Homologation of Monoterpenoids into New Sesquiterpenoids *via* Tandem Isomerisation/Claisen Rearrangement Reactions with Three-Component Ruthenium Catalysts, and Ru(methallyl)$_2$(COD) Revealed by High Throughput Screening Techniques

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Abstract: A catalytic system **B** based on a ruthenium source $Ru_3(CO)_{12}$, a bulky imidazolinium salt and Cs_2CO_3 appears very efficient for the transformation of a 1,7-diene into a γ,δ-unsaturated aldehyde *via* tandem isomerisation/Claisen reactions. 1,6-Dienes arising from the terpenoids menthone and myrtenal were selectively transformed into the corresponding unsaturated aldehydes with catalyst **B**. High throughput experiments were undertaken to evaluate other multicomponent catalysts: metal source/ligand/base for these tandem reactions. An unexpected catalyst was found to be Ru(methallyl)$_2$(COD) which can operate without additional ligand or reagent.

Keywords: alkene isomerisation; Claisen reaction; high throughput screening; ruthenium catalysts; terpenoids; unsaturated aldehydes

Introduction

Since its discovery in 1912,[1] the Claisen reaction and related [3,3]-sigmatropic rearrangements represent powerful methods for the formation of carbon-carbon bonds.[2] However, the required initial synthesis of vinyl ethers constitutes, most of the time, a difficulty in the access to the starting materials.[3] A potential alternative method consists in the combination of the isomerisation of allyl ethers into vinyl ethers followed by thermal Claisen rearrangement in the same reaction process.

Ruthenium species such as ruthenium hydride[4] or ruthenium carbonyl[5] derivatives are well-known catalyst precursors to perform alkene isomerisation, even in an enantioselective way.[6] Ruthenium alkene metathesis catalysts have also shown propensity to isomerise alkenes, in competition with the metathesis reaction.[7,8] The Claisen rearrangement of diallyl ethers is catalysed by $RuCl_2(PPh_3)_3$ at high temperature (150 °C),[9] whereas milder conditions are possible with iridium[10] and rhodium[11] complexes. Recently, it has been shown that an indenylidene-ruthenium catalyst was able to perform ring closing metathesis (RCM), isomerisation and Claisen rearrangement, successively.[8] By contrast, in the study of *in situ* prepared imidazolinylidene-ruthenium catalysts for RCM of 1,6-dienes and 1,6-enynes[12–14] we found initial results[15] showing that these catalysts did not perform RCM or cycloisomerisation of 1,7-dienyl ethers but selectively led to tandem isomerisation/Claisen rearrangement affording γ,δ-unsaturated aldehydes (Scheme 1).

We now report on (i) the use of *in situ* prepared catalysts, using imidazolinium salts and a ruthenium source, especially $Ru_3(CO)_{12}$, for the isomerisation/Claisen rearrangement of 1,7- and 1,6-dienyl ethers into γ,δ-unsaturated aldehydes, allowing the transformation of natural monoterpenoids into new sesquiterpenoids, and (ii) the use of high throughput experiments for the discovery of a simple and highly active new catalyst, Ru(methallyl)$_2$(COD), for alkene isomerisation and to perform this tandem reaction, without any additional ligand or reagent.

Results and Discussion

The Catalytic System A: Discovery and Tuning

In our preliminary study,[15] the first evidence of the use of an *in situ* generated catalytic system based on a ruthe-

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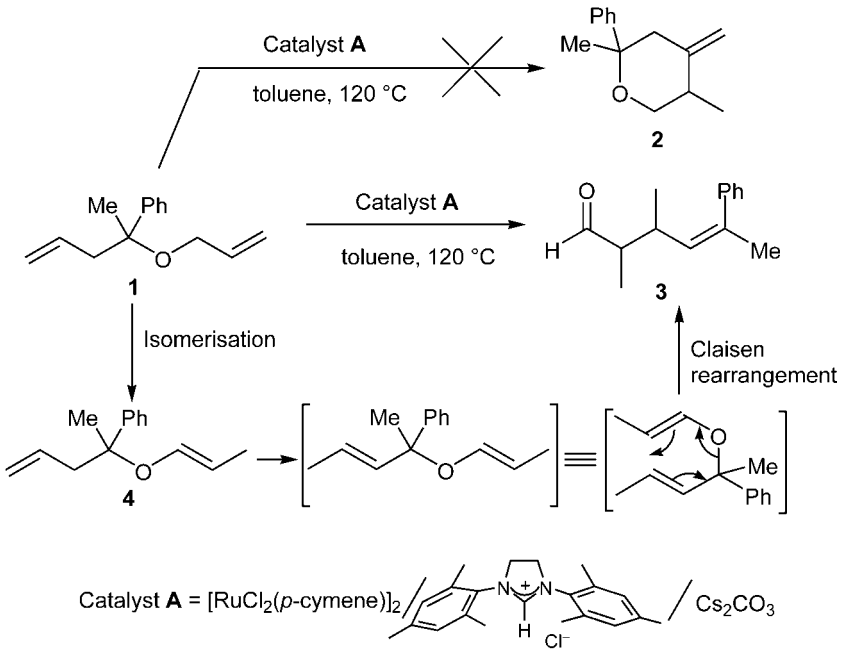


Scheme 1.

Table 1. Catalytic transformation of the dienyl ether **1**.[a]

Entry	Ru source	Imidazolinium	Time [h]	Conversion [%]	Compounds
1	$RuCl_2(p\text{-cymene})(PCy_3)$	None	16	100	**4**
2	$[RuCl_2(p\text{-cymene})]_2$	$Im(Mes)_2{}^+Cl^-$	12	50	**3**
3	$[RuCl_2(p\text{-cymene})]_2$	$Im[(i\text{-}Pr)_2Ph]_2{}^+Cl^-$	12	50	**3**
4	$RuCl_3 \cdot x\,H_2O$	$Im[(i\text{-}Pr)_2Ph]_2{}^+Cl^-$	6	100	**3**
5	$Ru_3(CO)_{12}$	$Im(Mes)_2{}^+Cl^-$	1	100	**4**
6	$Ru_3(CO)_{12}$	$Im[(i\text{-}Pr)_2Ph]_2{}^+Cl^-$	1	100	**3**

[a] All reactions are performed at 120 °C in toluene.

nium source and an imidazolinylidene precursor, for the tandem isomerisation/Claisen rearrangement was established (Scheme 1).

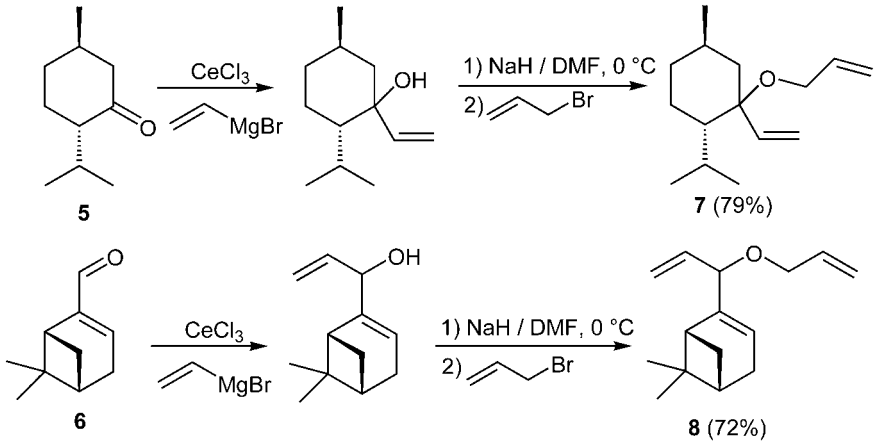
In the presence of the 1,7-diene **1**, the catalytic system **A**, based on $[RuCl_2(p\text{-cymene})]_2$, 1,3-bis(mesityl)imidazolinium chloride and cesium carbonate, did not give the expected cycloisomerisation product **2**,[14] but rather the γ,δ-unsaturated aldehyde **3** with 50% conversion.

A study on this three-component catalytic system, by combination of two types of imidazolinium salt with four ruthenium sources, led us to the most effective catalyst **B**, based on $Ru_3(CO)_{12}$, 1,3-bis(2,6-diisopropylphenyl)-imidazolinium chloride and cesium carbonate, which gave complete conversion of **1** into compound **3** (Table 1). $Ru_3(CO)_{12}$ especially reveals the strong differences in behaviour of the two imidazolinium salts: both allow isomerisation but only one, with isopropyl groups, favours the subsequent Claisen reaction (entries 5 and 6) This observation supports that the catalyst not only favours the isomerisation but also the Claisen rearrangement.

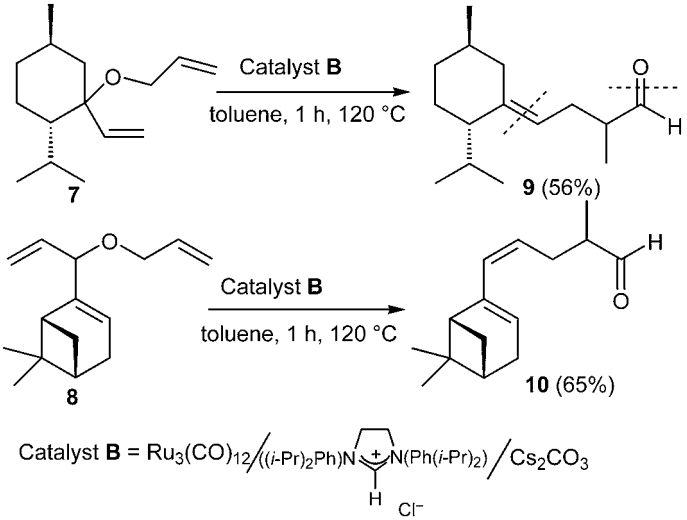
Starting from these observations, variations on the catalytic system and especially the use of bidentate ligands such as bisbenzoxazole,[16] chiral bisoxazoline and diimine,[17] associated with a ruthenium source, have shown isomerisation capability. The most efficient catalytic system **B** was then evaluated for terpenoids.

Terpenoid Transformations

Previous work on the modification of natural terpenoids, with a silylated enyne structure, *via* ruthenium-catalysed ring closing metathesis reactions has shown potential for the synthesis of new polycyclic molecules.[18] 1,6-Diene derivatives of terpenoids have been evaluated towards the three-component catalytic system **B**, based on $Ru_3(CO)_{12}$, 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride and cesium carbonate. Starting from natural (−)-menthone (**5**) and (−)-myrtenal (**6**), the 1,6-dienes **7** and **8** have been first prepared in good yields by reaction with vinylmagnesium bromide in



Scheme 2.



Scheme 3.

the presence of cerium trichloride followed by an allylation reaction of the resulting allyl alcohols (Scheme 2).

These dienes **7** and **8** have been reacted with the three-component catalytic system **B** (Scheme 3). The dienes **7** and **8** with 5/3 mol % of $Ru_3(CO)_{12}$, 5 mol % of imidazolinium salt and 10 mol % of Cs_2CO_3 were heated in toluene at 120 °C. After 1 hour at 120 °C, the dienes **7** and **8** were completely converted and the γ,δ-unsaturated aldehydes **9** and **10** were isolated in 56% and 65% yield, respectively.

Starting from the natural carbonyl compounds **5** and **6** these simple three successive modifications actually incorporate, into the C=O bond of **5** and **6**, a five-carbon fragment and represent a formal homologation of monoterpenoids into original non-natural sesquiterpenoids **9** and **10** by insertion of an isoprene skeleton into the carbonyl function.

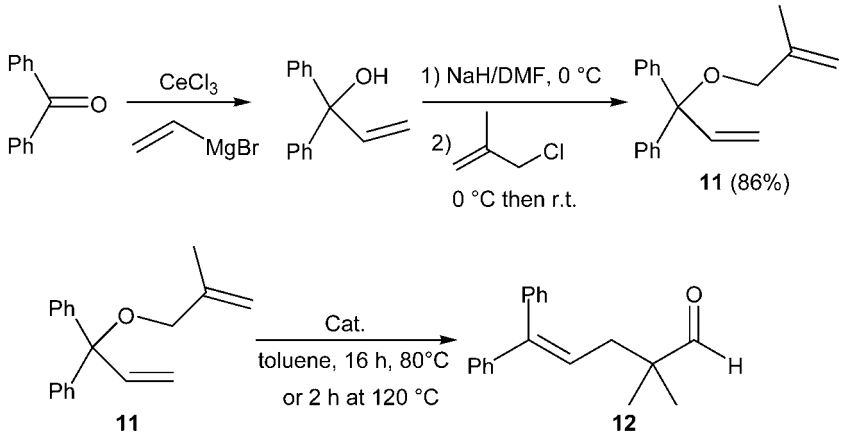
Screening of the Catalytic System using High Throughput Experiments

To investigate the activity of new multicomponent catalytic systems toward this isomerisation/Claisen reaction, the use of high throughput screening techniques appeared to be the best way to explore new combinations. Starting from the catalytic system **B**, based on a ruthenium source, an N-heterocyclic carbene precursor and a base, we have adopted a screening strategy to test new sources for each of these three components with the aim of discovering better or new catalysts for the transformation of dienes into γ,δ-unsaturated aldehydes.

The 1,6-diene **11** has been selected as test substrate for these experiments because it was easily obtained in two steps from benzophenone, and the isomerisation/Claisen rearrangement transformation led to the γ,δ-unsaturated aldehyde **12** as the sole possible isomer. Reaction of diene **11** with 5 mol % of catalyst **B** at 120 °C for 2 hours leads to the aldehyde **12** isolated in 90% yield. (Scheme 4).

Choice of the Catalytic Components

The high throughput screening has been performed using a 96-hole plate composed of 8 rows and 12 columns. On the columns 1–12 (Table 2) were introduced different combinations of ligand **L** and bases **B**, except in the column 12 which was free from any **L** and **B** sources for reference. On the rows (A–H) were placed the selected metallic source **M** except for the H row in which no metal complex was introduced for reference (Figure 1, Table 2).



Scheme 4.

Table 2. Arrangement of the catalytic systems on the 96-tube plate and conversion (%) of diene **11** into aldehyde **12**.

		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
		L1	**L2**	**L3**	**L4**	**L2**	**L3**	**L4**	**L1**	**L2**	**L3**	**L4**	**–**
		B1	**B1**	**B1**	**B1**	**B2**	**B2**	**B2**	**–**	**–**	**–**	**–**	**–**
A	**M1** = $[RuCl_2(p\text{-cymene})]_2$												
B	**M2** = $(p\text{-cymene})RuCl_2(PCy_3)$												
C	**M3** = $Ru_3(CO)_{12}$			***9%***									
D	**M4** = $[Ru_2(CO)_4(HCO_2)_2]_n$												
E	**M5** = $Ru_2(CO)_4(HCO_2)_2(PCy_3)_2$												
F	**M6** = $Ru(methallyl)_2(COD)$	***0%***	***100%***	***100%***	***100%***	***100%***	***100%***	***100%***	***1%***	***100%***	***100%***	***100%***	***100%***
G	**M7** = $[Ir(COD)Cl]_2$				***13%***			***20%***					
H	**–**												

Conversions are determined by ^1H NMR when aldehyde **12** was detected by TLC.

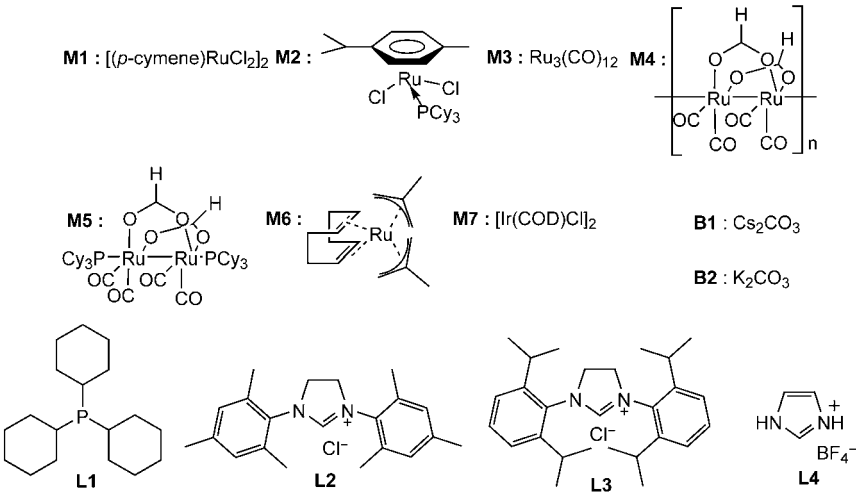


Figure 1.

HTS Reaction Preparation and Results

HTS reactions have been performed in a glove-box under an argon atmosphere and for practical reasons, in toluene at 80 °C over a sand bath without stirring. Each of the 96 tubes on the plate contained 350 μL of solution for the reaction. Thus, titrated solutions of the 1,6-diene **11** (0.1 mol/L), metal complex **M1**–**M7** (0.005 mol/L of metal atom) and ligands **L1**–**L4** (0.005 mol/L) have been prepared. Due to the poor sol-

ubility of the bases, Cs_2CO_3 **B1** and K_2CO_3 **B2**, in toluene, saturated solutions were prepared by 4 h stirring in toluene at room temperature and then used as such for the reaction. The tubes were first filled with the metal complex and ligand, followed by the heterogeneous base/toluene mixture containing the substrate. The 96-tube plate was then placed onto the sand bath at 80 °C during 16 hours.

The 96-tube plate was removed from the glove box (Figure 2) and thin layer chromatographic analyses of each tube were performed. By using an adequate elution system (diethyl ether/heptane, 1/20), the formation of the aldehyde **12** ($R_f = 0.3$) can be easily observed as compared to the starting diene **11** ($R_f = 0.9$). Only the tubes presenting the formation of the aldehyde **12** were evaporated to dryness and analysed by proton NMR. The reaction conversion was determined by measuring the ratio between the aldehyde proton of **12** and the protons of the terminal double bond of the starting compound **11**. The measured conversions (%) are indicated in Table 2 and Table 3.

According to the preparation of the HTS reaction plate, our previous catalytic system **B**, based on $Ru_3(CO)_{12}$ (**M3**), 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (**L3**) and cesium carbonate (**B1**), operated in tube C3. Under the experimental conditions (80 °C without stirring), the conversion into aldehyde **12** by ^{1}H NMR was only 9% (instead of 90% after 2 h at 120 °C). Starting from this result as reference, all the tubes presenting higher conversions were expected to contain a better catalytic system. Thus, the tubes G4 and G7, presenting the dimer $[Ir(COD)Cl]_2$ **M7** as the metallic source, showed better conversions than the catalytic system **B**. But the most impressive result came from the tubes of the line F for which the conversions were complete, except for F1 and F8. These tubes contained the complex Ru(methallyl)$_2$(COD) **M6** as the metal source. Thus, this complex is a better precursor than $Ru_3(CO)_{12}$ for the catalytic isomerisation/Claisen rearrangement reaction, F1 and F8 correspond to the addition of one equiv. of PCy_3 per metal atom, showing that this ligand inhibits the catalytic transformation. The most surprising result was observed in tube F12 containing the complex Ru(methallyl)$_2$(COD) **M6** alone without any additional ligand.

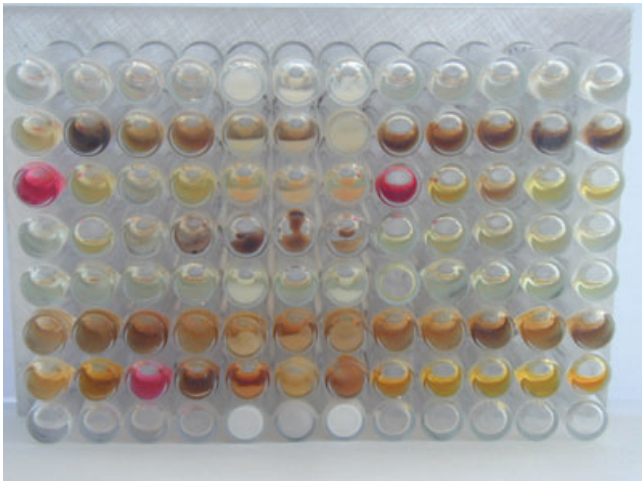


Figure 2. View of the 96-hole plate after reaction according to Table 2.

Table 3. Conversion of diene **11** into aldehyde **12** observed by proton NMR:

Tubes	Catalytic System	Conversion[a]
C3	**M3** + **L3** + **B1**	9%
D10	**M4** + **L3**	4%
F3	**M6** + **L3** + **B1**	100%
F8	**M6** + **L1**	1%
F12	**M6**	100%
G4	**M7** + **L4** + **B1**	13%
G7	**M7** + **L4** + **B2**	20%

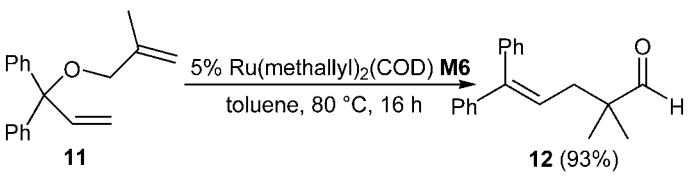
[a] % based on **12** aldehyde proton versus **11** (=CH_2) protons.

Ru(methallyl)$_2$(COD): New Efficient Catalyst for the Tandem Isomerisation/Claisen Rearrangement Reactions

From these primary results, the tandem reaction catalysed by 5 mol % of the complex Ru(methallyl)$_2$(COD) has been reproduced on a larger scale (see Scheme 5).

In toluene, at 80 °C, 0.95 mmol of the 1,6-diene **11** was completely converted, in 16 hours, into the aldehyde **12**, which was isolated in 93% yield after distillation. Different reaction temperatures and catalyst amounts have been tested and the conversions of the reaction have been followed by GC-MS (see Table 4).

At 80 °C, the diene **11** was converted in 85% into the aldehyde **12** after 4 hours of reaction. Only 15 minutes were necessary to totally convert the starting diene at 120 °C, which confirmed the impressive activity of the complex Ru(methallyl)$_2$(COD) revealed by HTS. However, no activity has been observed at 60 °C or at lower temperature. By using 1 mol % of the complex Ru(methallyl)$_2$(COD), 84% of the diene **11** was converted, after 3 hours of reaction at 120 °C. At lower temperature, the same amount of catalyst gave only 5% conversion af-



Scheme 5.

Table 4. Variations of the catalytic reaction conditions for the transformation of **11** into **12**.

Catalytic System	Temperature	Reaction Time	Conversion in **12**
5% Ru(methallyl)$_2$(COD)	40 °C	4 h	0%
5% Ru(methallyl)$_2$(COD)	60 °C	4 h	3%
5% Ru(methallyl)$_2$(COD)	80 °C	4 h	85%
5% Ru(methallyl)$_2$(COD)	120 °C	15 min	100%
1% Ru(methallyl)$_2$(COD)	120 °C	3 h	84%
1% Ru(methallyl)$_2$(COD)	80 °C	18 h	5%
1% Ru(methallyl)$_2$(COD) + 1% **L3** + 2% **B1**	80 °C	4 h	27%

ter 18 hours but, at 80 °C, if a ligand source such as an imidazolinium salt **L3** and cesium carbonate **B1** were used, the conversion reached 27% after only 4 hours.

Conclusion

The above results show that tandem isomerisation/Claisen rearrangement of 1,7- and 1,6-dienyl ethers is catalysed by *in situ* prepared ruthenium catalysts to selectively produce γ,δ-unsaturated aldehydes. An excellent catalyst appears to consist in the combination of $Ru_3(CO)_{12}$ and a bulky heterocyclic carbene precursor, an imidazolinium salt, and cesium carbonate. Application of this reaction has allowed the transformation of natural terpenoids such as (−)-menthone and (−)-myrtenal into new sesquiterpenoids.

After a high throughput screening of several catalytic precursors, more efficient and unpredictable catalytic systems have been discovered. Especially the complex Ru(methallyl)$_2$(COD), without any ligand or reagent addition, has presented an impressive activity for the tandem isomerisation/Claisen rearrangement. Its activity is by contrast totally inhibited by the simple addition of one equivalent of the bulky, electron-releasing PCy_3 ligand, expected to displace the COD group. Ru(methallyl)$_2$(COD) has shown a high efficiency to perform this tandem reaction with small amount of catalyst. This study shows another example of the use of HTS to reveal a novel catalytic system that knowledge and reasoning cannot predict. The capacity of Ru(methallyl)$_2$(COD) to interact with double bonds suggests that it has also potential for other catalytic alkene transformations.

Experimental Section

General Experimental Procedures

All experiments were carried out in Schlenk tubes under an inert atmosphere of nitrogen. The solvents were dried and distilled prior to use. ^{1}H and ^{13}C NMR analyses were recorded with a Bruker AC 200 MHz spectrometer and GC-MS were performed with a CE Instrument GC 8000 Top (capillary column OV1, 25 m × 0.35 mm, 0.1–0.15 μm) chromatograph linked to an Automass II Finnigan MAT (70 eV) apparatus.

Procedure A: Synthesis of the Allylic Alcohols

A Schlenk tube under a nitrogen atmosphere containing anhydrous $CeCl_3$ (0.1 equiv.) was first heated at 150 °C for 5 min and then cooled down to room temperature. Tetrahydrofuran (2 mL per mmol of ketone or aldehyde) was introduced followed by the ketone or the aldehyde (1 equiv.) and the reaction mixture was stirred for 30 min at room temperature. After a cooling down to 0 °C, vinylmagnesium bromide (1.0 M solution in tetrahydrofuran, 1.2 equivs.) was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and then for 16 h at room temperature. After quenching by slow addition of a 1 N HCl solution and extraction with diethyl ether, the corresponding allylic alcohol was obtained and used in the following step without purification.

Procedure B: Allylation Reaction

In a Schlenk tube under a nitrogen atmosphere was introduced sodium hydride (1.2 equivs.) and dry dimethylformamide (1.5 mL per mmol of alcohol). The reaction mixture was then cooled down to 0 °C and the alcohol (1 equiv.) in dimethylformamide (1 mL per mmol of alcohol) was slowly added. After 30 min stirring at 0 °C, allyl bromide (1.3 equivs.) was added dropwise and the stirring was continued for 30 min at 0 °C and 4 h at room temperature. The reaction mixture was then slowly hydrolysed by water and extracted twice with diethyl ether. The collected organic layers were then washed three times with water, dried over $MgSO_4$, filtered and evaporated to dryness. The crude product was then purified by flash chromatography over silica gel using a diethyl ether/heptane mixture.

Procedure C: General Procedure for Tandem Isomerisation/Claisen Rearrangement Reaction using $Ru_3(CO)_{12}$

In a Schlenk tube under a nitrogen atmosphere was introduced $Ru_3(CO)_{12}$ (5 mol %), the 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (5 mol %), cesium carbonate (10 mol %) and toluene (7.5 mL per mmol of diene). The reaction mixture was stirred for 5 min at room temperature and the diene was then added. After 1 hour heating at 120 °C, the solvent was removed under reduced pressure and the crude residue was ex-

tracted with heptane, filtered and evaporated to dryness. This material was then purified by chromatography over silica gel using the appropriate elution system (diethyl ether/heptane) or by a bulb-to-bulb distillation to afford the corresponding aldehyde as a colourless oil as a mixture of diastereoisomers.

1-Allyloxy-2-(*S*)-isopropyl-5-(*R*)-methyl-1-vinylcyclohexane (7)

Following Procedure A: To $CeCl_3$ (0.14 g, 0.58 mmol, 0.1 equiv.) in 15 mL of tetrahydrofuran was added (−)-menthone (**5**; 1.0 mL, 5.8 mmol, 1 equiv.) at room temperature. Vinylmagnesium bromide (7.0 mL, 7.0 mmol, 1.2 equivs.) was then added at 0 °C. Subsequent treatment afforded the corresponding allylic alcohol as a pale yellow oil which was used without purification for the next step.

Following Procedure B: The allylic alcohol (5.8 mmol, 1 equiv) in 6 mL of dimethylformamide was added to a solution of sodium hydride (60% in mineral oil, 0.28 g, 7.0 mmol, 1.2 equivs.) in 12 mL of dimethylformamide. After addition of allyl bromide (0.69 mL, 7.5 mmol, 1.3 equivs.) and subsequent treatment, the crude material was purified by flash chromatography over silica gel using diethyl ether/heptane (1:40) as eluent to afford the corresponding 1,6-diene **7** as a colourless oil; yield: 1.02 g (79%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80 (d, 3H, ^3J = 6.8 Hz, CH_3), 0.95 [d, 3H, ^3J = 7.1 Hz, CH(CH_3)$_2$], 0.97 [d, 3H, ^3J = 7.1 Hz, CH(CH_3)$_2$], 1.00–1.11 [m, 1 H, CH$_2$-CH(CH$_3$)], 1.40–1.81 (m, 6H, 3 × CH_2), 1.91 [dm, 1H, ^3J = 14.1 Hz, CHCH(CH$_3$)$_2$], 2.15 [hept × d, 1H, ^3J = 7.0 Hz, $^3J'$ = 1.8 Hz, CHCH(CH$_3$)$_2$], 3.72–3.90 (m, 2H, OCH_2CH=CH$_2$), 5.04–5.39 [m, 4H, 2 × (CH=CH_2)], 5.79–6.00 [m, 2H, 2 × (CH=CH$_2$)]; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 18.5 (2 × CH_3), 20.7 [(CH$_3$)$_2$CHCHCH$_2$CH$_2$], 22.4 [CH$_2$CH$_2$CH(CH$_3$)], 23.8 [CH$_2$CH$_2$CH(CH_3)], 27.5 [(CH$_3$)$_2$CHCHCH$_2$CH$_2$], 35.4 [CH$_2$CH_2CH(CH$_3$)], 41.2 [CH_2C(OR)], 51.8 [(CH$_3$)$_2$-CHCHCH$_2$CH$_2$], 62.4 (OCH$_2$CH=CH$_2$), 80.4 [C(OR)(vinyl)], 114.0 [C(R)$_2$CH=CH_2], 114.2 (OCH$_2$CH=CH_2), 136.2 (OCH$_2$CH=CH$_2$), 143.2 [C(R)$_2$CH=CH$_2$]; MS (EI): *m/z* (%) = 222 ([M]$^+$, 1.3), 207 (19), 179 (30), 165 (26), 151 (17), 137 (100), 125 (26), 123 (27), 111 (39), 109 (59), 97 (34), 95 (84), 93 (34), 83 (45), 81 (75), 79 (43), 69 (60), 67 (66), 57 (39), 39 (34).

2-(1-Allyloxyprop-2-enyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (8)

Following Procedure A: To $CeCl_3$ (0.32 g, 1.28 mmol, 0.1 equiv.) in 25 mL of tetrahydrofuran was added (−)-myrtenal (**6**; 2.0 mL, 12.6 mmol, 1 equiv.) at room temperature. Vinylmagnesium bromide (15.2 mL, 15.2 mmol, 1.2 equivs.) was then added at 0 °C. Subsequent treatment afforded the corresponding allylic alcohol as a pale yellow oil that was used without purification for the next step.

Following Procedure B: The allylic alcohol (12.6 mmol, 1 equiv.) in 13 mL of dimethylformamide was added to a solution of sodium hydride (60% in mineral oil, 0.60 g, 15.2 mmol, 1.2 equivs.) in 20 mL of dimethylformamide. After addition of allyl bromide (1.5 mL, 16.4 mmol, 1.3 equivs.) and subsequent treatment, the crude residue was purified by flash chromatography over silica gel using diethyl ether/heptane (1:40) as eluent to afford the corresponding 1,6-diene **8** as a colourless oil; yield: 1.98 g (72%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.75 (s, 3H, CH_3), 1.02–1.10 [m, 1H, C(CH$_3$)$_2$CH(CH$_2$)CH$_2$], 1.23 (s, 3H, CH_3), 1.96–2.52 [m, 5H, C(CH$_3$)$_2$CH(CH$_2$)C=CH, CH_2, CH_2], 3.80–4.08 (m, 2H, OCH_2CH=CH$_2$), 4.94–5.27 [m, 4H, 2 × (CH=CH_2)], 5.44–5.61 [m, 1H, CH(O-allyl)(vinyl)], 5.71–5.99 [m, 3H, 2 × (CH=CH$_2$), C=CHCH$_2$]; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.6/20.7 (CH_3), 26.3 (CH_3), 31.0/31.1 (CH_2), 37.3/37.5 (C(CH$_3$)$_2$), 40.4/40.9 [HC=CCH(C(CH$_3$)$_2$)(CH$_2$)], 41.7/41.9 [CH$_2$CH(C(CH$_3$)$_2$)(CH$_2$)], 42.6/42.9 (CH_2), 68.5/68.7 (OCH_2CH=CH$_2$), 75.6/75.9 [CH(OR)(vinyl)], 115.5/115.7 [CH(O-allyl)CH=CH_2], 116.9/117.1 (OCH$_2$CH=CH_2), 121.6/121.7 (C=CHCH$_2$), 134.5 (OCH$_2$CH=CH$_2$), 143.3 [CH(O-allyl)CH=CH$_2$], 145.8 (C=CHCH$_2$); MS (EI): *m/z* (%) = 218 ([M]$^+$, <1), 160 (15), 149 (29), 145 (15), 117 (67), 115 (12), 107 (21), 105 (19), 93 (29), 91 (56), 79 (66), 77 (36), 69 (18), 67 (37), 55 (25), 53 (13), 41 (100), 39 (28).

[1-Phenyl-1-(isoprop-2-enyloxy)prop-2-en-1-yl]benzene (11):

Following Procedure A: To $CeCl_3$ (0.41 g, 1.65 mmol, 0.1 equiv.) in 30 mL of tetrahydrofuran was added benzophenone (3.0 g, 16.5 mmol, 1 equiv.) at room temperature. Vinylmagnesium bromide (20.0 mL, 20.0 mmol, 1.2 equiv.) was then added at 0 °C. Subsequent treatment afforded the corresponding allylic alcohol as a pale yellow oil that was used without purification for the next step.

Following Procedure B: The allylic alcohol (16.5 mmol, 1 equiv.) in 15 mL of dimethylformamide was added to a solution of sodium hydride (60% in mineral oil, 0.86 g, 19.8 mmol, 1.2 equivs.) in 25 mL of dimethylformamide. After addition of 2-methylpropene chloride (2.2 mL, 19.8 mmol, 1.3 equivs.) and subsequent treatment, the crude residue was purified by flash chromatography over silica gel using diethyl ether/heptane (1:20) as eluent to afford an orange oil which was then bulb-to-bulb distilled to give the corresponding 1,6-diene **11** as a colourless oil; yield: 3.74 g (86%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.00 (s, 3H, CH_3), 3.94–4.00 [m, 2H, OCH_2-C(CH$_3$)=CH$_2$], 5.15–5.63 [m, 4H, C(CH$_3$)=CH_2, C(Ph)$_2$-CH=CH_2], 6.69–6.84 [m, 1H, C(Ph)$_2$CH=CH$_2$], 7.42–7.55 (m, 6H, H arom.), 7.62–7.72 (m, 4H, H arom.); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 20.6 (CH_3), 68.0 [OCH$_2$C(CH$_3$)=CH$_2$], 84.8 [C(Ph)$_2$(R)$_2$], 111.1 [C(Ph)$_2$CH=CH_2], 117.0 [OCH$_2$-C(CH$_3$)=CH$_2$], 127.8, 128.5, 128.7 (CH arom.), 141.0 [C(Ph)$_2$CH=CH$_2$], 143.4 (C quat. arom.), 144.9 [OCH$_2$C(CH$_3$)=CH$_2$]; MS (EI): *m/z* (%) = 264 ([M]$^+$, 1), 193 (32), 191 (15), 178 (18), 165 (14), 144 (12), 116 (19), 115 (100), 106 (43), 103 (19), 91 (40), 77 (45), 55 (69), 41 (13), 39 (25).

Tandem Isomerisation/Claisen Rearrangement Reaction to 4-(2-(*S*)-Isopropyl-5-(*R*)-methylcyclohexylidene)-2-methylbutyraldehyde (9)

Following Procedure C: $Ru_3(CO)_{12}$ (9.6 mg, 0.045 mmol, 5 mol % of ruthenium), 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (15.4 mg, 0.045 mmol, 5 mol %), Cs_2CO_3 (29.3 mg, 0.09 mmol, 10 mol %), 7.5 mL of toluene and diene

7 (200 mg, 0.9 mmol) were placed in a Schlenk tube under nitrogen. After 1 h at 120 °C, treatment and distillation, the aldehyde **9** was obtained as a colourless oil as a mixture of diastereoisomers; yield: 112 mg (56%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.79–0.90 [m, 9H, $CH(CH_3)_2$, $CH_2CH_2CH(CH_3)$], 1.04 [d, 3H, ^3J = 7.1 Hz, $CH(CH_3)CHO$], 1.16–1.25 [m, 1 H, $CH_2CH(CH_3)$], 1.59–1.99 [m, 7H, 3 × CH_2, $CHCH(CH_3)_2$], 2.10–2.46 [m, 4H, $CH(CH_3)CHO$, $CHCH(CH_3)_2$, $(R)_2C{=}CHCH_2$], 5.08 [t, 1H, ^3J = 7.2 Hz, $(R)_2C{=}CHCH_2$], 9.61–9.65 (m, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.0/13.1 [$CH(CH_3)CHO$], 19.7 [$CH_2CH_2CH(CH_3)$], 20.4/20.5 [$CH(CH_3)_2$], 26.4/26.6 [$(R)_2C{=}CHCH_2$], 28.2/28.4 [$CH_2CH_2CH(CH_3)$], 29.6/29.8 [$CH(CH_3)_2$], 31.6/31.7 [$CH_2CH_2CH(CH_3)$], 32.2 [$CH_2CH_2CH(CH_3)$], 35.0/35.1 [$CH_2C(R){=}CHCH_2$], 47.0/47.2 [$CHCH(CH_3)_2$], 51.2/51.3 [$CH(CH_3)CHO$], 117.5/117.6 [$(R)_2C{=}CHCH_2$], 142.5 [$(R)_2C{=}CHCH_2$], 205.2/205.3 (CHO); MS (EI): *m/z* (%) = 222 ($[M]^+$, 18), 204 (39), 179 (61), 164 (49), 162 (35), 151 (12), 149 (29), 137 (36), 135 (27), 123 (23), 119 (63), 111 (41), 109 (39), 107 (62), 97 (28), 95 (34), 93 (21), 91 (100), 83 (52), 81 (35), 79 (21), 77 (69), 69 (53), 67 (29), 57 (30), 53 (33), 43 (77), 39 (33).

Tandem Isomerisation/Claisen Rearrangement Reaction to 5-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-2-methylpent-4-enal (10)

Following Procedure C: $Ru_3(CO)_{12}$ (48.9 mg, 0.23 mmol, 5 mol % of ruthenium), 1,3-bis(2,6-diisopropylphenyl)imidazolinium chloride (97.7 mg, 0.23 mmol, 5 mol %), Cs_2CO_3 (149.2 mg, 0.46 mmol, 10 mol %), 30 mL of toluene and diene **8** (1.0 g, 4.6 mmol) were placed in a Schlenk tube under nitrogen. After 1 h at 120 °C, treatment and distillation, the aldehyde **10** was obtained as a colourless oil as a mixture of diastereoisomers; yield: 0.65 g (65%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.74 (s, 3H, CH_3), 0.98 [d, 3H, ^3J = 6.9 Hz, $CH(CH_3)CHO$], 1.03–1.12 [m, 1H, $C(CH_3)_2CH(CH_2)CH_2$], 1.23 (s, 3H, CH_3), 2.07–2.52 [m, 8H, $CH_2CH(CH_3)CHO$, $C(CH_3)_2CH(CH_2)C{=}CH$, CH_2, CH_2], 5.26–5.35 [m, 1H, $C{=}CHCH_2$], 5.43–5.73 [m, 2H, $CH{=}CHCH_2CH(CH_3)CHO$], 9.51–9.61 (m, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 11.7/12.0 [$CH(CH_3)CHO$], 21.2/21.3 (CH_3), 26.2/26.3 (CH_3), 31.2/31.3/31.4/31.5 [$CH_2CH(CH_3)CHO$, CH_2], 37.7/37.8 [$C(CH_3)_2$], 40.5/40.7 [$HC{=}CCH(C(CH_3)_2)(CH_2)$], 42.8/42.9 [$CH_2CH(C(CH_3)_2)(CH_2)$], 44.0/44.1 ($CH_2$), 52.7/52.8 [$CH(CH_3)CHO$], 118.8/118.9 ($C{=}CHCH_2$), 122.0/122.2 [$CH{=}CHCH_2CH(Me)CHO$], 133.8/134.0 [$CH{=}CHCH_2CH(Me)CHO$], 146.1/146.3 ($C{=}CHCH_2$), 204.7/204.9/205.1 (CHO); MS (EI): *m/z* (%) = 218 ($[M]^+$, 2.3), 145 (21), 131 (10), 119 (18), 117 (52), 105 (55), 93 (19), 91 (100), 79 (41), 77 (46), 69 (23), 67 (22), 65 (27), 55 (33), 53 (29), 41 (88), 39 (42).

High Screening Experimentations

Experiments were carried out in a glove-box under an argon atmosphere. Titrated solutions of substrate **11**, metal sources (**M1**–**M7**) and ligands (**L1**–**L4**) in toluene were prepared to obtain the concentrations: 0.1 mol·L^{-1}, 0.005 mol·L^{-1} and 0.005 mol·L^{-1}, respectively. Saturated basic solutions of Cs_2CO_3 **B1** and K_2CO_3 **B2** in toluene were obtained after 4 hours stirring at room temperature.

The 96 tubes, each one containing 350 μL of reaction mixture, were prepared following the combinations described in Table 2. The metallic sources (100 μL per tube) were first introduced over the lines (A–G) followed by the ligands (100 μL per tube) and the bases (50 μL per tube) over the columns (1–11). Line H was filled without metallic source and column 12 without ligand and base to use them as reference experiments. The tubes were shaken by hand over two minutes before the addition of the diene **11** (100 μL per tube). The tubes were then heated at 80 °C over a sand bath. After 16 hours, the 96-tube plate was taken out of the glove-box and thin layer chromatography on each sample on silica was performed using a mixture of diethyl ether/heptane (1/20) as eluent [R_f (**11**) = 0.9; R_f (**12**) = 0.3]. The conversion into the aldehyde **12** in the selected tubes was determined by ^{1}H NMR analysis after evaporation of these samples to dryness.

Tandem Isomerisation/Claisen Rearrangement Reaction Catalysed by the Complex Ru(methylallyl)$_2$ (COD) to give 2,2-Dimethyl-5,5-diphenylpent-4-enal[19] (12)

Into a Schlenk tube under a nitrogen atmosphere were introduced Ru(methylallyl)$_2$(COD) (15.0 mg, 0.047 mmol, 5 mol %) and 7 mL of toluene. The reaction mixture was stirred during 5 min at room temperature and the diene **11** (250 mg, 0.95 mmol) was then added. After 16 h heating at 80 °C, the solvent was removed under reduced pressure and the crude residue was extracted with heptane, filtered and evaporated to dryness. This material was then purified by a bulb-to-bulb distillation to afford the aldehyde **12** as a colourless oil; yield: 232 mg (93%); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1,12 (s, 6H, 2 × CH_3), 2,39 (d, 2H, $^3J_{HH}$ = 7.6 Hz, CH_2), 6,09 [t, 1H, $^3J_{HH}$ = 7.6 Hz, $(Ph)_2C{=}CHCH_2$], 7.18–7.30 (m, 6H, CH arom.), 7.38–7.49 (m, 4H, CH arom.), 9.48 (s, 1H, CHO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.2 (2 × CH_3), 36.6 (CH_2), 46.5 [$C(CH_3)_2$], 123.6 [$(Ph)_2C{=}CHCH_2$], 127.0, 127.1, 128.0, 128.2, 129.7 (C arom.), 139.5, 142.2 (C arom.), 144.3 [$(Ph)_2C{=}CH$], 205.5 (CHO); MS (EI): *m/z* (%) = 264 ($[M]^+$, 2), 193 (43), 180 (100), 178 (36), 165 (37), 115 (87), 91 (38), 51 (10), 43 (14), 41 (16), 39 (14).

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