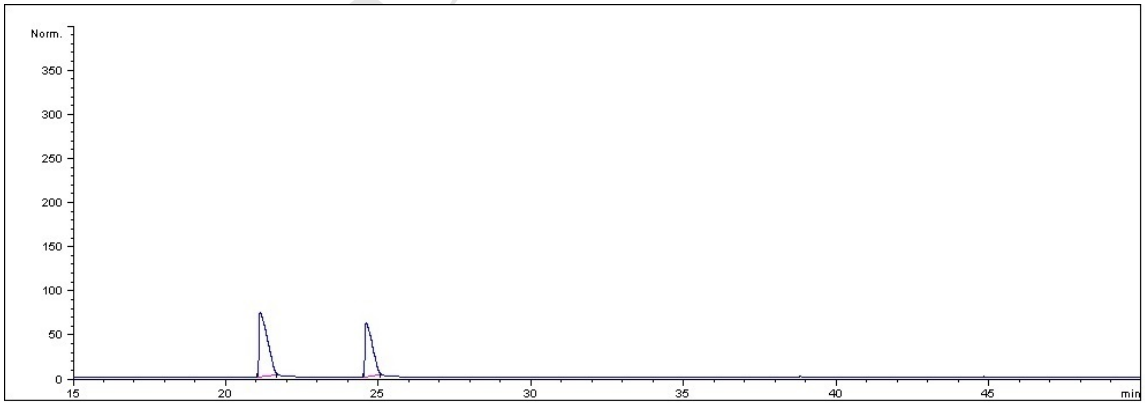

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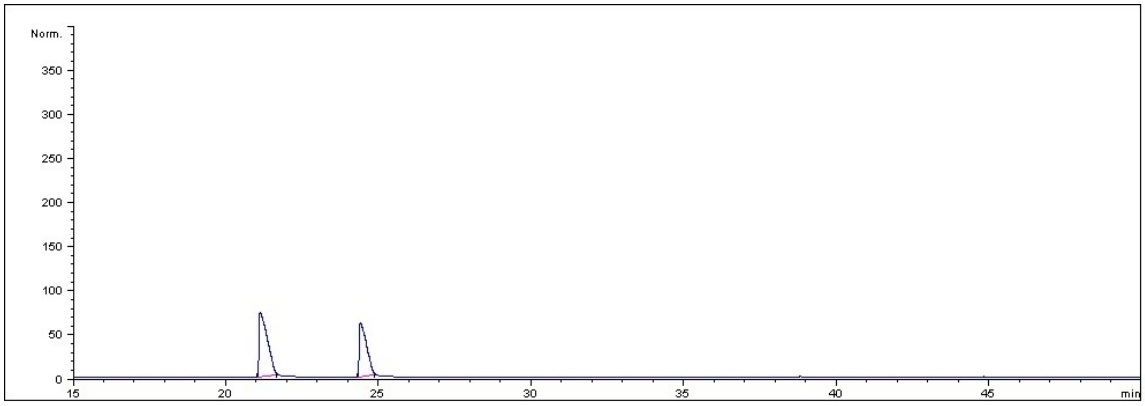

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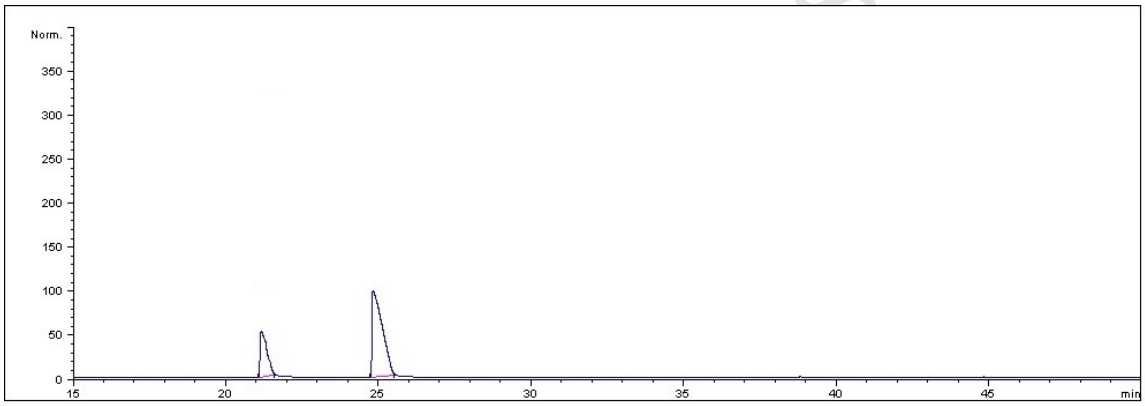

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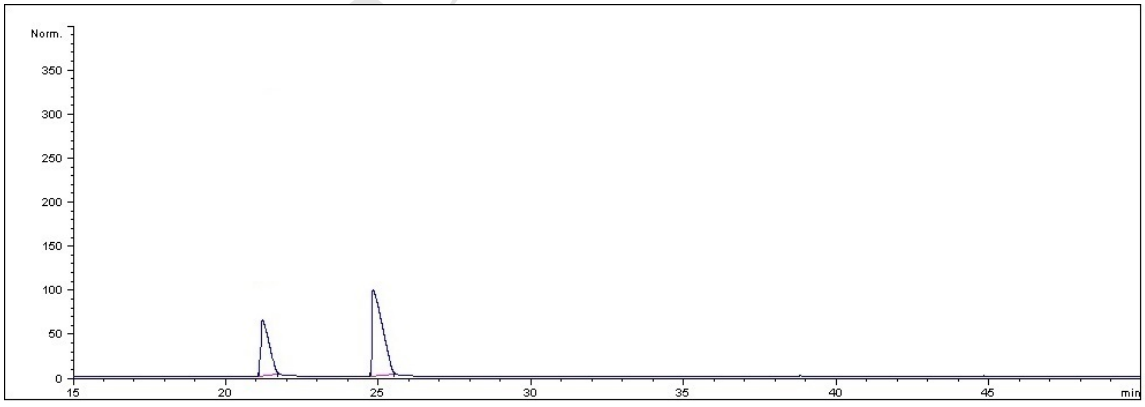

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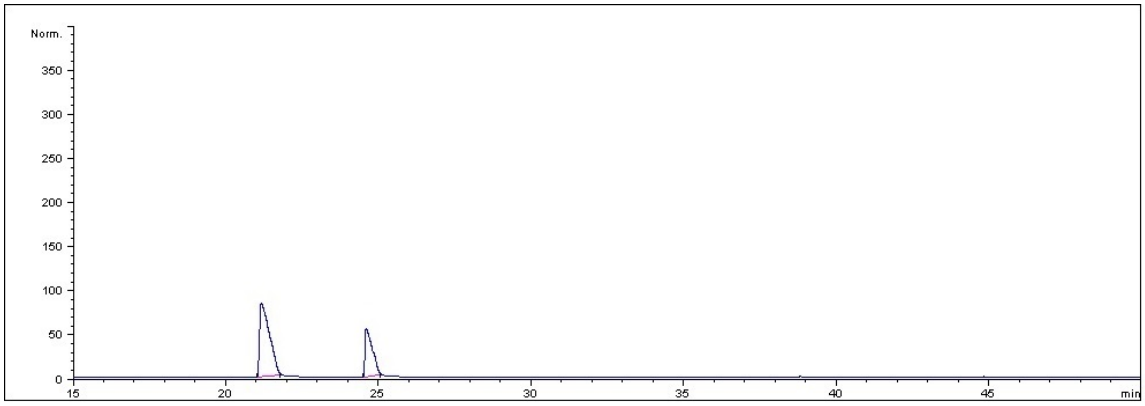

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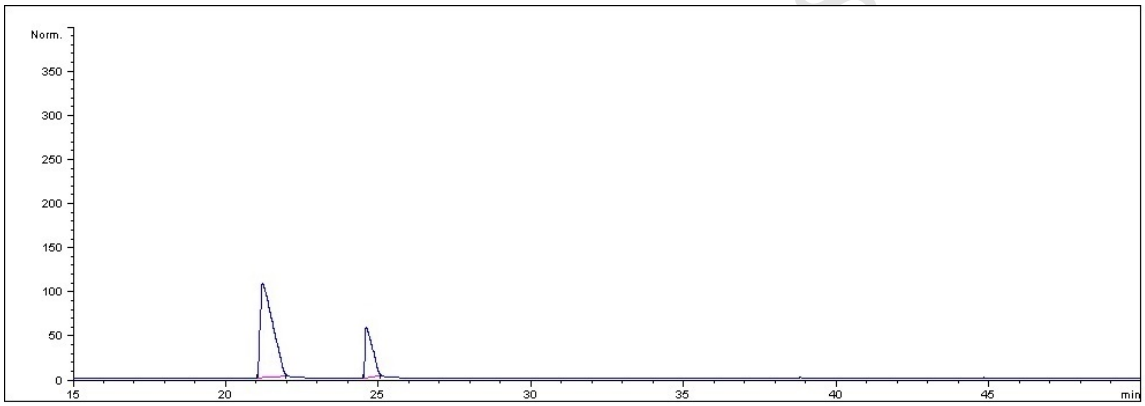

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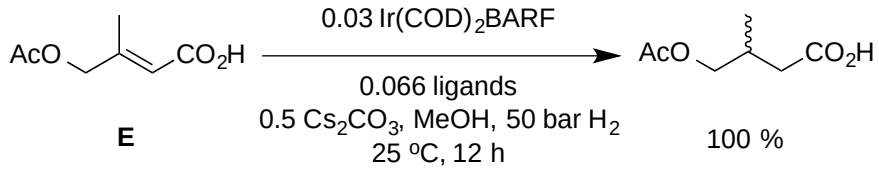

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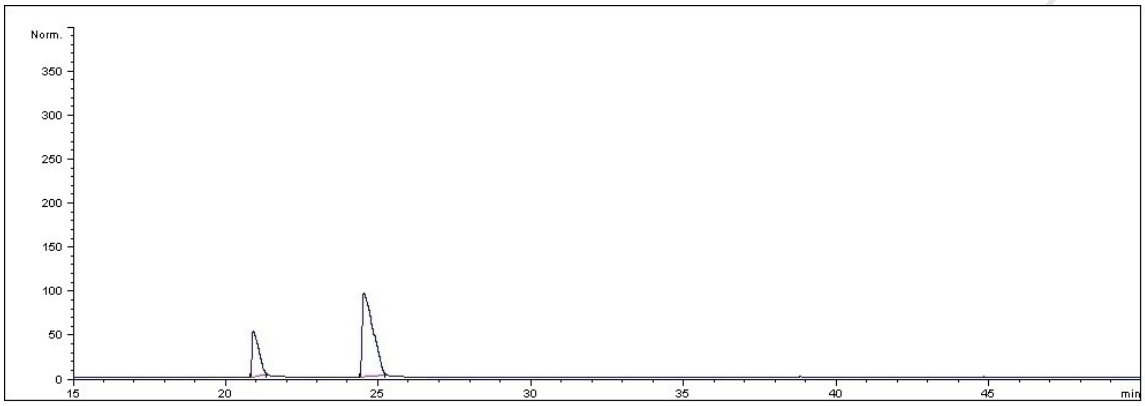

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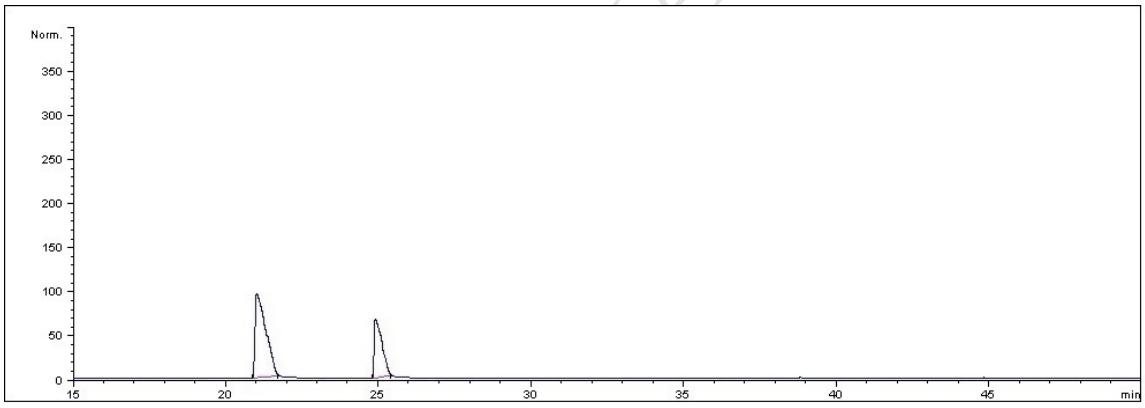

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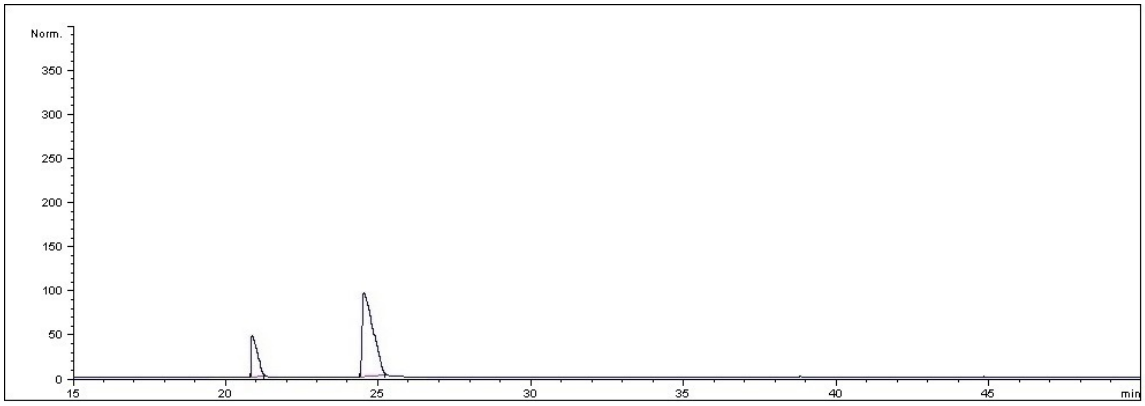

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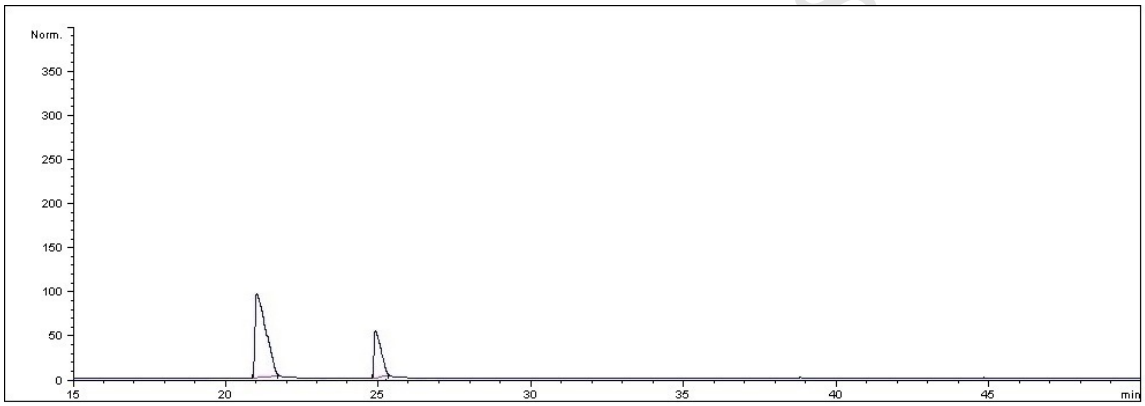

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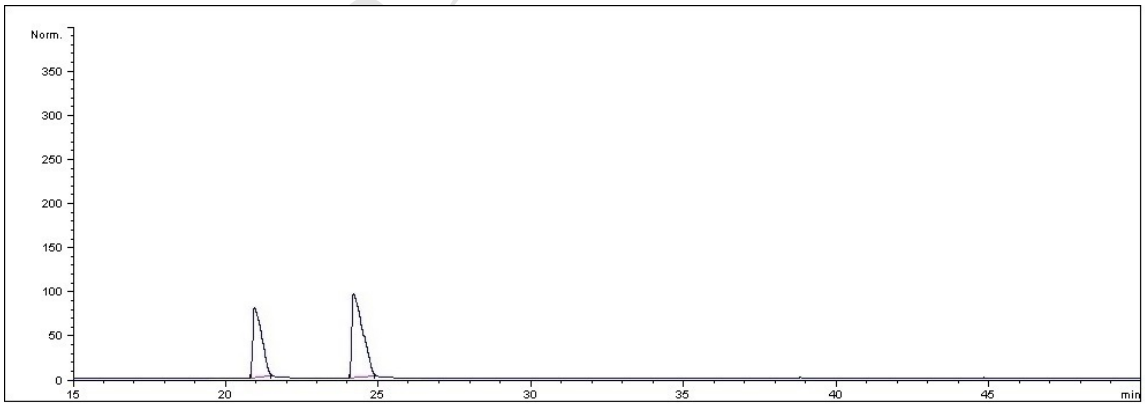

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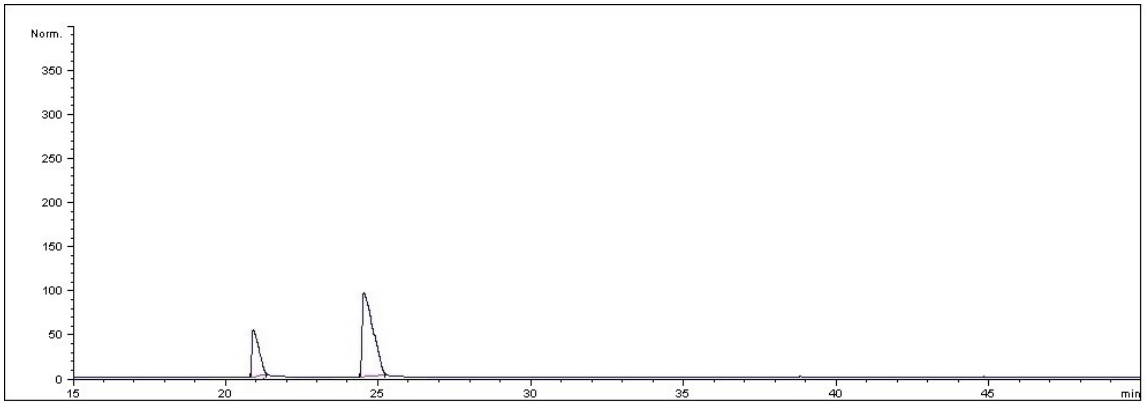

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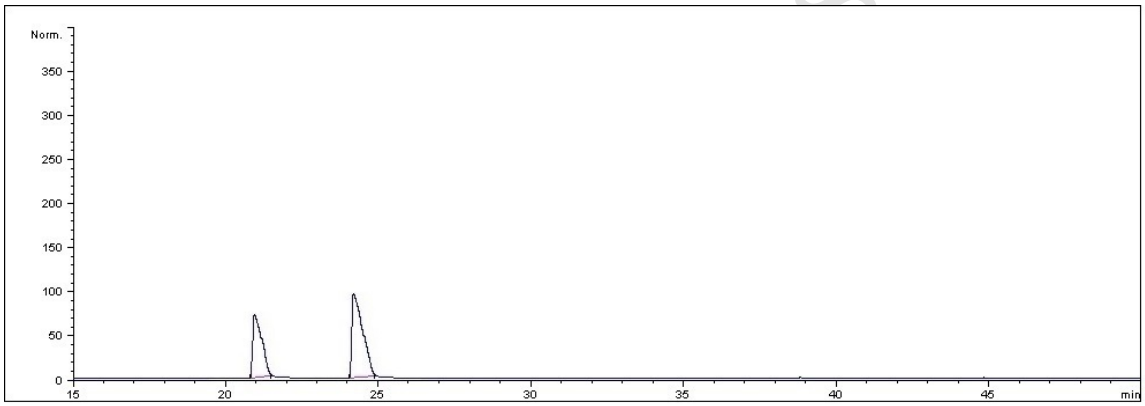

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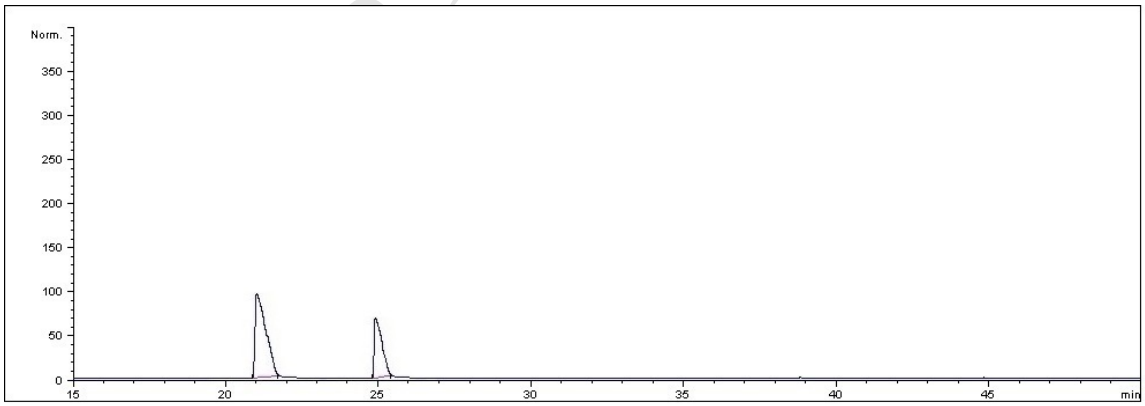

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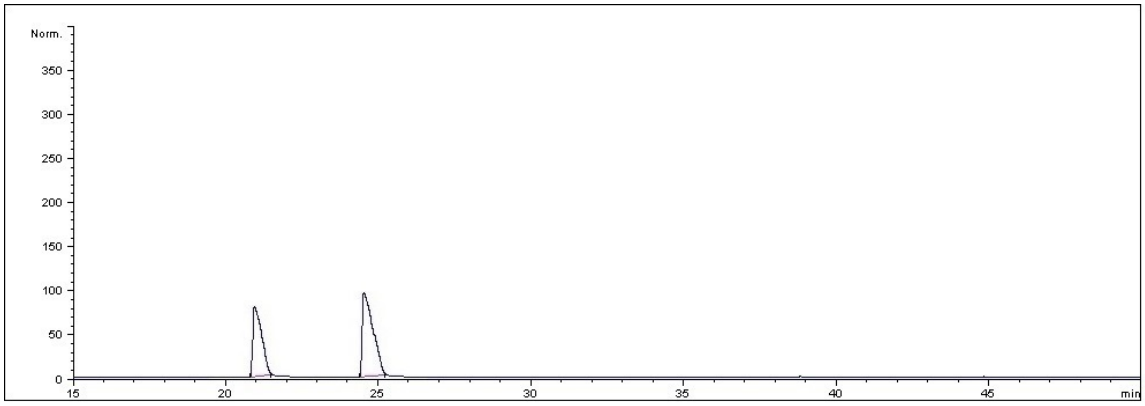

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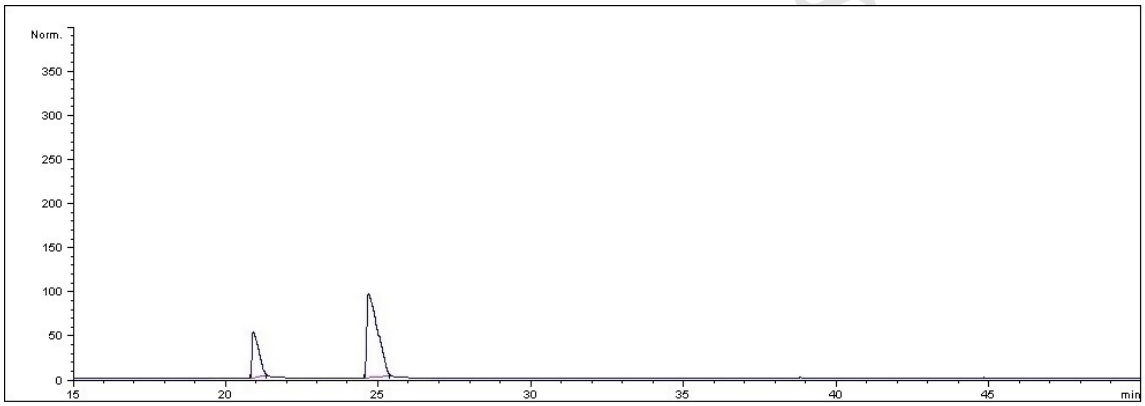

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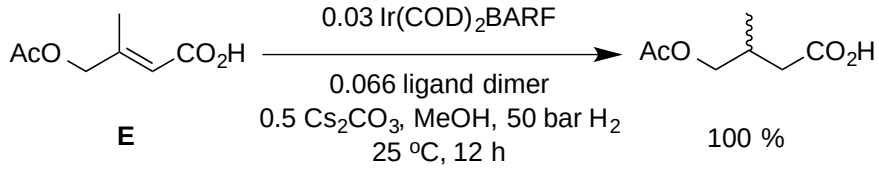

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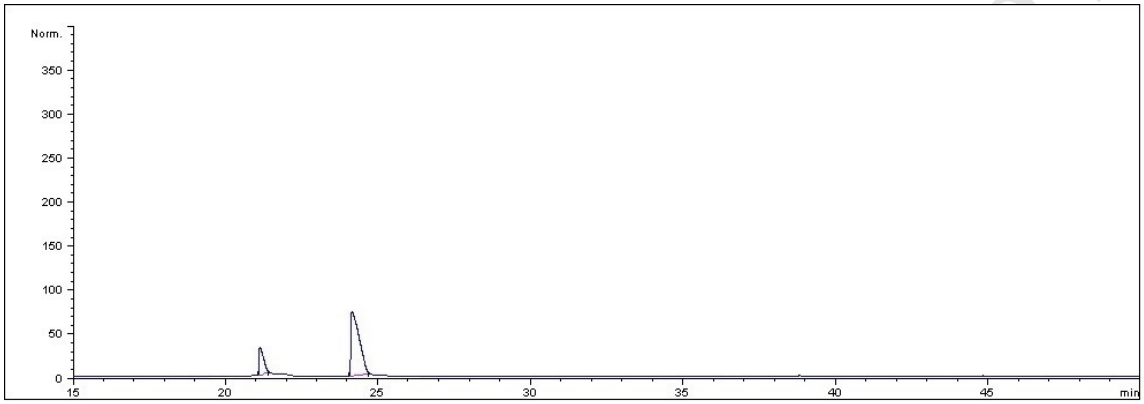

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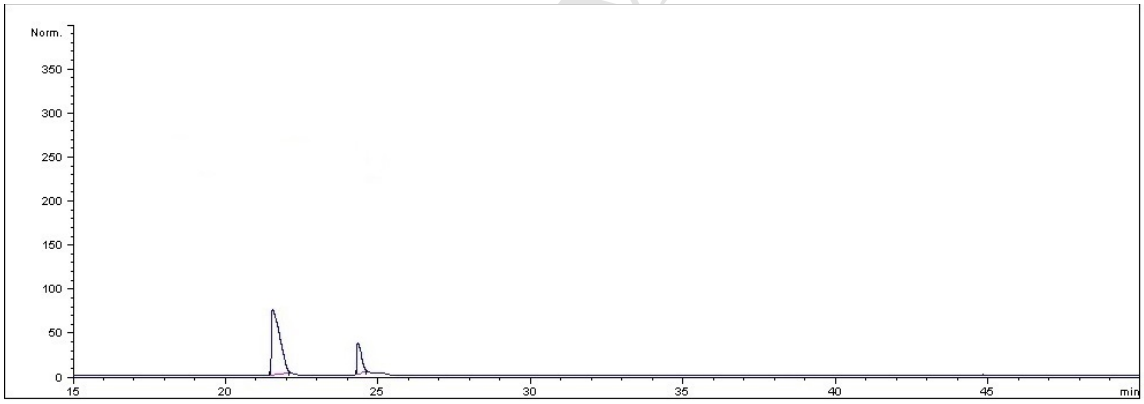

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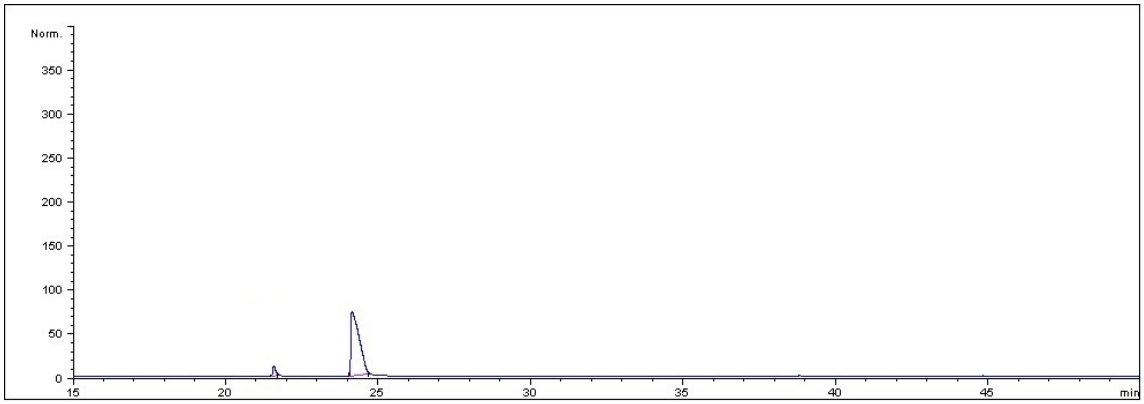

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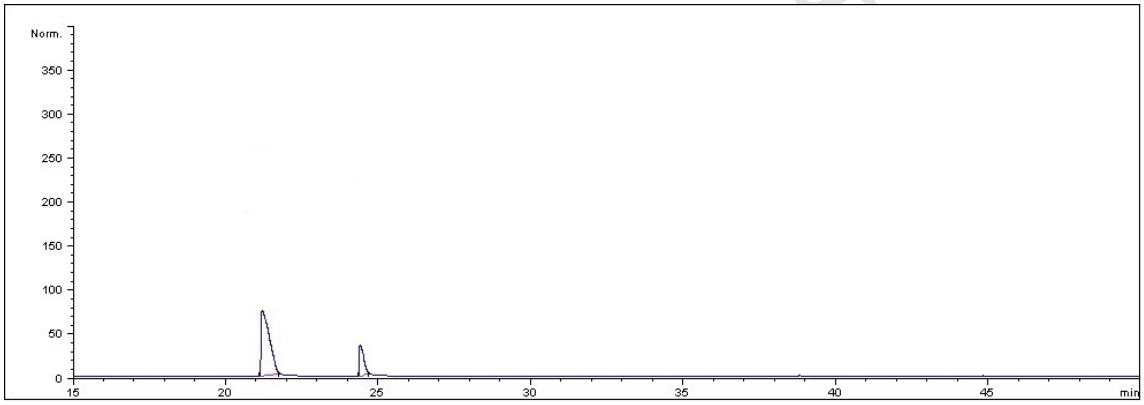

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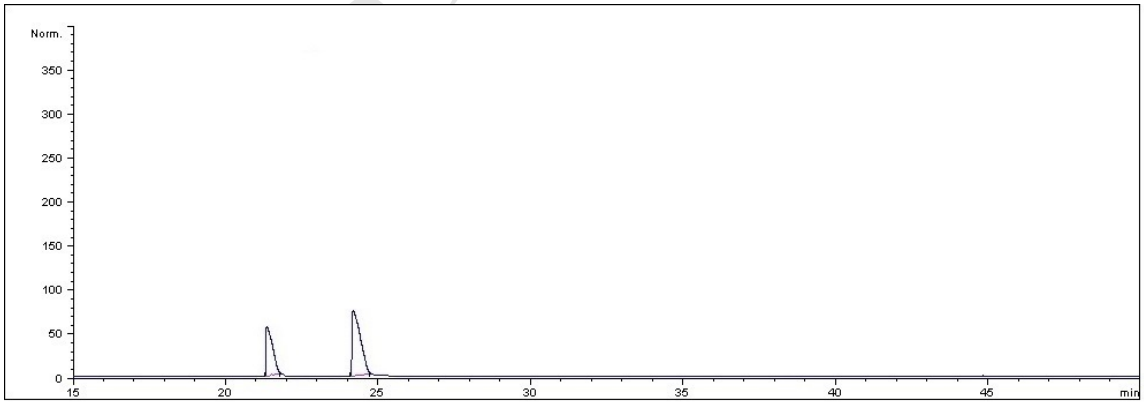

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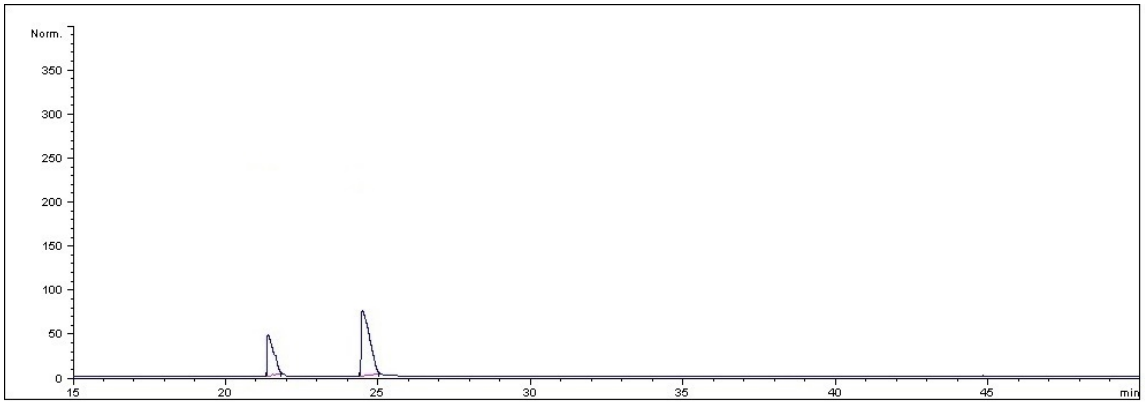

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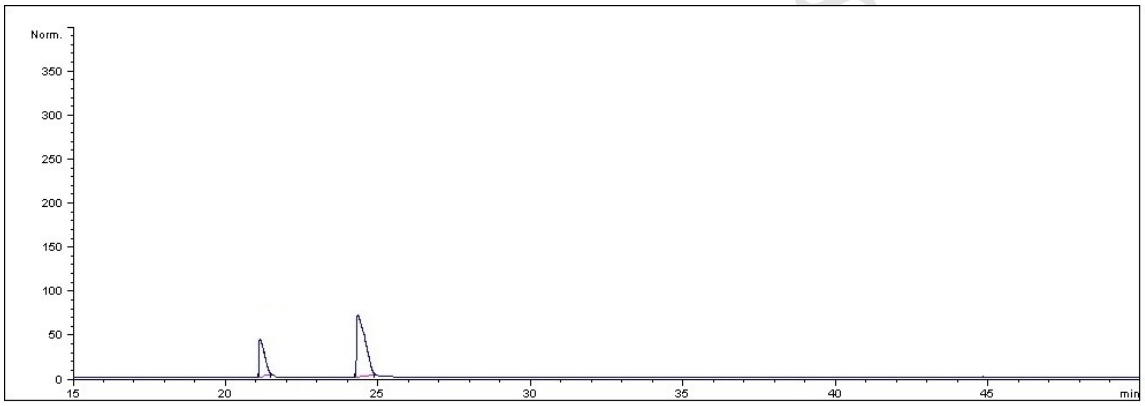

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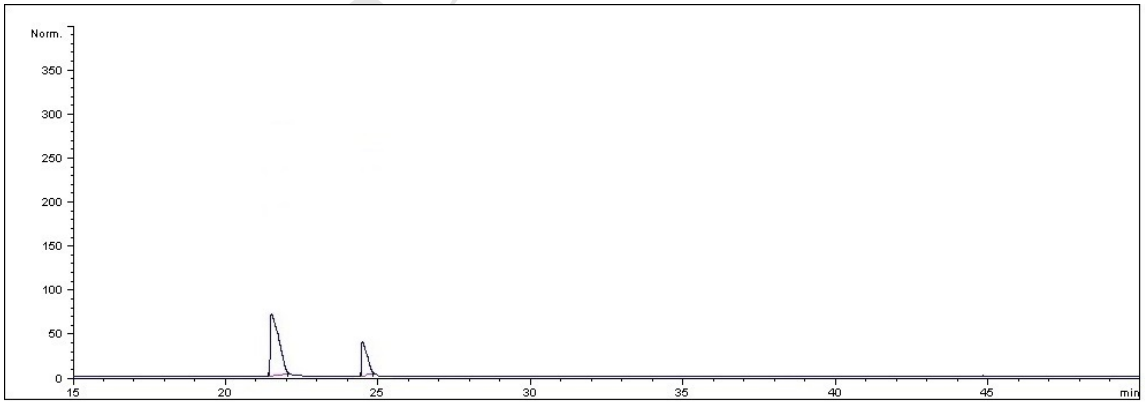

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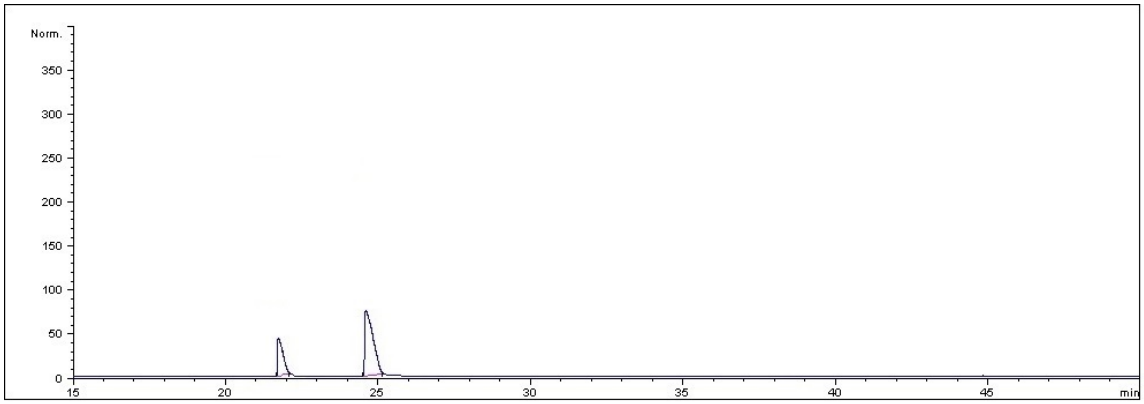

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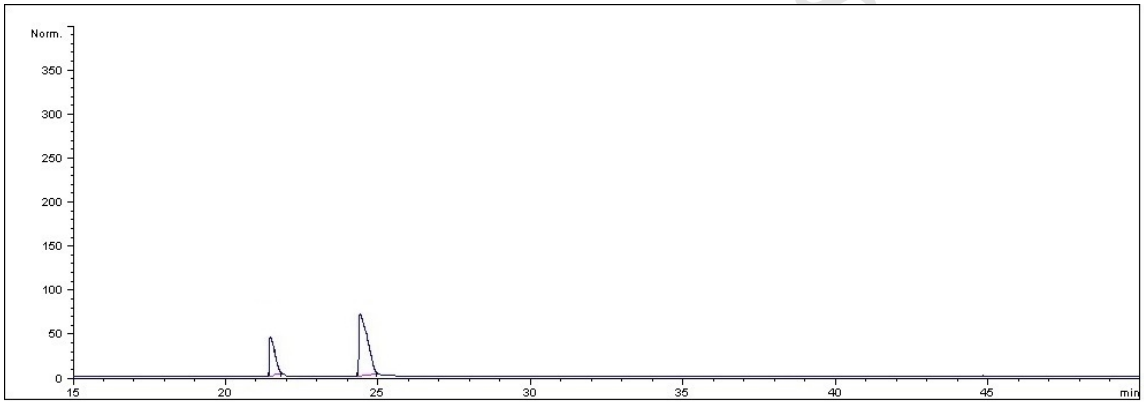

Hydrogenation using **1g' – 2g'**

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Metathesis For Catalyst Design:
Metacatalysis

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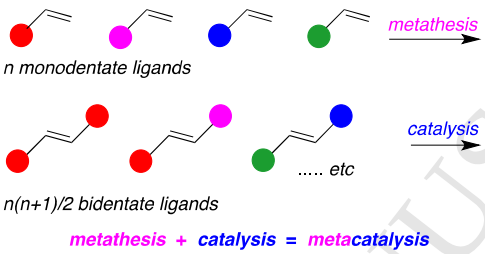
Sakunchai Khumsubdee and Kevin Burgess*
Department of Chemistry, Texas A & M University, Box 30012, College Station, TX 77841



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Metathesis For Catalyst Design: *Metacatalysis*

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ABSTRACT

Prior studies have shown an effective way to produce diverse ligand sets for catalyst discovery by using mixtures of monodentate forms to generate catalysts *in situ*. Research described here was performed to illustrate that alkene-functionalized monodentate ligands could be used in this way *and* in another that increases the diversity of the ligand library in an interesting way. Specifically, we hypothesized that as well as being used as monomers, these alkenes could be cross metathesized *in situ* immediately before the catalysis step. This combination of metathesis to form ligands *in situ*, then catalysis is referred to here as *metacatalysis*. In the event, a library of quinidine and quinine alkaloid-derived phosphites were tested as mixtures of monomers and dimers formed via metathesis *in situ*. The data obtained illustrated that metacatalysis can be used to identify ligands that positively and negatively modulate enantioselectivities in iridium-mediated hydrogenations of α,β-unsaturated carboxylic acid derivatives, relative to the mixtures of the monomeric forms used

1. Introduction

In situ catalyst formation by mixing *monodentate* ligands with a reactive metal salt or complex (Figure 1) has been used extensively for rapid identification of superior catalysts by Reetz,[1-4] Feringa/Vries,[5-8] and by others.[9-12] Those groundbreaking studies lead to several conclusions that were not appreciated before this approach was conceived. First, even though it was known that high enantioselectivities could be obtained using certain *monodentate* ligands,[13] formation of dynamic combinatorial mixtures of complexes in this way has proved to be an exceptionally efficient catalyst optimization strategy. Second, mixtures of two ligands sometimes give higher enantioselectivities than experiments in which two equivalents of either of the two pure ligands are used. Third, there are situations in which superior enantioselection has been achieved when one of the monodentate ligands is *achiral*. Fourth, time has shown that this approach is reasonably general, having been widely applied to asymmetric hydrogenations of alkenes with coordinating functional groups (CFGs),[1-8] and to 1,4-additions to electron-deficient alkenes,[14-17] allylic substitution,[18-20] hydrovinylation,[21,22] and cross coupling.[23]

In reality, mixtures in dynamic combinatorial catalysis usually are significantly more complicated than Figure 1a suggests. For instance, it is possible that active complexes with one or three ligands might be involved. Moreover, Hartwig has shown that ostensibly monodentate ligands in some reactions are, in fact, bidentate as a result of metalation processes.[24-27] In short, dynamic combinatorial catalysis trades some control of the mixtures being screened for the ability to make potential catalysts quickly.

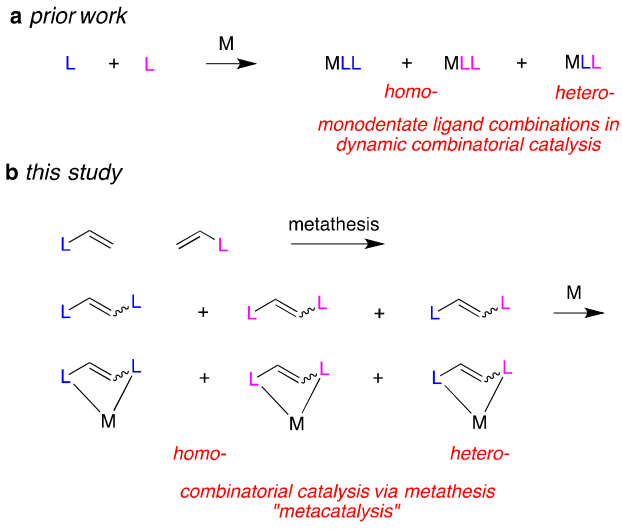


Figure 1. (**a**) Dynamic combinatorial catalysis is known; but, (**b**) can bidentate ligands be similarly formed via metathesis?

Efficiency is possible in dynamic combinatorial catalysis by generating different combinations of monodentate ligands. However, it would be highly desirable to produce *bidentate* ligands instead, without significantly compromising the

efficiency. This is because appropriately designed bidentate, chelating ligands have several attributes conducive to the design of stereoselective catalysts, mostly related to the fact that their complexes exist in fewer accessible low energy conformers. A superior bidentate ligand may exist corresponding to each effective combination of monodentate ligands identified in dynamic combinatorial chemistry; in practice the problem is finding this ligand.

Research described in this manuscript was undertaken to obtain proof-of-principle for the concept illustrated in Figure 1b. We envisaged olefin metathesis[28] could be used to convert alkene-containing ligands with one *P*-center into mixtures of compounds with two. In simple cases in which only the *P*-centers coordinate to the metal, this represents conversion of monodentate ligands to bidentate ones; metathesis to form a ligand that are then used *in situ* for catalytic reactions is referred here as *metacatalysis*. Thus, if the metathesis reactions are efficient enough that purification of the ligands before the test reaction is unnecessary, then metacatalysis could be almost as convenient as dynamic combinatorial processes featuring monodentate ligands, but have the distinction that bidentate "catalyst space" is covered.

2. Results and Discussion

Selection Of The Metathesis Substrates And Test Reactions. Several considerations guided selection of the alkenes that were used as metathesis substrates in this work. First, the alkenes should be conveniently assembled from commercial starting materials. Second, carbene intermediates in the catalytic cycle should not permit a stable 5-ring chelate to be formed since this would tend to depress the catalytic activity.[29] The third consideration follows because the previous one tends to impose design constraints that favor large-ring chelates, and because these would predominantly feature E-alkenes (assuming standard metathesis catalysts were used). Thus it was desirable to use monomers for which the anticipated macrocyclic chelates would be formed from large fragments; our hypothesis was that this would tend to decrease the number of accessible conformational states as a result of steric packing effects. Finally, it was necessary to avoid situations in which the corresponding combinations of monodentate ligands for the featured catalytic reaction already gave high stereoselectivity. In other words, the objective of this study was to see if metacatalysis could give improved enantioselectivities, so it was logical to choose situations that allowed for substantial improvement.

Based on the considerations outlined above, we elected to work with pseudo-enantiomeric phosphite derivatives of quinidine and quinine, **1** and **2** respectively (Figure 2). A monodentate ligand, **1e** where $(RO)_2$ = 1,2-diphenyl-1,2-ethylenedioxy, has been reported previously and used for Pd-mediated allylation reactions; enantioselectivities up to 88% were obtained.[30] In the event, ligands **1a – h** and **2g – h** were prepared in one-pot reactions and isolated in yields ranging from 30 - 85 % after flash chromatography.

Hydrogenations of largely unfunctionalized alkenes were selected as the test reactions, for the following reasons. Some of the most successful catalysts in these processes are iridium complexes with N,P-ligands;[31-33] systems **1** and **2** have the potential to use P- and N-atoms to coordinate in this way. Consequently, the archetypical hydrogenation of this kind was used to triage some of the monomers (reaction 1); based on our work and that by others,[31-33] N,P-based catalysts that hydrogenate this substrate with significant *ee*'s tend to have potential in other

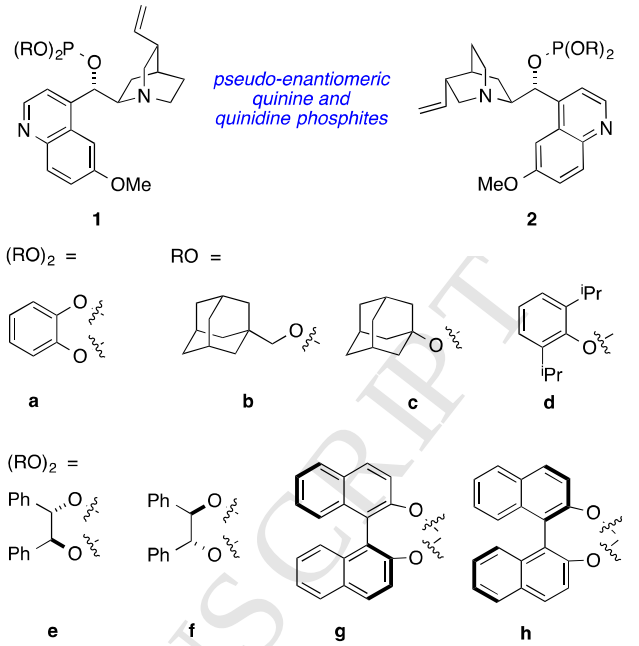
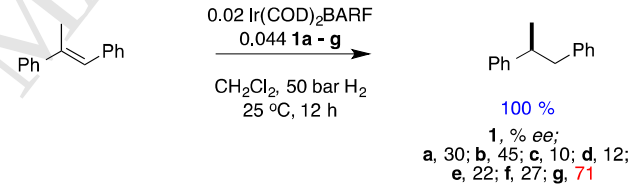


Figure 2. Alkene-phosphites featured in this work. Ultimately, the study focused on **1g** and **h**, and **2g** and **h**.

hydrogenations. The data accumulated indicated system **g** was most influential of the phosphite substituents, so that system and another the 2,2'-binaphthol-based ligand **h** were selected for further studies.



reaction 1

Metathesis Of The Alkene Monomers. Alkene metatheses of substrates **1g**, **h** and **2g**, **h** were studied as a prelude to the featured catalytic reactions. It was not obvious that these metatheses reactions would proceed with high conversions because even monosubstituted alkenes tend to react slowly if the allylic site is bulky.[34] Moreover, the alkenes featured here also contain phosphite centers that could similarly retard the catalysis. Throughout, we restricted our studies to the more convenient Ru-based metathesis catalysts; the related Mo-centered catalysts were not explored.

In the event, the Grubbs-Hoveyda second-generation system **A** gave good conversion of the monomers to the disubstituted alkenes **1g' – 1g'** and **2g' – 2g'** (Figure 3). This transformation was monitored by loss of the methylene ^{1}H and ^{13}C NMR signals while the vinylic C<u>H</u> shifted to the product resonance. Only one vinylic C<u>H</u> NMR signal was observed in each case indicates that only the *E*-isomer of the alkene was formed in detectable amounts. The ^{31}P NMR resonances of the products were within 0.5 ppm ($CDCl_3$) of the starting materials.

Test reactions performed using mixtures of ligands **1** and **2** gave mixtures with complicated ^{1}H and ^{13}C NMR spectra. ^{31}P NMR signals of the products in the crude reaction mixtures could not be resolved, and we were unable to separate the components of the mixture using either normal or reverse phase HPLC. In

retrospect it is clear that the product polarities in these metathesis

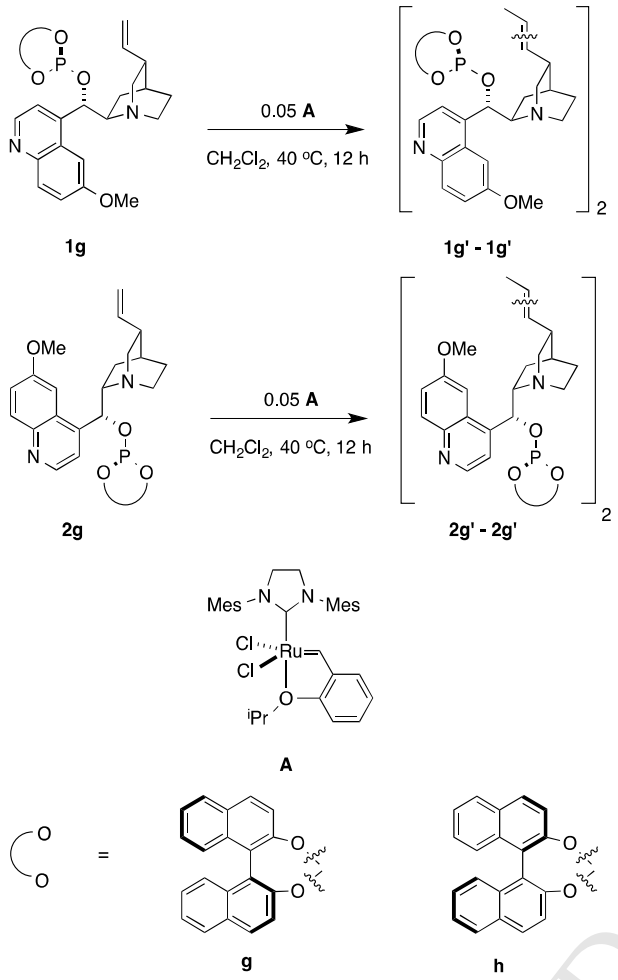


Figure 3. Alkene-phosphites **1g** and **h**, and **2g** and **h**, were dimerized by alkene metathesis reaction.

reactions are dominated by the amine-alkaloid parts; adding different hydrophobic fragments to the phosphite does not impart differences that are large enough even to see the isomers by analytical HPLC.

Crude Metathesis Reactions Do Not Give Viable Hydrogenation Catalysts. There have been reports of hydrogenation reactions mediated by Ru-based complexes for metathesis.[35] However, these processes did not feature trisubstituted alkenes without coordinating functional groups (CFGs) for which exceptional hydrogenation catalysts are required,[31] so it was necessary to test if complexes like **A** could mediate hydrogenation. In the event, they did not as indicated in Figure 4.

The rest of the paper concerns hydrogenations of α,β-unsaturated ester derivatives like **B**, **C**, **D** and **E** (see Figure 5, 6, 7 and 8). Similar control experiments were performed for these and in each case the hydrogenation product either could not be detected, or were less than 2 %.

Hydrogenations of Cinnamic Acids Derivatives With Monodentate Ligands. Hydrogenations of α,β-unsaturated acids and esters can be used to make chirons for polyketide-derived natural products and other materials,[36,37] but these reactions with simple substrates are difficult to perform with high enantioselectivities.[38] Consequently we decided to test combinations of our ligands in these reactions, beginning with a

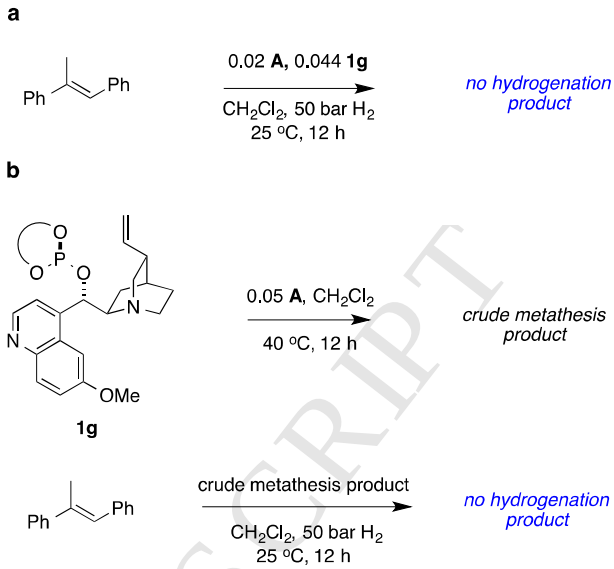


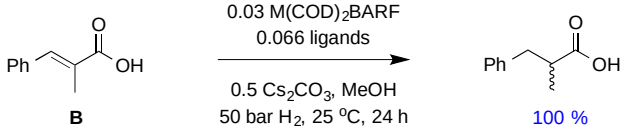
Figure 4. (**a**) Catalyst A did not mediate hydrogenation of *E*-1,2-diphenylpropene under the conditions shown. (**b**) Catalyst **A** was used to mediate metathesis, then hydrogen and a trisubstituted alkene were introduced; the latter was not hydrogenated.

substrate that is relatively easy to hydrogenate with significant enantioselectivity, α-methylcinnamic acid **B**.

The first step in probing the featured hydrogenation reactions was to establish "baseline data" representing enantioselectivities obtained using the monodentate ligands, *ie* precursors to the fragments to be connected via metathesis. Figure 5a showed that catalysts formed in situ from $Ir(COD)_2$ BARF and ligand **1g** in a ratio of approximately 1:2 gave complete conversion to product with an *ee* of 60 %.

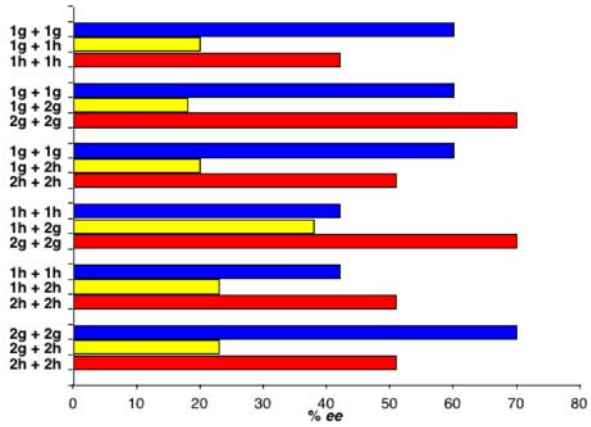
Another series of experiments was performed to compare rhodium- and iridium-based catalyst precursors in reactions using mixtures of the monodentate ligands **1g**, **1h**, **2g**, and **2h**; these data are shown in Figure 5. Throughout, 100 % conversion to the product was obtained under the conditions indicated. The data in Figure 6 clearly shows that the iridium complexes featured in part **a** generally gave superior enantioselectivities when compared to their rhodium analogs (**b**). For the Ir-data in part **a**, all the homo-combinations gave superior enantioselectivities than the heterocombinations (eg experiments with ~2 equivalents of ligand **1g**, and with ~2 equivalents of ligand **1h**, both gave better enantioselectivities than when **1g** and **1h** were used together in a 1:1 ratio; top of Figure 5a). In the Rh-series (Figure 5b) there are heterocombinations that proved to be more enantioselective than one of the homo-combinations, but never both.

Hydrogenations of α,β-Unsaturated Ester Derivatives With Monodentate Ligands. From the perspective of potential users, reduction of α-methylcinnamic acid **B** is probably less interesting than the corresponding reactions of α,ω-functionalized substrates like the alcohol **C** shown in Figure 6a, or the acetate **D** shown in Figure 6b. Data were collected only for the Ir-based complexes because such catalysts tend to be more suitable for this type of substrate (*ie* where the catalyst can be ligated by N,P-ligands and the substrate has functional groups that are only weakly coordinating),[38] and because Ir-based complexes were superior to the Rh-based ones for substrate **B**.



B 100 %

a M = Ir



b M = Rh

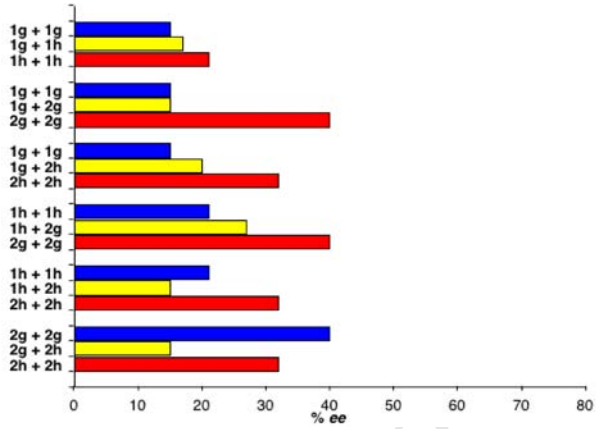
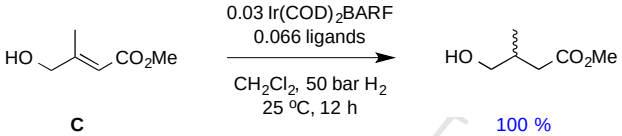


Figure 5. Hydrogenation of α-methylcinnamic acid **B** using catalysts formed from the monodentate ligands **1g**, **1h**, **2g**, and **2h** with: (**a**) $Ir(COD)_2^+$; and, (**b**) $Rh(COD)_2^+$.

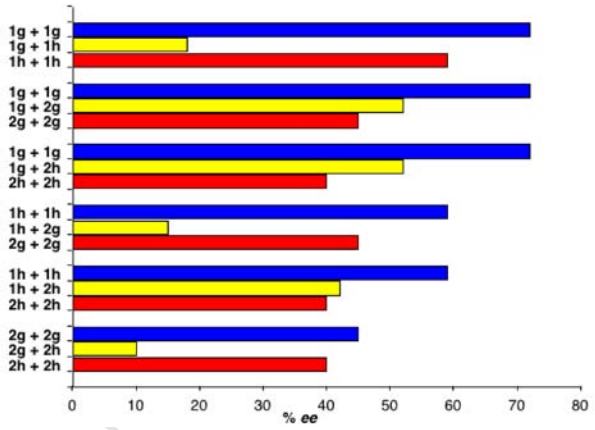
For alcohol **C**, Figure 6a shows that homocombinations of ligand **1g** (blue bars) gave the best enantioselectivities. In these iridium-mediated reactions, enantioselectivities for some heterocombinations (yellow bars) were superior to one homocombination, but there was no heterocombination that was superior to both the corresponding homocombinations. This is the same trend that was observed in the rhodium-catalyzed reactions in Figure 5.

Hydrogenations of α,β-Unsaturated Ester Derivatives With Bidentate Ligands Formed Via Metathesis. Having established enantioselectivities for the hydroxyester **C** and the acetoxyester **D** using monodentate ligands, we then used metathesis to form bivalent ligands from the same quinidine- and quinine-based phosphites in situ and tested these. In this, and all the other examples reported from this point on, the metathesis reactions were performed, the crude reaction mixtures were evaporated to dryness, dichloromethane, $Ir(COD)_2BARF$, and alkene substrate were added, then hydrogen was applied. Thus, no effort was made to purify the mixture of potential hydrogenation catalysts formed after the metathesis reactions.

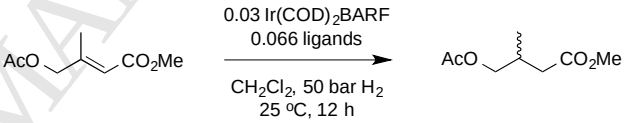
a



C 100 %



b



D 100 %

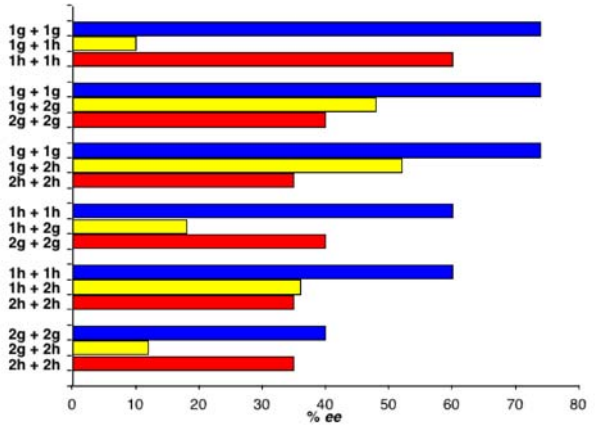


Figure 6. Hydrogenation of hydroxyester **C** (**a**) and acetoxyester **D** (**b**) using catalysts formed from the monodentate ligands **1g**, **1h**, **2g**, and **2h** with: $Ir(COD)_2^+$.

For example, in Figure 6, **1g** + **1h** refers to the combination of monodentate ligands, whereas in Figure 7, where these same monodentate ligands are subjected to metathesis as in Figure 3, **1g' - 1h'** refers to that heterocombination (which contains two homodimers and one heterodimer; see above). The bars in Figure 8 show the enantioselectivity differences obtained relative to the corresponding hydrogenations with the corresponding combinations of monodentate ligands; positive values indicate the dimer combinations gave superior enantioselectivities. Throughout, the sense of the enantioselection is governed by the

binaphthyl chirality, series **g** gives the *S*-enantiomer while the R-enantiomer is consistently formed from the **h** series. Enantioselectivity values (as opposed to differences) are indicated by the numbers on the bars themselves. Thus an improvement of up to 37 % *ee* was observed under the metacatalysis for the hydroxyester C (Figure 7a), and up to 34 % for the acetoxyester (7b). Interestingly, the same combination, **1h' – 2g'**, gave the maximum improvement for the hydroxyester C and the acetoxyester D. However, the overall best selectivities for these reactions were in the monomer combination series (**1g** + **1g** in Figure 6a and b) and not for the dimers formed via metathesis.

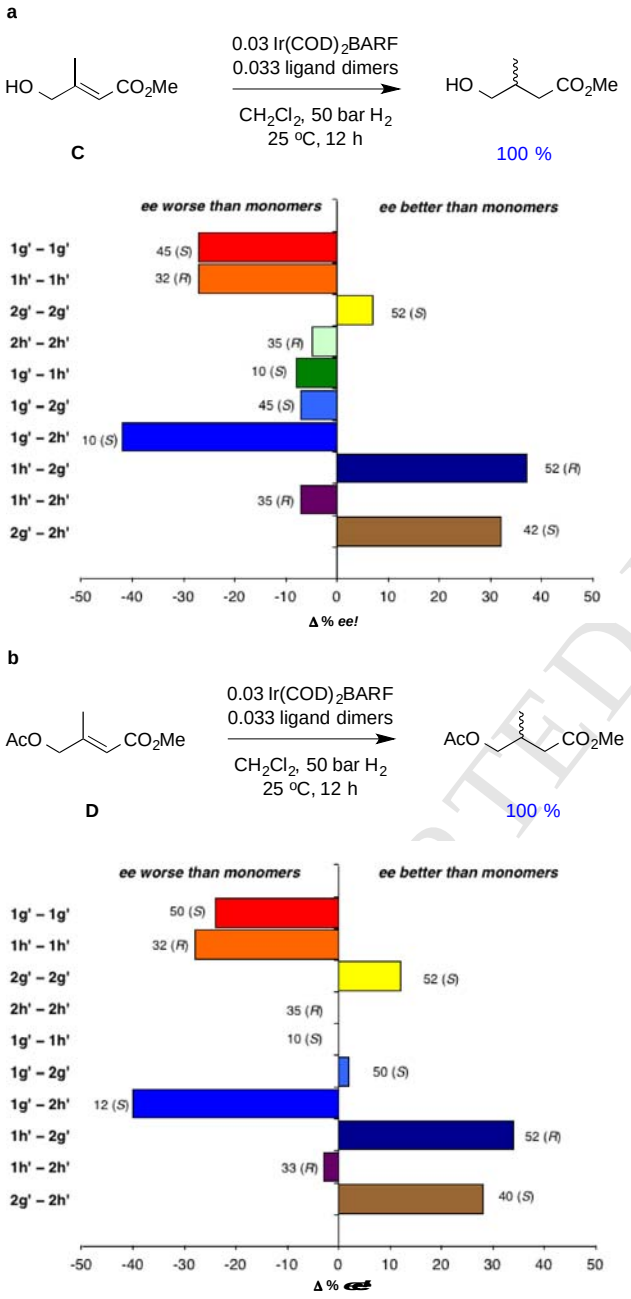


Figure 7. Hydrogenation of hydroxyester **C** (**a**) and acetoxyester **D** (**b**) using catalysts from the monodentate ligands **1g**, **1h**, **2g**, and **2h** after metathesis (as in Figure 3) then addition of $Ir(COD)_2^+$. The bars are calibrated to the corresponding combination of monodentate ligands, and the overall enantioselectivities are indicated by the numbers on the bars.

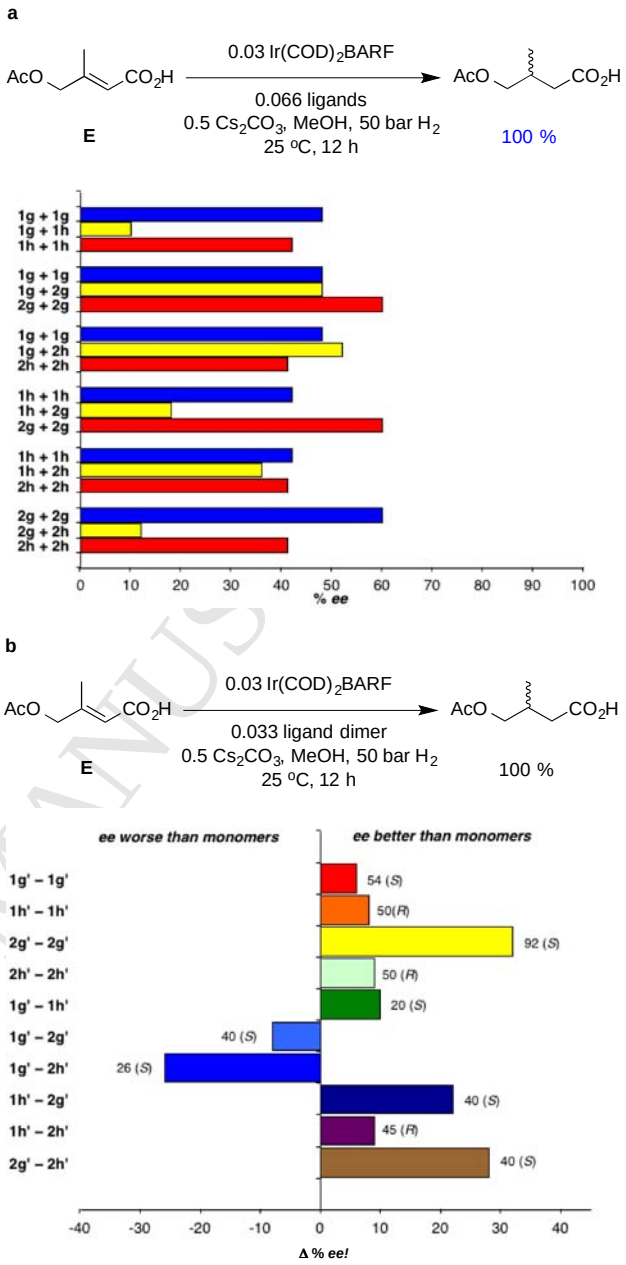


Figure 8. Hydrogenation of the acetoxy acid **E** using: (**a**) catalysts from the monodentate ligands **1g**, **1h**, **2g**, and **2h**; and (**b**) from the same ligands after metathesis (as in Figure 3). The bars in part b are calibrated to the corresponding combination of monodentate ligands, and the enantioselectivities are indicated by the numbers on the bars.

Finally, we decided to test one of the carboxylic acid substrates that correspond to one of Figure 7. For these experiments the acetoxy acid **E** was selected because acetates gave marginally higher enantiosectivities than the alcohols for the esters in Figure 6 with monodentate ligands. Data for hydrogenation of the acetoxy acid **E** (Figure 8) show a maximum improvement of 32 % *ee* (for **2g' – 2g'**). The best overall selectivity for the carboxylic acid hydrogenations in Figure 8 is for **2g** + **2g** and **2g' – 2g'**, *ie* the same combination in the monomer (**a**) and dimer (**b**) series. The optimal enantioselectivity was superior for the dimers (**b**) from metathesis relative to the monomers (**a**) (92 vs 60 % *ee* for the combinations involving **2g**).

Data was also collected for hydrogenation of the acetoxy acid **E** with and without metathesis using $Rh(COD)_2^+$ {rather than $Ir(COD)_2^+$ as in Figure 8}. Some of the reactions with metathesis showed improvements relative to the ones without, but the best overall enantioselectivity (75 %) was observed for a monomer combination. This data is shown in the supporting materials.

3. Conclusions

The paper must include the following: (1) Introduction, (2) Results/Discussion, (3) Conclusion, (4) Experimental Section and (5) References. Supplementary data and other sections are optional. You will usually want to divide your article into (numbered) sections and subsections (perhaps even subsubsections). Code section headings using the options in the 'Styles' menu. Headings should reflect the relative importance of the sections. Note that text runs on after a 4th order heading. Use the heading style for the whole paragraph, but remove the italic coding except for the actual heading. These studies have shown that ligands can be formed via metathesis reactions, then used in hydrogenation catalysts formed *in situ*, thus the concept of metathesis then catalysts, *metacatalysis*, is validated. Residual ruthenium complexes from the metathesis steps do not mediate hydrogenations of the substrates studied here. Relative to controls with monomeric starting materials (series **1** and **2**), metathesis of the ligands can have positive and negative effects on the enantioselectivities (see Figure 8 and 9b). Only four monomeric starting materials were used (**1g** and **h**, **2g** and **h**) to explore metacatalysis here, but in general for *n* ligands there would be $n(n + 1)/2$ possible combinations; if *n* is a larger number many combinations can be generated (*eg* for $n = 10$, the number of possibilities is 55)[39] so, just like mixing monodentate ligands, this is an effective form of combinatorial catalysis.[40-43] Overall enantioselectivities observed (up to 92 %) were good but not excellent, and there are several obvious reasons why this might be so. Throughout, the bisphosphites formed in this study would form huge chelates if they complexed in the M*PP* form, so they are likely to be somewhat flexible. Moreover, the alkene formed between the two monomeric fragments is almost certainly reduced in these reactions, and rapidly compared with the more substituted alkene substrates, hence the ligands change early in the hydrogenation. On the other hand, one of the objectives we had at the onset of this study was to see if we could find ligands via metathesis that were effective despite these factors, and indeed enantioselectivities of up to 92 % *ee* were obtained. Rational design is most effective for relatively simple systems for which some parameters can be predicted with certainty, whereas combinatorial methods tend to be relatively more effective as the opportunities for rational design diminish. Thus an attribute of the strategy described here is that the "ligand space" can be screened includes cases wherein the preferred mode of coordination of the ligands cannot be reliably predicted.

This research has shown that the dominant parameter governing stereodifferentiation by ligands **1** and **2** is the alkoxy *P*-substituent, and binaphthyl was the best studied here. The alkaloid fragment in the ligands has much less impact than the binaphthyl. Metathesis coupling of the alkaloid fragments is relatively slow, requiring 12 h in refluxing dichloromethane, though, given time, conversion to the dimeric forms **1'** and **2'**, was near complete.

The most enantioselective catalyst found in this study was from the metathesis coupling product **2g' – 2g'** (92 % *ee*, Figure 8b, third entry). This ligand, **2g' – 2g'**, is a *homo*-combination so it was not necessary to deconvolute mixtures from *hetero*-combinations to find the best ligand-metathesis products: we were able to demonstrate proof of concept without doing that. This is fortunate because, as alluded to above, the polarities of these particular molecules are dominated by the huge and similar alkaloid parts, hence we were unable to separate the various metathesis combinations even by analytical HPLC. There is an important conclusion to be drawn from this: separations in of ligands formed via metathesis can be problematic, so the "end game" in the method is likely to be easiest to implement if the alkenes combined have different polarities or other features that make homo- and hetero-combinations separable.

^{31}P study of the monomer **1g** showed that its chemical shift was shifted to 144.9 when $Ir(COD)_2^+$ was added. Same study was done for the *homo*-combination **1g' – 1g'**. The results showed that the ^{31}P chemical shift of dimer **1g' – 1g'** with $Ir(COD)_2^+$ was shifted to 145.2 ppm compared to the one without $Ir(COD)_2^+$ (148.5 ppm). Even though the chemical shift wasn't changed significantly, this study still indicated that there is chelation between P-centered of ligand with metal.

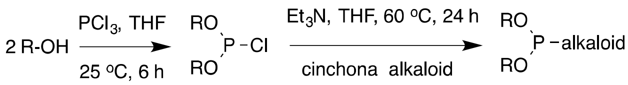
Based on observations from this work, further studies of metacatalysis might focus on ligand fragments that give more distinct differences between homo- and hetero-dimeric products. That strategy would be desirable because mixture analyses would be easier, and the diversity of ligands created would be greater. Another obvious modification would be to use alkene-monomers with potential complexing atoms that are closer to the metathesis site. This strategy would produce smaller chelates, but it is somewhat limited by the undesirable potential for deactivation of the metathesis catalyst by association of the complexing atom to the ruthenium carbene center. For this reason, the design of the alkene-monomers requires careful consideration.

Metacatalysis need not be restricted to hydrogenation reactions. Indeed, one intriguing possibility for alkaloid-based ligands would be to explore oxidation processes including, and related to, Sharpless' dihydroxylations, for which cinchona alkaloids are known to be highly effective.[44] Moreover, there are possibilities for using other transformations to join monomeric fragments *in situ*, the only obvious restrictions being that they should be efficient and generate no by-products that adversely effect the subsequent reactions. We suggest metacatalysis is an option for expanding the combinatorial methodology established by Reetz and others, and it has the advantage of generating diverse, potentially chelating ligands. On a broader level, our method complements others that allow generation of diverse libraries of bidentate ligands by combining monodentate ones;[39,45-71] notably, those include dynamic combinatorial libraries formed from fragments having complementary *H*-bonding topologies.[72-78]

4. Experimental section

General Procedures: All reactions were carried out under an inert atmosphere (nitrogen or argon where stated) with dry solvents under anhydrous conditions. Glassware for anhydrous reactions was dried in an oven at 140 ^oC for minimum 6 h prior to use. Dry solvents were obtained by passing the previously degassed solvents through activated alumina columns. Reagents were purchased at a high commercial quality (typically 97 % or higher) and used without further purification, unless otherwise stated. High field NMR spectra were recorded at 300 MHz for ^1H, 75 MHz for ^{13}C and 121 MHz for ^{31}P. Chemical shifts of 1H and 13C spectra were referenced to the NMR solvents. Flash chromatography was performed using silica gel (230–600 mesh).

Thin layer chromatography was performed using glass plates coated with silica gel 60 F254. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dq = double quartet m = multiplet, br = broad.



1 and **2**

General Procedure for Preparation of 1 and 2.

A solution of appropriate alcohol (2 equiv) or diol (1 equiv) in THF was added dropwise to phosphorus trichloride (0.42 g, 3 mmol) under nitrogen. The mixture was stirred at room temperature until completion (TLC). Subsequently, selected cinchona alkaloids (3 mmol) were added to the mixture followed by triethylamine (3 mL). The reaction was stirred and heated to 60 °C for 24 h, then the suspension was filtered and the mother liquor was concentrated to give a light yellow solid. This solid was dissolved in water and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure to give light yellow crude product. The product purified by flash column chromatography on silica gel using n-hexane/acetone/triethylamine (3:3:1) as the eluent.

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-(Benzo[*d*][1,3,2]dioxaphosphol-2-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **1a** (0.85 g, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, d, *J = 4.5* Hz), 7.90 (1H, d, *J = 9.3* Hz), 7.52 (1H, d, *J = 4.5* Hz), 7.24 (1H, dd, *J = 2.4*, *6.0* Hz), 7.16 (1H, d, *J = 2.7* Hz), 6.12-6.00 (2H, m), 5.72 (1H, d, *J = 3.3* Hz), 5.31 (1H, s), 5.10-5.08 (1H, m), 5.06-5.04 (1H, m), 3.82 (3H, s), 3.54-3.46 (1H, m), 3.08-2.76 (4H, m) 2.27-2.22 (1H, m), 2.16-2.07 (2H, m), 1.77 (1H, br), 1.57-1.47 (1H, m) 1.26 (1H, s), 1.13-1.04 (1H, m), 0.90-0.87 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ [illegible], 119.9, 118.9, 118.0, 116.5, 100.0, 70.6, 59.4, 55.3, 48.9, 45.8, 37.5, 27.8, 23.6, 18.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 143.5. HRMS (ESI): Exact mass calc'd for $C_{26}H_{27}N_2O_4P$ *ie* [M+H]$^+$ 463.1787. Found 463.1762.

bis(Adamantan-1-ylmethyl) ((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) phosphite; **1b** (0.5 g, 48%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.74 (1H, d, *J = 4.5* Hz), 8.02 (1H, d, *J = 9.3* Hz), 7.58 (1H, d, *J = 4.5* Hz), 7.53-7.05 (3H, m), 6.10-5.97 (2H, m), 5.28 (1H, d, *J = 3.6* Hz), 5.18-5.02 (1H, m), 4.03 (3H, s), 3.73-3.60 (2H, m), 3.48 (1H, d, *J = 6.6* Hz), 3.40-2.75 (4H, br), 2.10-1.81 (9H, m), 1.74-1.48 (20H, m), 1.45-1.23 (6H, m), 1.05-0.83 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 147.5, 145.6, 144.9, 137.0, 126.1, 122.5, 122.0, 119.5, 118.6, 75.4, 74.9, 74.7, 66.8, 61.7, 56.4, 49.9, 49.0, 39.9 (2 peaks), 39.8, 38.7, 38.6, 38.5, 38.3, 37.6, 37.5 (2 peaks), 37.1, 28.6, 28.4, 24.2, 19.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ 145.2. HRMS (ESI): Exact mass calc'd for $C_{42}H_{57}N_2O_4P$ *ie* [M+H]$^+$ 685.4134. Found 685.4198.

bis(Adamantan-1-yl) ((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) phosphite; **1c** (0.6 g, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.73 (1H, d, *J = 4.5* Hz), 7.98 (1H, d, *J = 9.3* Hz), 7.61 (1H, d, *J = 4.5* Hz), 7.33-7.29 (1H, m), 7.20-7.19 (1H, m), 6.06 (1H, dd, *J = 9.6*, *12.9* Hz), 5.99-5.92 (1H, b), 5.14 (2H, s), 5.12-5.08 (1H, m), 3.86 (3H, s), 3.64-3.59 (1H, m), 3.51, (10H, b), 3.17-3.00 (6H, m), 2.94-2.86 (4H, m), 2.39-2.30 (4H, m), 2.20-2.08 (3H, m) 2.19-1.84 (4H, m), 1.71-1.09 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ [illegible]; ^{31}P NMR (121 MHz, $CDCl_3$) δ 140.8. HRMS (ESI): Exact mass calc'd for $C_{40}H_{53}N_2O_4P$ *ie* [M+H]$^+$ 657.3821. Found 657.3797.

bis(2,6-Diisopropylphenyl)-((*S*)-(6-methoxyquinolin-4-yl)((1*S*,2*R*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl) phosphite; **1d** (0.6 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51-8.50 (1H, m), 8.15-8.13 (1H, m), 8.02-7.95 (2H, m), 7.33-7.29 (1H, m), 7.85-7.82 (1H, m), 7.42-6.97 (5H, m), 6.74-6.73 (1H, m), 5.93-5.69 (2H, m), 5.11-4.92 (4H, m), 3.48-3.142 (2H, m), 3.27-3.15 (1H, m), 2.97-2.46, (10H, m), 2.14-2.07 (2H, m), 1.59-1.55 (3H, m), 1.45-1.32 (3H, m), 1.29-1.26 (6H, m) 1.17-1.15 (6H, m), 1.00-0.88 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ [illegible] 133.6, [illegible] (2 peaks) [illegible] (2 peaks) [illegible], 101.0, 55.3, 50.0, 49.9, 49.7 (2 peaks), 49.6, 49.4, 49.3, 40.2, 39.9, 28.1, 28.0, 27.9, 27.5, 27.1, 26.3, 23.8, 23.6, 23.4, 23.1, 22.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 143.5. HRMS (ESI): Exact mass calc'd for $C_{44}H_{57}N_2O_4P$ *ie* [M+H]$^+$ 709.4134. Found 709.4202.

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-(((4*S*,5*S*)-4,5-Diphenyl-1,3,2-dioxaphospholan-2-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **1e** (0.3 g, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, d, *J = 4.4* Hz), 7.92 (1H, d, *J = 9.3* Hz), 7.50 (1H, d, *J = 4.5* Hz), 7.15-7.03 (5H, m), 6.95-6.76 (7H, m), 6.18-6.05 (2H, m), 5.80 (1H, d, *J = 3.3* Hz), 5.31 (1H, s), 5.10-5.02 (2H, m), 4.02 (3H, s), 3.62-3.47 (4H, m), 3.28-3.15 (2H, m) 2.27-2.22 (1H, m), 2.10-2.03 (2H, m), 1.73-1.68 (1H, m), 0.90-0.87 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ [illegible] (2 peaks), 130.2 (2 peaks), 129.7, [illegible], 119.3, 118.5, 117.9, 117.0, 100.1, 70.6, 64.8, 63.4, 59.4, 55.3, 48.3, 45.8, 37.3, 27.8, 23.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 144.1. HRMS (ESI): Exact mass calc'd for $C_{34}H_{35}N_2O_4P$ *ie* [M+H]$^+$ 567.2413. Found 567.2467.

(1*S*,2*R*,4*S*,5*R*)-2-((*S*)-(((4*R*,5*R*)-4,5-Diphenyl-1,3,2-dioxaphospholan-2-yl)oxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **1f** (0.4 g, 50%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (1H, d, *J = 4.5* Hz), 8.03 (1H, d, *J = 9.2* Hz), 7.61 (1H, d, *J = 4.5* Hz), 7.38-7.30 (5H, m), 7.11-6.94 (6H, m), 6.06-5.95 (2H, m), 5.15 (1H, s), 5.11 (2H, d, *J = 8.0* Hz), 3.91 (3H, s), 3.86-3.70 (1H, m), 3.27-2.85 (5H, m) 2.34-2.31 (1H, m), 2.22-2.16 (1H, m), 1.86 (1H, m), 1.69-1.59 (2H, m), 1.12-1.10 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ [illegible], 148.2, [illegible] 130.8 (2 peaks), 130.2 (2 peaks), 129.5, [illegible], 119.5, 118.1, 117.0, 100.0, 71.2, 64.5, 63.7, 59.5, 49.0, 47.5, 46.0, 37.8, 27.8, 18.8; ^{31}P NMR (121 MHz, $CDCl_3$) δ 144.2. HRMS (ESI): Exact mass calc'd for $C_{34}H_{35}N_2O_4P$ *ie* [M+H]$^+$ 567.2413 Found 567.2471.

(1*S*,2*R*,4*S*,5*R*)-2-((1*S*)-(Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **1g** (0.5 g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (1H, d, *J = 4.5* Hz), 8.05 (1H, d, *J = 9.3* Hz), 7.96-7.78 (2H, m), 7.70-7.51 (4H, m), 7.51-7.03 (9H, m), 6.24-6.06 (2H, m), 5.85-5.70 (1H, m), 5.29 (1H, s), 3.98 (3H, s), 3.25-3.16 (1H, m) 2.90-2.53 (2H, m), 2.05-1.90 (1H, m), 1.81-1.75 (1H, m), 1.52-1.27 (3H, m), 0.92-0.85 (3H. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 1[illegible]7.6, 147.9, 145.8, 145.3, 142.1, 135.7, 135.5, 132.7, 132.6, 132.5, 132.4, 132.2, 131.6, 131.5 (2 peaks), 131.3, 131.2 (2 peaks), 130.9, 130.7, 130.0, 129.5, 129.1, 128.8, 127.5, 127.3, 1[illegible]3.5, 119.3, 102.1, 80.1, 62.1, 55.8, 52.1, 50.9, 37.3, 27.8, 27.0, 26.1, 12.1; ^{31}P NMR (121 MHz, $CDCl_3$) δ

148.6. HRMS (ESI): Exact mass calc'd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2477.

(1*S*,2*R*,4*S*,5*R*)-2-((1S)-((11*bS*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **1h** (0.5 g, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (1H, d, *J = 4.5* Hz), 8.10 (1H, d, *J = 9.3* Hz), 8.05-7.82 (2H, m), 7.78-7.70 (4H, m), 7.65-7.08 (9H, m), 6.32-6.25 (2H, m), 5.80-5.70 (1H, m), 5.29 (1H, s), 3.96 (3H, s), 3.28-3.19 (1H, m), 2.92-2.53 (2H, m), 2.05-1.90 (1H, m), 1.78-1.75 (1H, m), 1.51-1.27 (3H, m), 0.92-0.85 (3H. m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 153.0, 147.5, 147.2, 147.1, 144.6, 144.2, 140.1, 139.9, 133.8, 131.9, 131.8, 131.7, 130.6, 129.2, 128.5, 128.2, 126.9, 126.0, 125.8, 124.6, 123.5, 121.7, 121.0, 118.7, 118.2, 115.0, 114.8, 112.6, 100.8, 679, 59.8, 55.8, 55.6, 55.5, 49.7, 49.1, 48.5, 46.0, 39.7, 39.6, 29.7, 27.9, 27.7, 27.6, 26.3, 26.2, 25.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.6. HRMS (ESI): Exact mass calc'd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2437.

(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11*bR*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **2g** (0.4 g, 80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63 (1H, d, *J = 4.5* Hz), 7.97-7.80 (5H, m), 7.53 (2H, d, *J = 3.3* Hz), 7.48-7.40 (1H, m), 7.29-7.04 (8H, m), 6.45-6.40 (2H, m), 5.65-5.48 (1H, m), 5.03 (1H, d, *J = 3.6* Hz), 4.98 (1H, s), 4.38-4.30 (1H, m), 3.63(3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.75-2.50 (1H, m), 2.04-1.97 (1H, m), 1.77-1.46 (1H, m), 1.32-1.15 (2H, m), 0.92-0.85 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (2 peaks), 132.4 (2 peaks), 132.2, 131.8 (2 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, ı□3.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7. HRMS (ESI): Exact mass calc'd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2437.

(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11*bS*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine; **2h** (0.3 g, 72 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (1H, d, *J = 4.8* Hz), 8.05-7.87 (5H, m), 7.80-7.66 (2H, m), 7.54-7.52 (1H, m), 7.42-7.16 (8H, m), 6.95-6.79 (2H, m), 5.60-5.49 (1H, m), 5.03-4.95 (1H, m), 4.41-4.37 (1H, m), 4.33-3.56 (4H, m), 3.30-3.23 (1H, m), 2.65-2.64 (1H, m), 2.31-1.78 (5H, m), 1.55-1.01(3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 152.3, 149.5, 149.4, 147.0, 144.3, 141.6, 141.5, 138.0 (2 peaks), 137.8, 137.7, 137.5, 134.4, 132.6, 131.7, 131.6, 131.1, 130.1, 128.2, 127.8, 127.0, 125.9 (2 peaks), 125.5, 125.0, 124.6, 122.8, 122.3 (2 peaks), 122.2 (2 peaks), 122.1, 122.0 (2 peaks), 118.9 (2 peaks), 59.4, 54.3, 37.1, 26.8, 24.2, 18.7; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7. HRMS (ESI): Exact mass calc'd for $C_{40}H_{35}N_2O_4P$ *ie* $[M+H]^+$ 639.2413. Found 639.2437.

General Procedure for Metathesis of Cinchona Alkaloid Ligands.

Appropriate cinchona alkaloid was added to 2nd Generation Hoveyda-Grubb's catalyst (5 mol %) in CH_2Cl_2 in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 ^oC for 12 h. Ar (balloon) was changed every 4 - 6 h. Solvent was removed under reduced pressure and the crude metathesis was used in the next step without further purification.

The following purification was used only for characterized homodimer to check the disappearance of monomer starting material. The product was purified by flash column chromatography on silica gel using n-hexane/CH_2Cl_2/ triethylamine (6:3:1) as the eluent.

(1*S*,2*R*,4*S*,5*R*)-2-((1*S*)-(Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **1g' – 1g'**. 35 % isolated yield. ^{1}H NMR (300 MHz, $CDCl^3$) δ 8.65 (1H, d, *J = 4.5* Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, *J = 3.3* Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, *J = 3.6* Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H, m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (2 peaks), 132.4 (2 peaks), 132.2, 131.8 (2 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, ı□3.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.6.

(1*S*,2*R*,4*S*,5*R*)-2-((1*S*)-((11*bS*)-Dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **1h' – 1h'**. 31 % isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J = 4.5* Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, *J = 3.3* Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, *J = 3.6* Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H, m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (2 peaks), 132.4 (2 peaks), 132.2, 131.8 (2 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, ı□3.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.6.

(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11*bR*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **2g' – 2g'**. 40 % isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J = 4.5* Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, *J = 3.3* Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, *J = 3.6* Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H, m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6, 132.4, 132.2, 131.8, 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, ı□3.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.8, 12.6; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7.

(1*S*,2*S*,4*S*,5*R*)-2-((1*R*)-((11*bS*)-dinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepin-4-yloxy)(6-methoxyquinolin-4-yl)methyl)-5-vinylquinuclidine dimer; **2h' – 2h'**. 35 % isolated yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J = 4.5* Hz), 7.94-7.80 (5H, m), 7.56 (2H, d, *J = 3.3* Hz), 7.45-7.40 (1H, m), 7.31-7.03 (8H, m), 6.02-5.98 (1H, m), 5.60-5.48 (1H, m), 5.03 (1H, d, *J = 3.6* Hz), 4.95 (1H, s), 4.41-4.30 (1H, m), 3.62 (3H, s), 3.34-3.29 (1H, m), 3.03-2.98 (1H, m), 2.94-2.54 (2H, m), 2.09-1.93 (1H, m), 1.76-1.47 (1H, m), 1.51-1.27 (2H, m), 0.95-0.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 153.2, 148.1, 145.5, 145.0, 139.5, 135.8, 135.3, 132.8, 132.6 (3 peaks), 132.4 (2 peaks), 132.2, 131.8 (3 peaks), 131.5, 130.0 (2 peaks), 128.9, 128.8, 125.8, ı□3.3, 119.5, 101.3, 79.8, 62.4, 55.3, 52.1, 50.8, 39.1, 27.8, 27.3, 26.3, 12.5; ^{31}P NMR (121 MHz, $CDCl_3$) δ 148.7.

Preparation of (*E*)-Methyl 4-Hydroxy-3-methylbut-2-enoate.

(*E*)-4-Methoxy-3-methyl-4-oxobut-2-enoic acid;

To a solution of (1-methoxy-1-oxopropan-2-yl)triphenyl-phosphonium bromide (42.9 g, 100 mmol, 1 equiv) in dry CH_3CN (300 mL) was added triethylamine (13.2 mL, 95 mmol, 0.95 equiv) and glyoxylic acid monohydrate (8.74 g, 95 mmol, 0.95 equiv) at 0°C. The solution was further stirred at 0°C for 2 h and at room temperature overnight. Half of the solvent was removed under reduced pressure, and ethyl acetate (100 mL) was added. The resulting solution was washed with saturated aqueous $NaHCO_3$ (3 × 50 mL). The combined aqueous layers were extracted with ethyl acetate (2 × 50 mL), acidified (pH 1 - 2) at 0 °C with concentrated HCl (50 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were evaporated to dryness, yielding a clear oil (10.5 g, 73 %) which was used for the next reaction without further purification.

(*E*)-4-Hydroxy-3-methylbut-2-enoic acid;

$LiBH_4$ (2 equiv) was added to (*E*)-4-methoxy-3-methyl-4-oxobut-2-enoic acid in THF (100 mL at 0 °C. The reaction mixture was then allowed to ambient temperature and stirred for 12 h. The mixture was poured into 1N HCl and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and solvent was removed under reduced pressure to yield the product as a white solid (16 g, 69 %) which was used for the next reaction without further purification.

(*E*)-Methyl 4-Hydroxy-3-methylbut-2-enoate, **C**;

To a solution of H_2SO_4 (5 mL) in 50 mL of MeOH, (*E*)-4-hydroxy-3-methylbut-2-enoic acid was added at room temperature. The mixture was stirred and refluxed for 4 h. After cooling to ambient temperature, solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2. The organic layer was washed with $NaHCO_3$, brine and dried over Na_2SO_4. Solvent was removed under reduced pressure to obtain product **C** as a clear oil (8 g, 62 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (1H, s), 4.29 (2H, s), 3.77 (3H, s), 1.79 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 167.2, 126.3, 52.8, 14.4. HRMS (ESI): Exact mass calc'd for $C_6H_{10}O_3$ ie $[M+H]^+$ 131.0708. Found 131.0710.

Preparation of (*E*)-Methyl 4-Acetoxy-3-methylbut-2-enoate, **D**.

To a solution of (*E*)-methyl 4-hydroxy-3-methylbut-2-enoate (1 mmol) and pyridine (3 mmol) in CH_2Cl_2 (7 mL), Ac_2O (1.5 mmol) was added at room temperature and the mixture was stirred until completion (TLC). After completion, the reaction mixture was diluted with CH_2Cl_2 (30 mL), washed with water (15 mL), brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by chromatography using 30% EtOAc/hexane to yield (92 %) product D as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (1H, s), 4.30 (2H, s), 3.85 (3H, s), 2.08 (3H, s), 1.81 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.8, 165.2, 126.9, 54.8, 23.6, 16.8. HRMS (ESI): Exact mass calc'd for $C_8H_{12}O_4$ *ie* $[M+H]^+$ 173.0814. Found 173.0881.

General Procedure for Hydrogenation Using Metathesis Catalysts (without Ir)

For monodentate ligand; 2nd Generation Hoveyda-Grubb's catalyst (0.3 mol %, same amount as use in study reaction) and **1g** was dissolved in CH_2Cl_2 (0.5 M). The mixture was stirred for 15 min, then alkene (0.25 mmol) was added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent.

For bidentate ligand; 2nd Generation Hoveyda-Grubb's catalyst (0.3 mol %, same amount as use in study reaction) and **1g** was dissolved in CH_2Cl_2 (0.5 M) in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 °C for 12 h. Ar (balloon) was changed every 4 - 6 h. Solvent and other volatile compounds were removed under reduced pressure. The residue was used for the next step without further purification.

New CH_2Cl_2 (0.5 M) was added to the residue, then alkene (0.25 mmol) was added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent.

Catalytic Hydrogenation Conditions

Condition A (for ester substrates);

For monodentate ligand study; $Ir(COD)_2BARF$ (3 mol %) and appropriate monodentate ligand (6.6 mol %) was dissolved in CH_2Cl_2 (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated ester (0.25 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.

For bidentate ligand study; Appropriate cinchona alkaloid was added to 2nd Generation Hoveyda-Grubb's catalyst (5 mol % based on cinchona alkaloid) in CH_2Cl_2 in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 ^{o}C for 12 h. Ar (balloon) was changed every 4 - 6 h. Solvent and other volatile compounds were removed under reduced pressure. The residue was used for the next step without further purification.

$Ir(COD)_2BARF$ (3 mol %) and appropriate cinchona alkaloid ligand (from previous step) was dissolved in CH_2Cl_2 (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated ester (0.25 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC or HPLC analysis.

Condition B (for acid substrates);

For monodentate ligand study; $Ir(COD)_2BARF$ or $Rh(COD)_2BARF$ (3 mol %) and appropriate monodentate ligand (6.6 mol %) was dissolved in MeOH (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated acid (0.25 mmol) and Cs_2CO_3 (0.13 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica

plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC analysis.

For bidentate ligand study; Appropriate cinchona alkaloid was added to 2nd Generation Hoveyda-Grubb's catalyst (5 mol % based on cinchona alkaloid) in CH_2Cl_2 in schlenk tube under Ar (Balloon). The mixture was stirred and heated to 40 °C for 12 h. Ar (balloon) was changed every 4 - 6 h. Solvent and other volatile compounds were removed under reduced pressure. The residue was used for the next step without further purification.

$Ir(COD)_2BARF$ or $Rh(COD)_2BARF$ (3 mol %) and appropriate cinchona alkaloid ligand (from previous step) was dissolved in MeOH (0.5 M). The mixture was stirred for 15 min, then corresponding unsaturated acid (0.25 mmol) and Cs_2CO_3 (0.13 mmol) were added to the mixture. The resulting mixture was degassed by three cycles of freeze-pump-thaw and then transferred to a Parr Bomb. The bomb was pressurized to 50 bar with hydrogen and the mixture was stirred at 300 rpm for 16 h. The bomb was then vented and solvent was evaporated. The crude product was passed through a short silica plug using 30% EtOAc/hexanes as the eluent. The enantiomeric ratio was then measured through chiral GC analysis.

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Supplementary Material

^{1}H and ^{13}C NMR spectra of **1a – h**, **2g – h**, GC traces after hydrogenation of 1,2-diphenylpropene, α-methylcinnamic acid **B**, hydroxyester **C**, acetoxyester **D**, acetoxy acid **E** with $Ir(COD)_2^+$, hydrogenation of α-methylcinnamic acid **B** with ligand **1g** and PPh_3 and hydrogenation of acetoxy acid **E** with $Rh(COD)_2^+$. The supplementary information was available online.

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