Microwave-Assisted Domino Hydroformylation without Syngas

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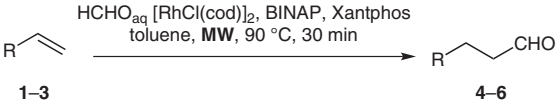
Abstract: Hydroformylation is a powerful reaction that has suffered for some negative prejudices related to the use of gaseous H_2 and CO. Now it is possible to carry out hydroformylation and different cyclohydrocarbonylations, even on complex substrates, using aqueous formalin as H_2 and CO surrogate in few minutes under microwave irradiation. The catalytic system developed by Morimoto (Rh/BINAP for decomposition of formaldehyde and Rh/Xantphos for hydroformylation) is compatible with microwave dielectric heating and with complex substrates containing ligand atoms allowing rapid domino hydroformylation cyclization reactions without using the external supply of gaseous H_2 and CO (gas cylinder) and without any particular safety limitation or device.

Key words: microwaves, hydroformylation, homogeneous catalysis, domino reactions

Hydroformylation of alkenes is a perfect example of efficient C–C bond formation in an atom economical fashion.[1] This reaction, via an hydrometallation, introduces an aldehyde onto a double bond, providing a new functional group suitable for additional transformations. Tons of aldehydes are produced every year by hydroformylation making it the largest applied process in homogeneous catalysis.[2] Recently, the design of ligands with improved chemo- and regioselectivity has given a new glance to the hydoformylation of olefins. Not only the linear/branched ratio is now under control but even the presence of functional groups on the alkene substrate is well tolerated. Consequently, the application of hydroformylation in domino processes has been exploited as a strategy to prepare many heterocycles.[3,4] Despite the above-mentioned improvements, the potential of the hydroformylation reaction is still under-utilized by the community of organic chemists in the design of synthetic sequences. The use of gaseous H_2 and CO (the so called syngas) at high pressure (5–80 bar) and temperature (60–120 °C) for long reaction times (12–36 h) requires special devices such as stainless-steel autoclaves. Moreover, a dedicated safety laboratory is mandatory for the management of high-pressure gas.[5] These facilities, not always available especially in academia, are the main obstacles to the diffusion of hydroformylation into organic and medicinal chemistry research laboratories. Recent improvements have been the development of efficient catalysts to work at room temperature and atmospheric syngas pressure[6] or the application of microwave dielectric heating to reduce the reaction time.[7] However, in any case, the use of syngas is required still limiting the friendliness of the process. Recently, Morimoto and co-workers reported the results of a highly selective hydroformylation of terminal alkenes using formaldehyde as a substitute of syngas.[8] While Rh(I) BINAP catalyzes the decomposition of formaldehyde into CO and H_2, Rh(I)Xantphos catalyzes the further hydroformylation. The reaction was described on some simple linear alkenes giving, after 20 hours at 90 °C, the corresponding aldehydes in good yields. This procedure attracted immediately our attention by its simplicity.[9,10] By the way, if these conditions would be widely applicable, hydroformylation could be usable by everybody without practical limitations. As it was not obvious that the catalytic system Rh(I)/BINAP/Xantphos could be applied to substrates that contains coordinative functional groups, we decided to investigate the application of the procedure to domino cyclohydrocarbonylation using also microwave dielectric heating to speed up the process and let it even more affordable. At first, we wanted to verify if the system formaldehyde/Rh(I) complex could be used as a syngas substituted under microwave dielectric heating.

Table 1 Microwave-Assisted Formalin-Based Hydroformylation of Terminal Alkenes



Entry	Alkene[a]	Aldehyde	Yield (%)[b] (l/b ratio)[c]
1	**1** R = C_6H_{13}	**4** R = C_6H_{13}	90 (98:2)
2	**2** R = Bn	**5** R = Bn	87 (95:5)
3	**3** R = PMBO$(CH_2)_2$	**6** R = PMBO$(CH_2)_2$	92 (98:2)

[a] Reaction conditions: alkene (1 mmol), formalin (0.5 mL), [RhCl(cod)]$_2$ (0.01 mmol), BINAP (0.02 mmol), Xantphos (0.02 mmol), toluene (5 mL) sealed vial, MW, 150 W (value previously settled on the microwave oven), max internal pressure recorded $1.06 \cdot 10^6$ Pa, 90 °C, 30 min.

[b] Yield of isolated and fully characterized products.

[c] Linear/branched aldehyde ratio determined by integration of the aldehyde peaks in the ^{1}H NMR spectra of the crude reaction mixture.

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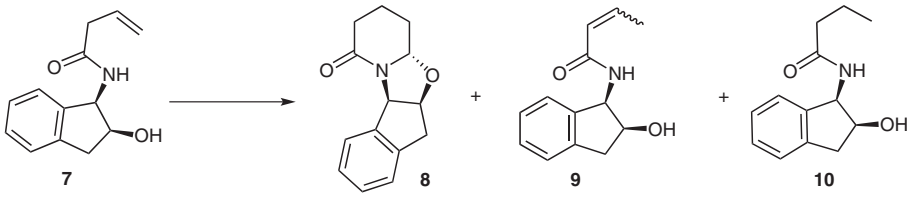
Thus 1-octene **1** was submitted to reaction with formalin (37% aq fomaldehyde) in toluene with $[RhCl(cod)]_2$ in the presence of the two ligands BINAP and Xantphos (entry 1, Table 1). After heating at 90 °C for 30 minutes, we observed a conversion of 95% and nonanal **4** was isolated in 90% yield. The analysis of the crude showed the presence of less than 2% of the branched aldehyde. The same conditions were applied to other linear alkenes with good results (entries 2 and 3, Table 1).

Encouraged by these results, we decided to apply the formalin-based hydroformylation to compound **7**, a substrate known to undergo domino hydroformylation–cyclization reaction.[11] β,γ-Unsaturated amides are known to be prone to double-bound isomerization and conjugation with the carbonyl. Results of the investigation are reported in Table 2. Applied to substrate **7**, the standard conditions [BINAP, Xantphos, and Rh(I)] gave an excellent conversion (entry 1). Three compounds were formed, the major adduct was the expected cyclized product **8** together with the acrylamide **9** resulting from the double-bound isomerization and the reduced compound **10**. Increasing the reaction time (entry 2) produced few changes in the product distribution. These results are comparable to the traditional conditions using syngas and Xantphos (entry 3), whereas the combination of Biphephos and syngas demonstrated a real benefit for the formation of **8** (entry 4). Unfortunately, the hydroformylation of **7** with formalin did not proceed with Biphephos and BINAP as partners (entry 5). These preliminary experiments demonstrate that the reaction conditions have to be carefully controlled in order to favor the hydroformylation over the side reactions. Changing the solvent for EtOH (entry 7) or THF (entry 8) did not afford better results. When Biphep (for formalin decomposition) and Nixantphos (for hydroformylation) were associated to Rh(I), the conversion to **8** in terms of selectivity and yield was improved (entries 9 and 10).[8] Lowering the temperature and increasing the reaction time is beneficial for the production of cyclocondensed **8**. The time saving by using microwaves instead of traditional heating is demonstrated comparing entries 10 and 11. An attempt to use paraformaldehyde as syngas source,[8] was unsuccessful giving a complex mixture of byproducts (entry 12). Our results demonstrate that the association of Rh(I), Biphep, Nixantphos, and formalin (Morimoto's conditions) could be a suitable substitute for syngas in domino hydroformylation assisted by microwave heating. It is worth noting that, in this case, only *trans*-**8** was isolated (entries 9–11), whereas under the previous settled conditions (entry 4),[11] a 4:1

Table 2 Optimization of MW-Assisted Domino Formalin-Based Hydroformylation



Entry	Catalyst, ligands/Source of CO/H_2	Reaction conditions	Products (%)[a]
1	$[RhCl(cod)]_2$, BINAP, Xantphos/formalin	toluene, MW, 90 °C, 30 min	**8** (55); **9** (28); **10** (17)
2	$[RhCl(cod)]_2$, BINAP, Xantphos/formalin	toluene, MW, 90 °C, 90 min	**8** (60); **9** (27); **10** (13)
3	$[RhCl(cod)]_2$, Xantphos/syngas	toluene, MW, 90 °C, 90 min	**8** (45); **9** (30); **10** (10)[b]
4	$Rh(CO)_2acac$, Biphephos/syngas	toluene, MW, 90 °C, PTSA, 90 min	**8** (91);[c] **9** (5); **10** (4)
5	$Rh(CO)_2acac$, BINAP, Biphephos/formalin	toluene, MW, 90 °C, PTSA. 90 min	**8** (<2); **9** (48); **10** (35)[b]
6	$[RhCl(cod)]_2$, BINAP, Xantphos/formalin	toluene, MW, 130 °C, 30 min	**8** (67); **9** (15); **10** (18)
7	$[RhCl(cod)]_2$, BINAP, Xantphos/formalin	EtOH, MW, 130 °C, 30 min	**8** (41); **9** (3); **10** (46)[b]
8	$[RhCl(cod)]_2$, BINAP, Xantphos/formalin	THF, MW, 130 °C, 30 min	**8** (58); **9** (30); **10** (12)
9	$[RhCl(cod)]_2$, BIPHEP, Nixantphos/formalin	toluene, MW, 130 °C, 30 min	**8** (76); **9** (14); **10** (10)
10	$[RhCl(cod)]_2$, BIPHEP, Nixantphos/formalin	toluene, MW, 90 °C, 30 min	**8** (89);[d] **9** (7); **10** (4)
11	$[RhCl(cod)]_2$, BIPHEP, Nixantphos/formalin	toluene, oil bath, 90 °C, 20 h	**8** (84);[e] **9** (9); **10** (2) + sm
12	$[RhCl(cod)]_2$, BIPHEP, Nixantphos/paraformaldhyde	toluene, MW, 90 °C, 90 min	[f]

[a] Ratio determined by ^1H NMR analysis of the crude reaction mixture.
[b] Additional byproducts isolated.
[c] Compound 8 was isolated in 83% yield after column chromatography as a 4:1 mixture of *trans*/*cis* isomers.
[d] Compound **8** isolated in 80% yield after column chromatography as a single *trans* isomer.
[e] Compound **8** isolated in 78% yield after column chromatography as a single *trans* isomer.
[f] Complex mixture of byproducts.

mixture of *trans*/*cis* diastereomers was formed. In order to demonstrate the scope of the process, various terminal olefins **11–19** were submitted to the above-optimized reaction conditions, {$RhCl(cod)]_2$, BIPHEP, Nixantphos, toluene, MW, 90 °C, 30 min} and the results are collected in Table 3.[12,13]

The domino hydroformylation occurred always with good to acceptable yields demonstrating the wide scope of the process. In entries 1–3 of Table 3, the chiral amides **11–13** gave the corresponding oxazolidinones **20–22** in good to moderate yields via transient acyliminium. It is worth noting that compound **13** derived from methionine, gave low yield of **22** (entry 3 in Table 3) due to persistance of unreacted starting material. As in the case of PTSA, (entry 5 in Table 1) the pH variation decreases the efficiency of the process (probably due to formaldehyde decomposition). Interestingly, olefin **14** afforded bicyclic adehyde **23** after an intramolecular Mannich reaction (entry 4). As expected, the allyl or homoallylic alcohols **15–18** gave the corresponding lactols **24–27** (entries 5–7) in good yields. In the last case, only one of the two possible cyclizations occurred, even increasing the reaction time. However, an analogous result was obtained using syngas under microwave dielectric heating.

Finally, homoallylamine **19** gave internal enamide **28** in moderate yield (entry 8).[7a]

In conclusion we have demonstrated that the system of formalin/Rh(I)/BIPHEP/Nixantphos (or BINAP/Xantphos), assisted by microwave heating can be successfully applied for hydroformylation of complex substrates designed for domino processes. In our opinion, most of the negative prejudices attached to the hydroformylation reaction are relieved by the use of formalin in place of syngas, and the community of organic and medicinal chemists may now consider the implementation of the hydroformylation reaction in a synthetic plan as easy as the Suzuki, Heck, or metathesis reactions.

Acknowledgment

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Reference and Notes

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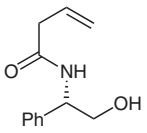
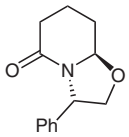
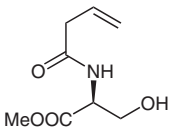
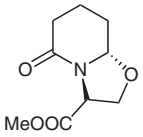
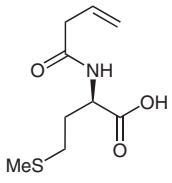
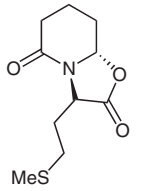
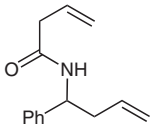
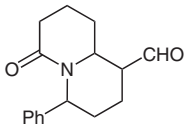
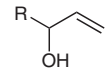
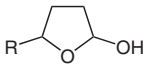
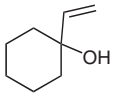
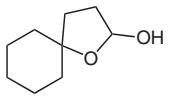
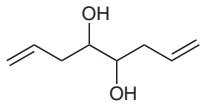
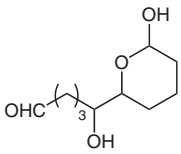
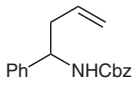
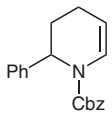
Table 3 Scope of the MW-Assisted Domino Formalin-Based Hydroformylation Cyclization Reaction

Entry	Starting material	Product[a]	Yield (%)[b]
1	 **11**	 **20**	79[c]
2	 **12**	 **21**	64[c]
3	 **13**	 **22**	35[c]
4	 **14**	 **23**	56[e]
5	 **15** R = Bu **16** R = Ph	 **24** R = Bu **25** R = Ph	**24** 85[d] **25** 76[d]
6	 **17**	 **26**	76
7	 **18**	 **27**	78[e]
8	 **19**	 **28**	65

[a] Reaction conditions: alkene (1 mmol), formalin (0.5 mL), [RhCl(cod]2] (0.01 mmol), BIPHEP (0.02 mmol), Nixantphos (0.02 mmol), toluene (5 mL) sealed vial, MW, 150 W (value previously settled on the microwave oven), max internal pressure recorded $1.06 \cdot 10^6$ Pa, 90 °C, 30 min.

[b] Yield of isolated and fully characterized products.

[c] Diasteromeric ratio (dr) > 98:2.

[d] dr = 50:50.

[e] dr = 75:25 (relative configuration not defined).

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(13) **(3*S*,8a*R*)-3-Phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]-pyridin-5-one (20) – General Procedure**
A MW vessel was charged with $[RhCl(cod)]_2$ (2.5 mg, 0.005 mmol), BIPHEP (5.2 mg, 0.01 mmol), and Nixantphos (5.5 mg, 0.01 mmol) under nitrogen (the reaction was carried out without degassing the solution, an experiment done on a degassed solution, gave comparable results). After adding toluene (3 mL), alkene **11** (103 mg, 0.5 mmol), and formalin (37%, 205 μL, 2.5 mmol), the mixture was heated for 30 min at 90 °C by microwave irradiation at 250 W (value previously settled on the microwave oven, model Discover from CEM). The solvent was removed in vacuo and the product purified by column cromatography (eluent hexane–EtOAc, 4:1) and isolated as a waxy material (85 mg, 79% yield, dr > 98:2). Characterization as in ref. 12. Compounds **24**–**26** were described in ref. 7d and compound **28** in ref. 5. New compounds isolated in this work:
1-Oxaspiro[4.5]decan-2-ol (26)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.41 (s-like, 1 H), 3.85 (br s, 1 H), 2.11–1.90 (m, 4 H), 1.58–1.40 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.7, 89.9, 38.7, 35.5, 34.4, 32.2, 25.8, 23.7). ESI-LRMS: *m/z* = 179 $[M + Na]^+$, 157 $[M + H]^+$.
5-Hydroxy-5-(6-hydroxytetrahydro-2*H*-pyran-2-yl)-pentanal (27)
^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.77 (s, 1 H_a), 9.74 (t, *J* = 1.6 Hz, 1 H_b), 5.48 (s, 1 H_a, 1 H_b), 4.07–4.02 (m, 2 H_a, 2 H_b), 2.54–2.50 (m, 2 H_a), 2.48–2.44 (m, 2 H_b), 1.88–1.45 (m, 10 H_a, 10 H_b). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 201.9, 102.1, 101.4, 78.8, 78.1, 43.2, 34.3, 30.5, 29.8, 28.0, 27.3, 23.9, 19.2, 17.7. ESI-LRMS: *m/z* = 257 $[M + MeOH + Na]^+$.