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Rhodium-catalyzed cascade reactions: A methylenation–hydroboration homologative process

Hélène Lebel *, Chehla Ladjel

Département de Chimie, Université de Montréal, P.O. Box, 6128, Station Downtown, Montréal, Qc., Canada H3C 3J7

Abstract

A very efficient rhodium-catalyzed cascade process allowing the transformation of aldehydes and ketones into their corresponding one or two-carbon homologated alcohol products through a methylenation–hydroboration sequence is reported. Wilkinson's complex is used to catalyze both reactions in a one-pot procedure that does not require the isolation of the alkene intermediate. © 2005 Elsevier B.V. All rights reserved.

Keywords: Rhodium; Wilkinson's catalyst; Methylenation; Hydroboration

1. Introduction

The Wilkinson's complex, $RhCl(PPh_3)_3$ [1] is well known to catalyze a variety of reactions with alkenes, such as hydrogenation [2], hydrosilylation [3], hydroformylation [4], and hydroboration reactions [5]. Recently, our group has reported the methylenation of a variety of carbonyl derivatives catalyzed by Wilkinson's complex in the presence of trimethylsilyldiazomethane, triphenylphosphine and 2-propanol, producing the corresponding terminal alkene in high yield (Eq. 1) [6,7]

$$ \qquad (1) $$
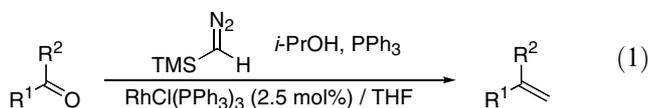
Moreover, we have shown that multicatalytic processes including our rhodium-catalyzed methylenation reaction allowed the formation of various substituted alkenes directly from alcohols, without the isolation of any intermediate [8]. Another cascade process will consist in using the dual catalytic activity of Wilkinson's complex

toward both carbonyl derivatives and alkenes, to functionalize in situ our methylene unit. In this article, we present a new rhodium-catalyzed cascade process involving a methylenation–hydroboration reaction sequence, to produce the corresponding organoborane. This intermediate can be further submitted to an oxidation reaction to produce the corresponding alcohol, or to a second homologation reaction with either $LiCHCl_2$ or $LiCH_2Cl$ [9].

2. Results and discussion

2.1. Rhodium-catalyzed methylenation–hydroboration cascade with aliphatic aldehydes

The use of Wilkinson's complex allows the hydroboration of alkenes with catecholborane to occur at room temperature, where heat is required for the uncatalyzed reaction [5]. We first investigated the rhodium-catalyzed methylenation–hydroboration cascade with aliphatic aldehydes by using catecholborane as our hydroborating agent to produce, after the oxidative work-up, the corresponding terminal alcohol. Indeed, treatment of

* Corresponding author. Tel.: +5143435826; fax: +5143432177.
E-mail address: helene.lebel@umontreal.ca (H. Lebel).

hydrocinnamaldehyde (**1**) with 1.1 equivalent of triphe-
nylphosphine, 2-propanol, and 1.4 equivalent of trim-
ethylsilyldiazomethane in the presence of 3 mol% of
Wilkinson's catalyst in THF for two hours, followed
by the addition of catecholborane produced the desired
organoborane after an additional two hours of reaction.
In this one-pot procedure, not only is the rhodium
catalyst required for the methylenation reaction, but
also for the hydroboration reaction. At the outset, oxi-
dation with hydrogen peroxide and sodium hydroxide
of the organoborane intermediate led to a disappoint-
ing 62% yield of the corresponding alcohol **2** (Table 1,
entry 1).

It was found that adding dioxane, either with the
catecholborane or with the oxidative reagent further im-
proves the isolated yield (75–79%, entries 4–5) of the de-
sired 4-phenylbutanol (**2**). The reaction could be also
performed with dioxane as the only solvent, although
it is then necessary to heat the methylenation reaction
to 60 °C (entry 6). Two equivalents of catecholborane
are required, as only 40% conversion is observed in
the presence of 1.5 equivalent and less then 10% conver-
sion with 1.1 equivalent (entries 2–3). We postulate that
catecholborane either reacts or complexes the triphe-
nylphosphine oxide generated from the methylenation
reaction. Both hydrogen peroxide and sodium perbo-
rate [10] could be used as oxidative reagents (entries 5
vs. 7).

We have extended these one-pot methylenation–hyd-
roboration reaction conditions to a variety of aldehydes
using the two oxidative procedures (Table 2). The corre-
sponding alcohol could be isolated with 63–84% yields,
which are typically similar or higher than the yields ob-
tained for the step-by-step approach, in which the al-
kene intermediate is isolated. The reaction conditions
are compatible with silyl- and benzyl-protected alcohols

as well as α-branched aldehydes (entries 4–15).
Although in most cases, the difference in yields for both
oxidative protocol was not noteworthy, in some cases,
the isolated yields were significantly higher when using
the sodium borate procedure (entries 4–5 and 16–17).
The chemoselectivity of this cascade process is excep-
tional, as both rhodium-catalyzed reactions could distin-
guish between functional groups that differed only by
the substitution. The rhodium-catalyzed hydroboration
is chemoselective for terminal double bonds thus, the tri-
substituted alkene of the diene produced by the methyl-
enation of citronellal (**11**) stays intact (entries 16–17).
Furthermore, as we can perform chemoselective methyl-
enation of aldehydes over ketones, it is possible to ob-
tain keto alcohol product **14** in good yields (entry 20).
No only the aromatic ketone did not react during the
rhodium-catalyzed methylenation reaction, but was
not reduced during the hydroboration step.

2.2. Rhodium-catalyzed methylenation–hydroboration cascade with aromatic aldehydes

The regioselectivity of the rhodium-catalyzed hyd-
roboration of aromatic aldehydes typically favors the
corresponding secondary organoborane. The regioselec-
tivity is strongly dependant on the reaction conditions,
including the catalyst and its ligands, as well as the bor-
ane reagent [11]. Under our standard cascade reaction
conditions, using Wilkinson's catalyst and catecholbo-
rane, we observed mainly the formation of the second-
ary organoborane but only with a moderate ratio: for
instance the organoborane derived from *p*-bromobenz-
aldehyde was obtained with a 4:1, branched:linear ratio
(Table 3, entry 1). However, this ratio could be signifi-
cantly improved by using a cationic rhodium complex,
[Rh(COD)$_2$]BF$_4$ in the presence of pinacolborane,

Table 1

Optimization of rhodium-catalyzed methylenation hydroboration cascade process of hydrocinnamaldehyde

Entry	Methylenation (solvent, °C)	Hydroboration (RO$_2$ B–H (equiv.)/solvent)	Oxidation	Conv. (yield)[a]
1	THF, 25 °C	2 equiv./THF	H$_2$O$_2$, NaOH$_{aq}$	>98% (62%)
2	THF, 25 °C	1.1 equiv./dioxane	H$_2$O$_2$, NaOH$_{aq}$	<10%
3	THF, 25 °C	1.5 equiv./dioxane	H$_2$O$_2$, NaOH$_{aq}$	40%
4	THF, 25 °C	2 equiv./dioxane	H$_2$O$_2$, NaOH$_{aq}$	>98% (79%)
5	THF, 25 °C	2 equiv./THF	H$_2$O$_2$, NaOH$_{aq}$ Dioxane	>98% (75%)
6	Dioxane, 60 °C	2 equiv./dioxane	H$_2$O$_2$, NaOH$_{aq}$	>98%
7	THF, 25 °C	2 equiv./dioxane	NaBO$_{3aq}$	>98% (55%)
8	THF, 25 °C	2 equiv./THF	NaBO$_3$/dioxane	>98% (70%)

Isolated yields in parentheses.
[a] Conversion by GC–MS.

Table 2
Rhodium-catalyzed methylenation hydroboration of aliphatic aldehydes

1- RhCl(PPh$_3$)$_3$ (3 mol%), TMSCHN$_2$ (1.4 equiv)
PPh$_3$ (1.1 equiv), i-PrOH (1.1 equiv) / THF
2- Catecholborane (2 equiv.)
3- Oxidation
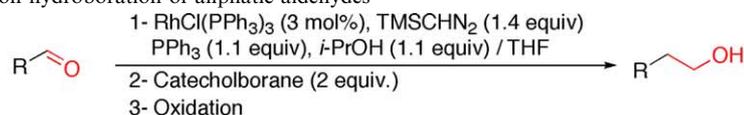
| Entry	Substrates	Conditions[a]	Products	Yields[b]
1		A		79%
2	Ph ↘↘↘=O **1**	B	Ph ↘↘↘↘OH **2**	70%
3		C		76%
4		A		72%
5	TIPSO↘↘↘↘=O **3**	B	TIPSO↘↘↘↘↘OH **4**	83%
6		C		54%
7		A		61%
8	BnO↘↘↘↘=O **5**	B	BnO↘↘↘↘↘OH **6**	68%
9		C		71%
10		A		55%
11	Ph↘↘↘=O **7** TIPSO	B	Ph↘↘↘↘OH **8** TIPSO	63%
12		C		46%
13		A		75%
14	O↗NBOC **9** =O	B	O↗NBOC **10** OH	71%
15		C		53%
16		A		70%
17	↘↘↘↘↘=O **11**	B	↘↘↘↘↘OH **12**	84%
18		C		74%
19		A		65%
20	Ph↘↘↘↘↘=O O **13**	B	Ph↘↘↘↘↘OH O **14**	57%
21		C		66%

^{a} Condition A: catecholborane/dioxane; H$_2$O$_2$, NaOH/H$_2$O. Condition B: catecholborane/THF; NaBO$_3$/H$_2$O + dioxane. Condition C: step-by-step approach with H$_2$O$_2$, NaOH oxidative protocol.
^{b} Isolated yields.

leading to an 8:1 branched:linear ratio (entry 2). The methylenation reaction was carried out in dioxane at 50 °C to generate the catalytically active species, presumably [(Ph$_3$P)Rh(COD)]$^+$, then hydroboration was performed at room temperature for 12 h. Other styrene derivatives could be in-situ prepared and converted into the corresponding branched organoboranes with good ratios (entries 3–4). It was only with an electron-donating substituent that the reaction became unselective leading to a 1.5:1 branched:linear ratio (entry 5).

2.3. Rhodium-catalyzed methylenation–hydroboration cascade with ketones

In the case of non-symmetrical ketone derivatives, only the primary organoborane was observed. Optimi-

zation of our cascade procedure was required to account for the reactivity of ketones towards the methylenation reaction. Our previous report on methylenation of ketones has shown that an excess of 2-propanol was essential to perform the reaction with 1 equivalent of triphenylphosphine [6b]. Typically, 10 equivalents of 2-propanol was used; however such an excess of alcohol is not compatible with the hydroboration reaction. Further optimization showed that the amount of 2-propanol could be decreased, when using an excess of triphenylphosphine. Indeed, the methylenation was carried out in the presence of an excess of trimethylsilyldiazomethane (2.5 equiv.), 2-propanol (2 equiv.) and triphenylphosphine (2 equiv.), and with 5 mol% of Wilkinson's catalyst in THF at 60 °C. Three equivalents of catecholborane in dioxane were then added to produce

Table 3
Rhodium-catalyzed methylenation hydroboration of aromatic aldehydes

1- [Rh(COD)$_2$]BF$_4$ (3 mol%),
TMSCHN$_2$ (1.4 equiv),
PPh$_3$ (1.1 equiv), *i*-PrOH (1.1 equiv)
Dioxane, 50 °C, 3 h
2- Pinacolborane (2 equiv), rt, 12 h
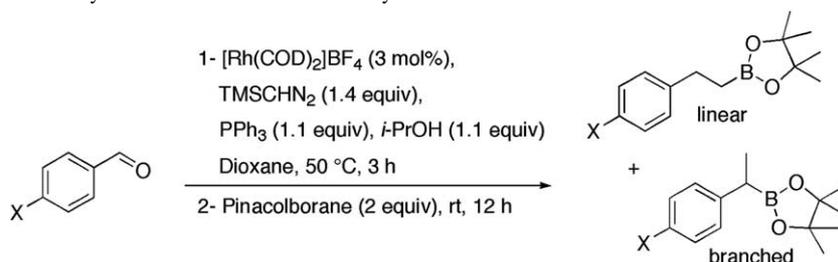
Entry	X	Yield[a]	Ratio B:L[b]
1[c]	Br	–	4:1
2	Br	62%	8:1
3	H	67%	9:1
4	Me	61%	5:1
5	OMe	65%	1.5:1

[a] Isolated yields.
[b] Determined by GC–MS.
[c] Reaction was performed using 3 mol% of RhCl(PPh$_3$)$_3$ and 2 equiv. of catecholborane.

the desired organoborane after 2 h at room temperature. Oxidation with hydrogen peroxide and sodium hydroxide led to the formation of the desired primary alcohol with 80–81% yields (Eqs. 2 and 3)

1- RhCl(PPh$_3$)$_3$ (3 mol%), TMSCHN$_2$ (2.0 equiv)
PPh$_3$ (2.0 equiv), *i*-PrOH (2.0 equiv) / THF, 60 °C
2- Catecholborane / dioxane, rt
3- H$_2$O$_2$, NaOH
81%

(2)

1- RhCl(PPh$_3$)$_3$ (3 mol%), TMSCHN$_2$ (2.0 equiv)
PPh$_3$ (2.0 equiv), *i*-PrOH (2.0 equiv) / THF, 60 °C
2- Catecholborane / dioxane, rt
3- H$_2$O$_2$, NaOH
80%

(3)
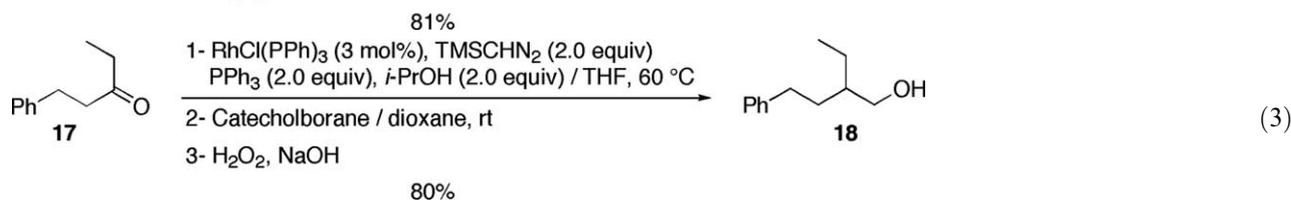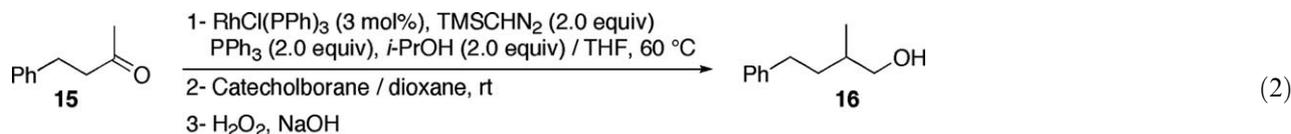
2.4. Rhodium-catalyzed methylenation–hydroboration-homologation cascade

There are a number of transformations that can be performed on the organoborane species, other than the simple oxidation. For instance, a homologation reaction could be performed when adding LiCHCl$_2$, before the oxidative work-up [9]. Indeed the organoborane species **19** initially generated from hydrocinnamaldehyde (**1**), could be directly treated with the anion of dichloromethane (LiCHCl$_2$) to produce the chloro one-carbon homologated organoborane product (Scheme 1). The oxidation reaction conditions could be adjusted in such way that either ester **20** or aldehyde **21** could be directly obtained without further steps. Corresponding ester **20**

was produced in 64% yield from a 5-steps sequence whereas aldehyde **21** could be generated with 62% yield, from a 4-steps sequence indicating that each individual step was about 90% yield. It is also possible to produce the two-carbon homologated alcohol product by using LiCH$_2$Cl generated by lithium–halogen exchange from bromochloromethane. The homologated organoborane species is then submitted to oxidation reaction to furnish the desired alcohol **22** in 60% yield from a 4-steps sequence. These two-carbon homologation sequences are thus particularly efficient, as it is not required to isolate any intermediate and as the reagent and/or the oxidation level could be adjusted to furnish the requisite product.

3. Conclusion

In conclusion, an efficient cascade process has been developed to perform a rhodium-catalyzed
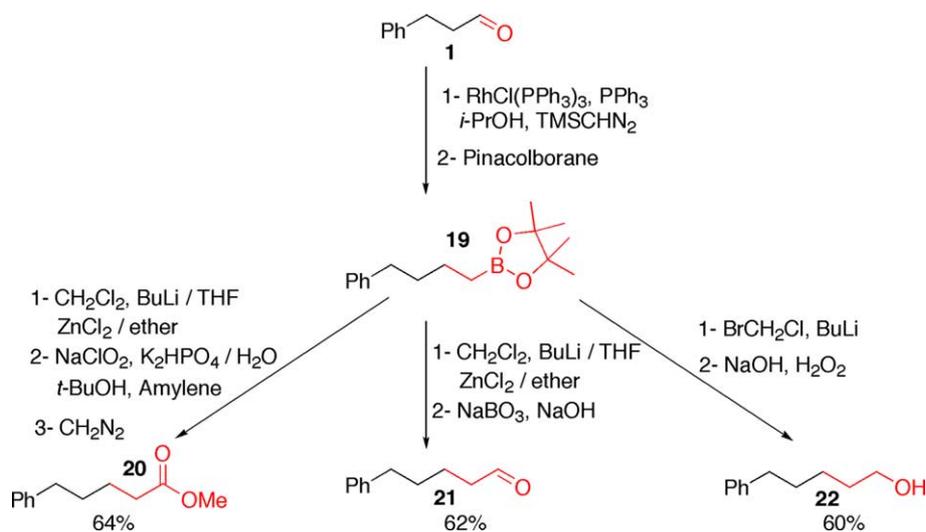
Scheme 1. Rhodium-catalyzed methylenation hydroboration homologation process.

methylenation–hydroboration sequence in one single step. In this process, the Wilkinson's complex played a dual role, as it catalyzed both the methylenation and the hydroboration reaction. Aliphatic aldehydes and ketones produced the corresponding primary alcohol after the oxidation step, whereas aromatic aldehydes led to the formation of the corresponding secondary organoborane species. Furthermore, a second homologation could be performed in situ on the organoborane species, before the oxidation step, to lead to a 2-carbons homologation sequence with high yield. Overall this process illustrates the power of Wilkinson's complex at catalyzing very different type of organic reactions.

4. Experimental

4.1. General considerations

All the non-aqueous reactions were performed under an oxygen-free atmosphere of argon. The solvents were dried using standard method prior to use. RhCl(PPh$_3$)$_3$ is commercially available, but was prepared according to the literature [1]. 2-propanol was distilled over calcium hydride. [Rh(COD)$_2$]BF$_4$ was prepared according to the literature procedure [12]. The commercial available aldehydes were purified using standards methods prior to use. Triphenylphosphine was purchase from Aldrich Chemical Co. and used without further purification. Catecholborane and pinacolborane are commercially available but was prepared according to the literature procedure [13,14]. Analytical thin layer chromatography (TLC) was performed using EM Reagent 0.25 mm silica gel 60-F plates. Flash chromatography was performed using EM Silica Gel 60 (230–400 mesh) with the indicated solvent system. Infrared spectra were recorded on a Perkin–Elmer Spectrum

One FTIR spectrometer. ^{1}H NMR spectra were recorded in CDCl$_3$, on a Brucker Av-400, a Brucker ARX-400, a Brucker AMX-300, or a Brucker AV-300 spectrometers (400, 400, 300, and 300 MHz, respectively). Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet and br = broad), coupling constant in Hz, integration. ^{13}C NMR spectra were recorded in CDCl$_3$, on a Brucker Av-400, a Brucker ARX-400, a Brucker AMX-300, or a Brucker AV-300 spectrometers (100, 100, 75, and 75 MHz, respectively) with complete proton decoupling. Chemical shifts are reported in ppm from the central peak of CDCl$_3$ (76.9 ppm) on the δ scale. Mass spectra were obtained on a LC-MSD TOF Agilent Technologies (ESI) high resolution. Analytical gas chromatography with mass spectroscopy (GC–MS) was carried out on a Hewlett–Packard 6890 series gas chromatograph equipped with a split mode capillary injector and electron impact mass detector. Unless otherwise noted, injector and detector temperatures were 250 °C and the carrier gas was hydrogen (2 mL/min) with a HP-5MS column.

4.2. Catalytic methylenation–hydroboration of aliphatic aldehydes

To a solution of chlorotris(triphenylphosphine)rhodium (0.027 g, 0.030 mmol) and triphenylphosphine (0.290 g, 1.10 mmol) in THF (10.0 mL) under argon atmosphere, was added 2-propanol (0.084 mL, 1.10 mmol) followed by the aldehyde (1.00 mmol). To the resulting red mixture, was added trimethylsilyldiazomethane (0.197 mL of a 7.10 M solution, 1.40 mmol). Gas evolution was observed and the resulting mixture

was stirred at room temperature. When the methylenation is completed by TLC analysis, catecholborane (0.210 mL, 2.00 mmol) was slowly added and the reaction was stirred at room temperature. When the hydroboration was completed by TLC analysis, the resulting organoborane was oxidized following method A or B.

4.3. Oxidation method A: $H_2O_2/NaOH$

When the hydroboration is completed by TLC analysis, the flask was opened to air and dioxane (3.0 mL) was added; the reaction mixture was then cooled to 0 °C. A solution of NaOH (3.0 mL of a 2.0 M solution, 6.00 mmol) was added followed by H_2O_2 (3.00 mL of a 35% solution, 36.0 mmol). The reaction mixture was warmed to room temperature and stirred under air atmosphere for another 3 h. The mixture was then extracted with ethyl ether (2×10 ml), and the combined organic layers were washed with saturated solutions of NH_4Cl (10 mL), $NaHCO_3$ (10 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude alcohol was purified by flash chromatography on silica gel.

4.4. Oxidation method B: $NaBO_3$

When the hydroboration is completed by TLC analysis, the flask was opened to air and dioxane (3.0 mL) followed by water (3.0 mL) and sodium perborate (0.240 g, 3.00 mmol) were added sequentially to the flask; The reaction mixture was maintained at room temperature for 3 h with vigorous stirring under air atmosphere. The two phases were separated, and the aqueous layer was extracted with ether (3×5 mL). The combined organic layers were washed with brine (10 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure. The crude alcohol was purified by flash chromatography.

4.5. Catalytic methylenation–hydroboration of aromatic aldehydes

To a solution of $[Rh(COD)_2]BF_4$ (0.012 g, 0.030 mmol) and triphenylphosphine (0.290 g, 1.10 mmol) in dioxane (10.0 mL) under argon atmosphere, was added 2-propanol (0.084 mL, 1.10 mmol) followed by the aldehyde (1.00 mmol). The mixture was heated at 50 °C and trimethylsilyldiazomethane (0.197 mL of a 7.10 M solution, 1.40 mmol) was added. When the reaction is completed by TLC analysis, the mixture was allowed to cool to room temperature and pinacolborane (0.290 mL, 2.00 mmol) was added dropwise. The reaction mixture was then stirred over night. The solvent was removed under reduced pressure, the crude organoborane was purified by flash chromatography. The ratio branched/linear of the boronate ester was obtained by GC/MS.

4.6. Catalytic methylenation–hydroboration of ketones

To a solution of chlorotris(triphenylphosphine)rhodium (0.027 g, 0.030 mmol) and triphenylphosphine (0.520 g, 2.00 mmol) in THF (10.0 mL) under argon atmosphere, was added 2-propanol (0.150 mL, 2.00 mmol) followed by the ketone (1.00 mmol). The resulting mixture was heated at 60 °C and trimethylsilyldiazomethane (0.280 mL of a 7.10 M solution, 2.00 mmol) was added dropwise. When the reaction is completed by TLC analysis, the mixture is allowed to cool to room temperature and catecholborane (0.319 mL, 3.00 mmol) was added. When the hydroboration is completed by TLC, the resulting organoborane was oxidized following method A.

4.7. Catalytic methylenation–hydroboration–homologation

To a solution of chlorotris(triphenylphosphine)rhodium (0.013 g, 0.015 mmol) and triphenylphosphine (0.144 g, 0.550 mmol) in THF (5.00 mL) under argon atomosphere, was added 2-propanol (0.042 mL, 0.55 mmol) followed by the hydrocinnamaldehyde (0.670 mg, 0.500 mmol). To the resulting red mixture, was added trimethylsilyldiazomethane (0.098 mL of a 7.10 M solution, 0.700 mmol). Gas evolution was observed and the resulting mixture was stirred at room temperature. When the reaction is completed by TLC analysis, pinacolborane (0.145 mL, 1.00 mmol) was slowly added and the reaction was stirred at room temperature. When the hydroboration was completed by TLC analysis, the volume was reduced to roughly 2 mL under reduced pressure. $LiCHCl_2$ (1.00 mmol) was generated by the dropwise addition of *n*-BuLi (0.470 mL of a 2.10 M solution in hexane, 1.00 mmol) to a mixture of dichloromethane (0.500 mL, 7.80 mmol) in THF (3.50 mL) at -100 °C. The solution was stirred for 10 min before the addition of the organoborane. $ZnCl_2$ (0.50 mL of a 1.0 M solution in Et_2O, 0.50 mmol) was then added. The reaction was warm up to room temperature overnight. The volatiles were then removed under a vigorous flow of argon. The residue was quenched with 2 mL of saturated NH_4Cl solution, extracted with light petroleum ether (4×10 mL), dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was then oxidized following method C or D.

4.8. Oxidation method C: synthesis of 5-phenylpentanoic acid methyl ester (**20**) [15]

The residue obtained from 4.7 was dissolved in *t*-BuOH (10 mL) and amylene (2.0 mL). A solution (20 mL) of $NaClO_2$ (0.600 g, 6.00 mmol) and K_2HPO_4 (0.920 g, 7.20 mmol) was prepared; 10 mL of this solution were added and the reaction was stirred for 24 h, under air atmosphere. The other 10 mL were added

and the reaction was stirred for another 72 h. The volatiles were removed in vacuo, and the resulting aqueous residue was extracted with ether (3×10 mL) and ethyl acetate (3×10 mL). The combined organic extracts were washed with water (2×15 mL) and then extracted with saturated aqueous $NaHCO_3$ (2×15 mL). The combined basic aqueous layers were then slowly acidified to pH 2 with concentrated HCl. The aqueous solution was extracted with ethyl acetate (4×25 mL). The organic extracts were then combined, washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo. The resulting white solid was dissolved in CH_2Cl_2 (2 mL) and diazomethane (1.07 mL of a 0.70 M solution in ether, 0.75 mmol) was added dropwise. The mixture was stirred at room temperature for 1 h. The solvent was evaporated and the crude product was purified by flash chromatography (10% ethyl acetate/hexane) to produce 0.061 g (64% yield) of the desired ester. R_f 0.32 (10% ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.28 (m, 2H), 7.22–7.19 (m, 3H), 3.69 (s, 3H), 2.66 (t, $J = 5$ Hz, 2H), 2.36 (t, $J = 10$ Hz, 2H), 1.72–1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 142.5, 128.8, 128.7, 126.2, 51.9, 36.0, 34.4, 31.3, 25.0.

4.9. Oxidation method D: synthesis of 5-phenylpentanal (21) [16]

The residue obtained from 4.7 was then dissolved in THF (5 mL). Sodium perborate (0.120 g, 1.50 mmol) was added to the flask followed by 5 mL of water and a solution of NaOH (0.25 mL of a 2 M solution, 0.50 mmol). The mixture was stirred at room temperature, under air atmosphere, over night. The mixture was then extracted with ethyl ether (4×10 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and evaporated in vacuo. The crude product was purified by flash chromatography (10% ethyl acetate/hexane) to produce 0.048 g (62% yield) of the desired aldehyde. R_f 0.27 (10% ethyl acetate/hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 7.32–7.28 (m, 2H). 7.22–7.18 (m, 3H), 2.66 (t, $J = 6$ Hz, 2H), 2.48 (t, $J = 8$ Hz, 2H), 1.79–1.64 (m, 4H). ^{13}C NMR (100 MHz, CDCl3) δ 202.2, 141.6. 128.03, 128.0, 125.5, 43.4, 35.3, 30.5, 21.3.

4.10. Catalytic methylenation–hydroboration–homologation: synthesis of 5-phenyl-1-pentanol (22)

To a solution of chlorotris(triphenylphosphine)rhodium (0.013 g, 0.015 mmol) and triphenylphosphine (0.144 g, 0.550 mmol) in THF (5.00 mL) under argon atomosphere, was added 2-propanol (0.042 mL, 0.550 mmol) followed by the hydrocinnamaldehyde (0.670 mg, 0.500 mmol). To the resulting red mixture, was added trimethylsilyldiazomethane (0.098 mL of a

solution 7.10 M, 0.700 mmol). Gas evolution was observed and the resulting mixture was stirred at room temperature. When the reaction is completed by TLC analysis, pinacolborane (0.145 mL, 1.00 mmol) was slowly added and the reaction was stirred at room temperature. When the reaction is completed by TLC analysis, the volume was reduced to roughly 2 mL under reduced pressure. Bromochloromethane (0.350 mL, 0.550 mmol) was then added and the reaction solution was cooled to -78 °C; *n*-BuLi (0.260 mL of a 2.10 M solution in hexane, 0.55 mmol) was added dropwise. The reaction was warmed to ambient temperature over night. The volatiles were removed under a flow of argon. The residue was quenched with 5 mL of saturated NH_4Cl, extracted with light petroleum (4×10 mL) dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was then submitted to oxidation following the method A. The crude alcohol was purified by flash chromatography (30% ethyl acetate/hexane) to give 0.051 g (60% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.29 (m, 2H), 7.23–7.19 (m, 3H), 3.67 (t, $J = 6.5$ Hz, 2H), 2.67 (t, $J = 8$ Hz, 2H), 1.75–1.59 (m, 5H), 1.49–1.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 128.8, 128.7, 126.1, 63.3, 36.3, 33.1, 31.7, 25.9.

Appendix A. Supplementary data

Characterization data for compounds **2**, **4**, **6**, **8**, **10**, **12**, **14**, **16** and **18**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jorganchem.2005.03.058.

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