Journal of Organometallic Chemistry 866 (2018) 184–188

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

# Tandem hydroformylation/aldol condensation reactions: Synthesis of unsaturated ketones from olefins

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ARTICLE INFO

*Article history:*
Received 22 March 2018
Received in revised form
12 April 2018
Accepted 21 April 2018
Available online 23 April 2018

*Keywords:*
Tandem reaction
Hydroformylation
Aldol condensation
Platinum
Unsaturated ketone

ABSTRACT

Platinum-catalysed tandem hydroformylation/aldol condensation reaction of vinyl aromatics and ketones toward the corresponding α,β-unsaturated ketones were performed under syngas atmosphere in the presence of acid co-catalysts. The *in situ* generated catalysts modified with various ligands proved to be efficient under applied conditions. The presence of acids promotes side reactions like hydrogenation of the alkene substrate and that of the aldehyde to the corresponding alkane and alcohol, respectively. Interestingly, the hydrogenation of the condensed products is not preferred, only trace amounts of saturated products can be detected by GC-MS. In general, moderate yields can be achieved with several ketones using styrene and α-methylstyrene as substrate in hydroformylation reaction. Linear aldehydes proved to be more active in aldol condensation step, furthermore, aromatic and cyclic ketones are also feasible coupling partners to generate the corresponding unsaturated ketones. Contrary to the preceding literature, ketones possessing α-methylene group(s) showed exclusive preference for methylene functionalization in the aldol condensation reaction.

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## 1. Introduction

Hydroformylation represents an efficient and selective method for the transformation of alkenes to valuable aldehydes [1–3]. The reaction discovered accidently by Otto Roelen in 1938, represents one of the large scale catalytic reactions. It has an especially high importance among homogenous catalytic reactions in industry today. Regioselective hydroformylation of propene to n-butyraldehyde (basic compound of 2-ethylhexanol used as alcohol component in the production of diisooctyl phthalate plasticizer), or the enantioselective hydroformylation of vinylaromatics to 2-arylpropanals (intermediate of non-steroidal anti-inflammatory drugs (NSAIDs)) are only two important examples for the process [4]. Beside the well-studied cobalt- and rhodium-containing catalysts, platinum-phosphine-tin(II)halide type systems were also developed focusing on the enantioselective reactions [5–9], and reaction mechanism. Seminal work by Casey et al. on the kinetics of enantioselective hydroformylation [10] and asymmetric hydroformylations of a set of 4-substituted styrenes by our group [11,12] were carried out to rationalise the reversal of enantioselectivity as a function of temperature.

In most cases the aldehydes are not the final products and the reactivity of these substantial materials allow us to perform numerous additional reactions even under hydroformylation conditions. Aldehydes can be considered as ideal substrates for further transformations, like oxidations, reductions or condensation reactions. In the presence of N- or O-nucleophiles versatile domino reactions are known like hydroaminomethylation, cyclohydrocarbonylation, acetalization or aldol condensation [13,14]. The first hydroformylation/aldol condensation reactions were reported by Breit and Eilbracht with rhodium catalysts using proline organocatalyst [15,16]. Breit described hydroformylation/Knoevenagel condensation reaction in the presence of piperidine base and acetic acid [17], and further tandem decarboxylative Knoevenagel reactions, which allowed an efficient one-pot synthesis of α,β-unsaturated acids and esters [18]. Recently, Beller and co-workers developed an efficient hydroformylation/aldol condensation/hydrogenation protocol using piperidine and benzoic acid cocatalysts [19,20]. In this study, a set of substrates and ketones proved to be suitable for the production of normal chain saturated ketones, *i.e.*, the consecutive hydrogenation of the unsaturated ketones formed via condensation was observed. Examples of intramolecular hydroformylation/aldol reactions of unsaturated ketones were also

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https://doi.org/10.1016/j.jorganchem.2018.04.031
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reported, which afforded the corresponding cyclic aldol adducts in good yields [21].

Herein, we present the application of platinum(II)-phosphine complexes and *para*-toluenesulfonic acid as efficient catalyst systems for domino hydroformylation/aldol condensation reactions. Styrene and α-methylstyrene as model substrates are transformed to *unsaturated ketones* under moderate conditions in the presence of various ketones used as solvents or reactants.

## 2. Experimental

### 2.1. General

The $PtCl_2(PhCN)_2$ [22] precursor was synthesized as described earlier. Toluene was distilled and purified by standard methods [23] and stored under argon. Styrene, tin(II) chloride (anhydrous) and ketones were used as obtained from Sigma-Aldrich without any further purification. All reactions were carried out under argon atmosphere using standard Schlenk technique.

The GC and chiral GC measurements were run on a Chrom-Card Trace GC-Focus GC gas-chromatograph. The enantiomeric excesses were determined on a capillary Cyclodex-column. The $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance III 500 spectrometer. Chemical shifts are reported in ppm relative to TMS (downfield) for $^1H$ and $^{13}C$ NMR spectroscopy.

### 2.2. Tandem hydroformylation/aldol condensation experiments

In a typical experiment, $PtCl_2(PhCN)_2$ (4.7 mg, 0.01 mmol), diphosphine (0.01 mmol), and tin(II) chloride (3.8 mg, 0.02 mmol), *para*-toluenesulfonic acid (17.2 mg, 0.1 mmol) and 0.115 mL (1.0 mmol) of styrene was transferred under argon into a 100 mL stainless steel autoclave. Either 10 mL of ketone (Method A) or a mixture of 8 mL of toluene and 2 mL of the appropriate ketone (Method B) was added as solvent. The reaction vessel was pressurized to 80 bar total pressure ($CO/H_2 = 1/1$) and placed in an oil bath of appropriate temperature and the mixture was stirred with a magnetic stirrer. Sample was taken from the mixture and the pressure was monitored throughout the reaction. After cooling and venting of the autoclave, the pale yellow solution was removed and immediately analysed by GC.

### 2.3. Characterization of the products

#### 2.3.1. 5-Phenyl-3-hexene-2-one (**2$^i$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.34–7.20 (5H, m, *Ph*), 6.92 (1H, dd, 7.0 Hz, 16.5 Hz, CHC*H*CH), 6.06 (1H, d, 16.5 Hz, COC*H*), 3.63–3.59 (1H, m, PhC*H*), 2.23 (3H, s, $COCH_3$), 1.43 (3H, d, 7 Hz, $CHCH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 199.2, 151.9, 143.5, 129.9, 129.0, 127.6, 127.1, 42.5, 27.2, 20.4. MS *m/z* (rel int. %): 176 (3), 116 (20), 91 (100), 65 (13).

#### 2.3.2. 6-Phenyl-3-hexene-2-one (**2$^n$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.34–7.20 (5H, m, *Ph*), 6.84 (1H, dt, 6.7 Hz, 16.0 Hz, $CH_2CH$), 6.12 (1H, d, 16.0 Hz, C*H*CO), 2.82 (2H, t, 7.5 Hz, $PhCH_2$), 2.58 (2H, td, 7,5 Hz, $CH_2CH$), 2.25 (3H, s, $CH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 198.4, 146.9, 140.7, 131.7, 128.5, 128.3, 126.2, 34.5, 34.1, 26.9. MS *m/z* (rel int. %): 176 (34), 118 (65), 91 (100), 65 (24).

#### 2.3.3. 3-Methyl-6-phenyl-3-hexene-2-one (**4a$^i$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.34–7.22 (5H, m, *Ph*), 6.14 (1H, d, 7.0 Hz, C*H*C), 3.92–3.86 (1H, m, PhC*H*), 2.19 (3H, s, $COCH_3$), 1.89 (3H, s, $CCH_3$), 1.46 (3H, d, 6.9 Hz, $CHCH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$) 199.8, 147.2, 141.0, 133.1, 128.8, 128.6, 126.9, 39.0, 28.2, 21.1, 11.3; MS *m/z* (rel int. %): 188 (1), 159 (29), 116 (18), 91 (100), 65 (12).

#### 2.3.4. 3-Methyl-5-phenyl-3-hexene-2-one (**4a$^n$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.34–7.22 (5H, m, *Ph*), 6.67 (1H, t, 7.0 Hz, C*H*), 2.82 (2H, t, 7.5 Hz, $PhCH_2$), 2.60 (2H, td, 7.4 Hz, 7.5 Hz, $CH_2CH$), 2.30 (3H, s, $COCH_3$), 1.76 (3H, s, $CCH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 199.7, 142.1, 141.0, 138.2, 128.6, 128.5, 126.2, 34.8, 30.8, 25.4, 11.1. MS *m/z* (rel int. %): 188 (4), 173 (4), 145 (5), 116 (20), 91 (100), 65 (12).

#### 2.3.5. 2-Methyl-7-phenyl-5-octene-4-one (**4b$^i$**)

MS *m/z* (rel int. %): 216 (8), 159 (100), 131 (92), 118 (46), 91 (71), 77 (28), 57 (24). (NMR characterization of the analytically pure sample was failed due to low yield. Using *i*Bu-Me-ketone both condensed products and branched aldehyde were obtained in low yield. Therefore, only the condensation product **4b$^n$**) obtained from the normal aldehyde was isolated in analytically pure form.)

#### 2.3.6. 2-Methyl-8-phenyl-5-octene-4-one (**4b$^n$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.34–7.20 (5H, m, *Ph*), 6.86 (1H, td, 6.8 Hz, 15.6 Hz, C*H*CO), 6.13 (1H, d, 15.6 Hz $CH_2CH$), 2.82 (2H, t, 7.5 Hz, $PhCH_2$), 2.59–2.54 (2H, m, $CH_2CH$), 2.41 (2H, d, 7.0 Hz, $COCH_2$), 2.19–2.13 (1H, m, $CH(CH_3)_2$), 0.95 (6H, d, 6.6 Hz $CH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 200.4, 145.9, 140.8, 131.2, 128.5, 128.4, 126.2, 49.2, 34.5, 34.1, 25.2, 22.7. MS *m/z* (rel int. %): 216 (1), 158 (29), 130 (13), 91 (100), 65 (13).

#### 2.3.7. 4-Methyl-6-phenyl-4-heptene-3-one (**4c$^i$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.38–7.19 (5H, m, *Ph*), 6.72 (1H, d, 9.5 Hz, C*H*C), 3.90 (1H, dq, 6.9 Hz, 9.5 Hz, $CH_3CH$), 2.72 (2H, q, 7.4 Hz, $CH_2CH_3$), 1.90 (3H, s, $CCH_3$), 1.46 (3H, d, 7.0 Hz, $CHCH_3$), 1.11 (3H, t, 7.3 Hz, $CH_2CH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 202.0, 144.5, 143.0, 135.5, 128.8, 127.0, 126.6, 38.9, 30.5, 21.1, 11.6, 8.8. MS *m/z* (rel int. %): 202 (29), 173 (67), 145 (100), 128 (34), 105 (81), 77 (39), 57 (22).

#### 2.3.8. 4-Methyl-7-phenyl-4-heptene-3-one (**4c$^n$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.34–7.22 (5H, m, *Ph*), 6.67 (1H, t, 7.1 Hz, C*H*), 2.81 (2H, t, 7.5 Hz, $PhCH_2$), 2.70–2.66 (2H, m, $CH_2CH$), 2.59 (2H, q, 7.3 Hz, $CH_2CH_3$), 1.77 (3H, s, $CCH_3$), 1.11 (3H, t, 7.3 Hz, $CH_2CH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$); 202.5, 141.0, 140.6, 137.5, 128.6, 128.4, 126.2, 34.8, 30.8, 30.4, 11.4, 8.8. MS *m/z* (rel int. %): 202 (1), 173 (29), 145 (10), 116 (13), 91 (100), 65 (13).

#### 2.3.9. 1,4-Diphenyl-2-pentene-1-one (**4d$^i$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.91–7.24 (10H, m, *Ph*), 7.21 (1H, dd, 6.8 Hz, 15.5 Hz, C*H*CO), 6.86–6.80 (1H, m, C*H*CHCO), 3.77–3.72 (1H, m, PhC*H*), 1.51 (3H, d, 7.1 Hz, $CH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 191.1, 153.1, 143.4, 137.9, 132.6, 128.7, 128.5, 128.4, 127.4, 126.7, 124.4, 42.5, 20.5. MS *m/z* (rel int. %): 238 (11), 133 (32), 120 (83), 105 (100), 91 (39), 77 (75), 51 (19).

#### 2.3.10. 1,5-Diphenyl-2-pentene-1-one (**4d$^n$**)

$\delta_H$ (500 MHz, $CDCl_3$): 7.89–7.20 (10H, m, *Ph*), 7.09–7.04 (1H, m, $CH_2CH$), 6.87 (1H, d, 15.0 Hz, C*H*CO), 2.86–2.81 (2H, t, 7.0 Hz, $PhCH_2$), 2.66–2.62 (2H, m, $CH_2CH_2$); $\delta_C$ (125.7 MHz, $CDCl_3$): 190.8, 148.8, 140.7, 137.8, 132.6, 128.5, 128.5, 129.5, 128.3, 126.5, 126.1 34.5, 34.4. MS *m/z* (rel int. %): 236 (5), 145 (4), 116 (25), 105 (26), 91 (100), 77 (22), 65 (12), 51 (10).

#### 2.3.11. 1,4-Diphenyl-2-methyl-2-pentene-1-one (**4e$^i$**)

$\delta_H$ (500 MHz, $CDCl_3$) 7.66–7.21 (10H, m, *Ph*), 6.42 (1H, d, 9.6 Hz, C*H*C), 3.96 (1H, qd, 7.2 Hz, 9.5 Hz, PhC*H*), 2.08 (3H, s, $CCH_3$), 1.44 (3H, d, 7.0 Hz, $CHCH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 199.0, 147.4, 140.3, 137.5, 131.5, 129.8, 129.4, 128.7, 128.4, 128.0, 127.9, 39.2, 22.7, 14.1. MS *m/z* (rel int. %): 250 (49), 235 (37), 145 (51), 128 (31), 105 (100), 77 (96), 51 (25).

*2.3.12. 1,5-Diphenyl-2-methyl-2-pentene-1-one (**4e$^n$**)*

$\delta_H$ (500 MHz, $CDCl_3$): 7.58–7.21 (10H, m, *Ph*), 6.32 (1H, t, 7.5 Hz, C*H*), 2.80 (2H, t, 7.3 Hz, PhC$H_2$), 2.70–2.66 (2H, m, C$H_2$CH), 1.95 (3H, s, C$H_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 198.8, 145.0, 141.0, 138.6, 131.4, 129.4, 129.3, 128.5, 128.4, 128.0, 127.9, 34.7, 21.3, 12.5. MS *m/z* (rel int. %): 250 (7), 159 (13), 116 (19), 91 (100), 77 (33), 51 (10).

*2.3.13. 2-(2-phenylpropylidene)-cyclopentanone (**4f$^i$**)*

$\delta_H$ (500 MHz, $CDCl_3$): 7.35–7.20 (5H, m, *Ph*), 6.72–6.69 (1H, m, C*H*C), 3.68–3.61 (1H, m, PhC*H*), 2.65 (2H, m, CC$H_2$), 2.38–2.32 (2H, m, COC$H_2$), 2.00–1.93 (2H, m, $CH_2CH_2$), 1.45 (3H, d, 7.0 Hz, C$H_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 204.1, 139.5, 128.7, 128.5, 128.3, 127.0, 126.6, 40.1, 38.6, 26.7, 21.5, 19.8. MS *m/z* (rel int. %): 200 (65), 185 (21), 144 (43), 129 (100), 105 (38), 91 (32), 77 (31), 51 (16).

*2.3.14. 2-(3-phenylpropylidene)-cyclopentanone (**4f$^n$**)*

$\delta_H$ (500 MHz, $CDCl_3$): 7.33–7.20 (5H, m, *Ph*), 6.61 (1H, t, 7.5 Hz, C*H*), 2.80 (2H, t, 7.5 Hz, PhC$H_2$), 2.58–2.55 (2H, m, C$H_2$CH), 2.52–2.47 (2H, m, CC$H_2$), 2.35–2.31 (2H, m, COC$H_2$), 1.98–1.93 (2H, m, $COCH_2CH_2$); $\delta_C$ (125.7 MHz, $CDCl_3$): 207.0, 141.1, 138.0, 134.7, 128.4, 128.4, 126.1, 39.8, 34.6, 31.6, 26.7, 19.8. MS *m/z* (rel int. %): 200 (5), 182 (2), 141 (3), 116 (20), 91 (100), 65 (18).

*2.3.15. 2-(2-phenylpropylidene)-cyclohexanone (**4g$^i$**)*

$\delta_H$ (500 MHz, $CDCl_3$): 7.33–7.20 (5H, m, *Ph*), 6.77 (1H, d, 10.0 Hz, C*H*C), 3.74–3.71 (1H, m, PhC*H*), 2.66–2.61 (4H, overlapping COC$H_2$ and CC$H_2$), 1.79–1.76 (4H, overlapping $COCH_2CH_2$, and $CCH_2CH_2$), 1.42 (3H, d, 6.9 Hz, C$H_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 201.7, 141.3, 138.0, 130.2, 129.3, 128.5, 127.8, 36.2, 34.3, 29.7, 26.3, 23.4, 21.0. MS *m/z* (rel int. %): 214 (56), 171 (33), 129 (100), 118 (60), 91 (56), 77 (32), 55 (16).

*2.3.16. 2-(3-phenylpropylidene)-cyclohexanone (**4g$^n$**)*

$\delta_H$ (500 MHz, $CDCl_3$) 7.33–7.20 (5H, m, *Ph*), 6.68 (1H, t, 7.4 Hz, C*H*), 2.79 (2H, t, 7.6 Hz, PhC$H_2$), 2.47–2.40 (6H, m, overlapping C$H_2$CH, COC$H_2$ and CC$H_2$)), 1.87–1.82 (2H, m, $COCH_2CH_2$), 1.71–1.67 (2H, m, $CCH_2CH_2$); $\delta_C$ (125.7 MHz, $CDCl_3$): 201.1, 141.2, 137.9, 136.9, 128.9, 128.4, 126.0, 40.2, 34.7, 29.8, 26.7, 23.5, 23.3.; MS *m/z* (rel int. %): 214 (6), 116 (20), 91 (100), 65 (23).

*2.3.17. 3-Methyl-6-phenyl-3-heptene-2-one (**5a**)*

MS *m/z* (rel int. %): 202 (1), 130 (3), 105 (100), 98 (26), 91 (4), 77 (13), 51 (4).

*2.3.18. 4-Methyl-7-phenyl-4-heptene-3-one (**5c**)*

$\delta_H$ (500 MHz, $CDCl_3$): 7.36–7.23 (5H, m, *Ph*), 6.57 (1H, t, 6.9 Hz, C*H*C), 2.98.2.91 (1H, m, PhC*H*), 2.64–2.60 (2H, m, $CHCH_2$), 2.57–2.53 (2H, m, $CH_3CH_2$), 1.77 (3H, s, $CCH_3$), 1.35 (3H, d, 6.9 Hz, $CHCH_3$), 1.08 (3H, t, 7.3 Hz, $CH_2CH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 202.5, 146.2, 140.2, 137.6, 128.5, 126.8, 126.3, 39.6, 37.7, 30.4, 21.7, 11.5, 8.9. MS *m/z* (rel int. %): 216 (3), 187 (2), 159 (26), 144 (11), 131 (19), 117 (100), 112 (91), 105 (66), 91 (39), 77 (10), 57 (90).

*2.3.19. 1,5-Biphenyl-2-methyl-2-hexene-1-one (**5e**)*

$\delta_H$ (500 MHz, $CDCl_3$): 7.54–7.19 (10H, m, *Ph*), 6.22 (1H, t, 7.2 Hz, C*H*C), 2.96–2.91 (1H, m, PhC*H*), 2.62–2.59 (2H, m, $CHCH_2$), 1.95 (3H, s, $CHCH_3$), 1.36 (3H, d, 6,9 Hz, $CCH_3$); $\delta_C$ (125.7 MHz, $CDCl_3$): 198.9, 146.2, 138.5, 137.0, 131.4, 129.4, 128.6, 128.4, 127.9, 126.9, 126.4, 39.7, 37.8, 22.0, 12.7. MS *m/z* (rel int. %): 254 (1), 160 (47), 105 (100), 77 (28), 51 (8).

*2.3.20. 2-(2-Phenyl-butylidene)-cyclopentanone (**5f**)*

$\delta_H$ (500 MHz, $CDCl_3$) 7.33–7.21 (5H, m, *Ph*), 6.55 (1H, t, 7.5 Hz, C*H*C), 2.94 (1H, m, PhC*H*), 2.45 (4H, overlapping COC$H_2$ and CC$H_2$), 1.89 (4H, overlapping $COCH_2CH_2$, and $CCH_2CH_2$), 1.33 (3H, d, 7.0 Hz, C$H_3$); $\delta_C$ (125.7 MHz, $CDCl_3$) 206.9, 146.2, 138.3, 134.0, 128.4, 127.0, 126.2, 39.8, 38.6, 34.3, 29.5, 21.6, 19.8.; MS *m/z* (rel int. %): 214 (2), 130 (10), 110 (32), 105 (100), 91 (5), 77 (14), 51 (10).

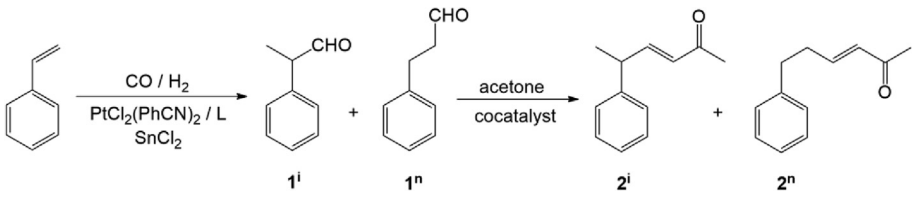
## 3. Results

To develop the catalytic system for a general synthesis of unsaturated ketones, the reaction of phenylpropanal regioisomers, obtained in the hydroformylation of styrene, and acetone to give 5-phenyl-3-hexene-2-one (**2$^i$**) or 6-phenyl-3-hexene-2-one (**2$^n$**) was chosen as model system (Scheme 1). In general, the catalytic experiments were carried out at 100 °C, under 80 bar pressure of 'syngas', with catalyst to substrate ratio of 1/100. We decided to perform the initial optimisation attempts in the presence of an effective chiral catalyst system obtained *in situ* from $PtCl_2(PhCN)_2$, (*R*)-BINAP and $SnCl_2$.

In order to improve the yield of the condensation step, several acid or base co-catalysts were tested (Table 1, entries 1–5). In the presence of benzoic acid and *t*BuOK the hydroformylation reaction was blocked. Using HCl or trichloroacetic acid (TCA) low yield of the desired ketones and lots of by-products (ethylbenzene and alcohols) were observed. The application of *para*-toluenesulfonic acid (PTSA) seemed to be satisfactory for further optimisation reactions, since the condensation step was slightly increased and the by-product formation was suppressed in the presence of PTSA (entry 5).

Decreasing the reaction temperature the yield of target products is low, while at higher temperatures the hydrogenation of the C=C double bond of the substrate and reduction of the formyl functionality to the corresponding alcohol prevailed (entry 7 and 9, respectively). The distribution of the side products clearly shows, that hydrogenation of the styrene was preferential compared to aldehyde reduction. Increased temperature and acid concentration facilitates the reduction reaction (entries 9, 19 and 11), furthermore, significantly higher alcohol formation occurred using (*S*,*S*)-BDPP as ligand (entry 10).

Next, we planned to examine the efficiency of *in situ* generated platinum catalysts incorporated with a series of chiral and achiral bidentate ligands (entries 10–17). All the tested ligands proved to be effective under acidic conditions, only dipamp and josiphos gave lower yields of aldehydes. The ratio of the formed aldehyde regioisomers (**1$^i$**/**1$^n$**) are varied in the range of 20/80 to 59/41




**Scheme 1.** Tandem hydroformylation/aldol condensation reactions with acetone.

**Table 1**
Tandem hydroformylation/aldol condensation reactions using acetone as ketone reactant.[a]

| Entry | Ligand | Cocatalyst | Temperature [°C] | Reaction time [h] | Conv.[b] [% ] | 1 (iso/n) | 2 (iso/n) | other(A/B)[c] |
|---|---|---|---|---|---|---|---|---|
| 1 | (*R*)-binap | Benzoic acid | 100 | 48 | 0 | 5 (20/80) | – | – |
| 2 | (*R*)-binap | tBuOK | 100 | 24 | 0 | – | – | – |
| 3 | (*R*)-binap | HCl | 100 | 24 | 81 | 44 (36/64) | 7 (29/71) | 30 (93/7) |
| 4 | (*R*)-binap | TCA | 100 | 24 | 90 | 65 (37/63) | 7 (37/63) | 18 (61/39) |
| 5 | (*R*)-binap | PTSA | 100 | 24 | >99 | 74 (41/59) | 21 (43/57) | 5 (80/20) |
| 6 | (*R*)-binap | 2 PTSA | 100 | 24 | 80 | 44 (43/57) | 18 (33/67) | 18 (39/61) |
| 7 | (*R*)-binap | PTSA | 60 | 48 | 60 | 56 (41/59) | 2 (n.d.) | 2 (99/1) |
| 8 | (*R*)-binap | PTSA | 120 | 2 | 36 | 19 (32/68) | 1 (15/85) | 16 (88/12) |
| 9 | (*R*)-binap | PTSA | 120 | 24 | >99 | 39 (38/62) | 11 (64/36) | 50 (80/20) |
| 10 | (*S,S*)-bdpp | PTSA | 100 | 24 | >99 | 50 (36/64) | 19 (84/16) | 31 (52/48) |
| 11 | (*R*)-diop | PTSA | 100 | 24 | 96 | 71 (38/62) | 4 (50/50) | 21 (81/19) |
| 12 | (*S,S*)-dipamp | PTSA | 100 | 24 | 28 | 9 (44/56) | 1 (n.d.) | 18 (94/6) |
| 13 | (*R,S*)-josiphos | PTSA | 100 | 24 | 48 | 35 (26/74) | 4 (25/75) | 9 (89/11) |
| 14 | (*R*)-segphos | PTSA | 100 | 24 | >99 | 52 (37/63) | 12 (49/51) | 36 (81/19) |
| 15 | (*R*)-dm-segphos | PTSA | 100 | 24 | 88 | 49 (33/67) | 10 (60/40) | 29 (86/14) |
| 16 | dppp | PTSA | 100 | 24 | >99 | 51 (49/51) | 12 (33/67) | 37 (95/5) |
| 17 | dppb | PTSA | 100 | 24 | >99 | 29 (55/45) | 21 (14/86) | 50 (90/10) |
| 18[d] | (*R*)-binap | PTSA | 100 | 24 | 97 | 68 (49/51) | 9 (44/56) | 20 (75/25) |
| 19[d] | (*R*)-binap | PTSA | 120 | 24 | >99 | 44 (59/41) | 18 (83/17) | 38 (61/39) |

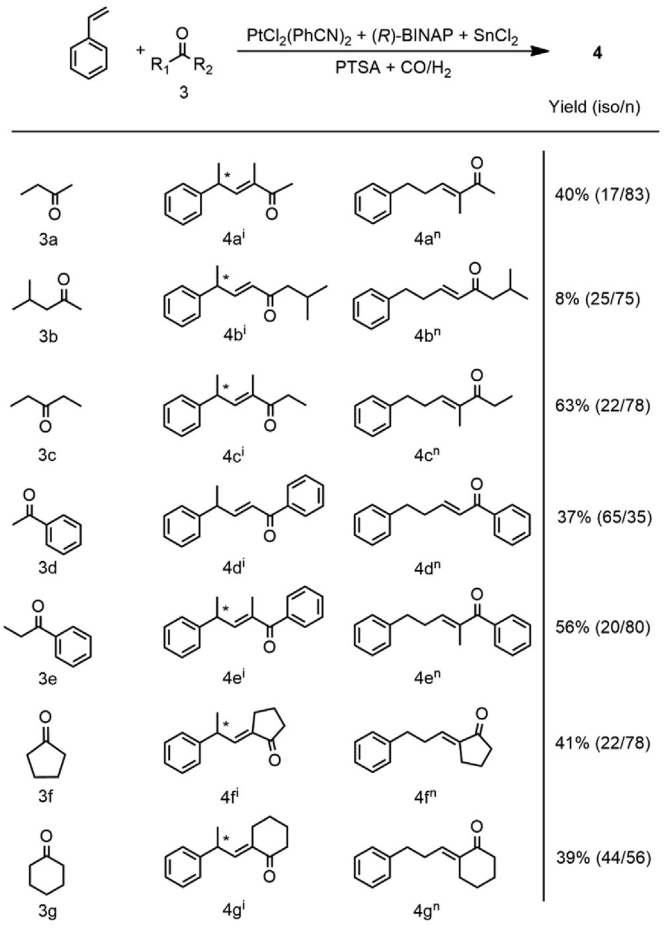
[a] Reaction conditions: 0.01 mmol of $PtCl_2(PhCN)_2$, 0.01 mmol ligand, 0.02 mmol $SnCl_2$, 1 mmol styrene, 0.1 mmol co-catalyst, $pCO = pH_2 = 40$ bar.
[b] Styrene converted (to aldehydes (**1**), to condensation products (**2**) via aldehydes and to side products).
[c] Hydrogenated by-products: ethyl benzene (A) and alcohols (B) (due to aldehyde reduction); the ratio of the by-products in brackets.
[d] Method B was used (see experimental).

depending on the catalyst. As expected from platinum-containing hydroformylation catalysts, generally the linear aldehyde was formed in excess, that is, in general, the regioselectivity toward linear products varied between 51 and 68%. The only exception is the achiral dppb and the high temperature experiment with binap using method B (entries 17 and 19 respectively). The aldol condensation step cannot be enhanced by the variation of the P-ligands. The best results can be achieved by using binap with yields of 21%. Comparing the regioselectivity toward linear aldehyde ($\mathbf{1}^n$) and the regioselectivity toward the formed unsaturated ketone ($\mathbf{2}^n$), it can be stated that the latter is generally higher. It means, that the condensation of the linear aldehydes are preferred to the branched ones. Interestingly, the opposite tendency can be observed using bdpp and segphos type ligands (entries 10, 14 and 15), where linear selectivity of the ketones decreased during the aldol condensation step. The same phenomena can be observed at elevated temperatures.

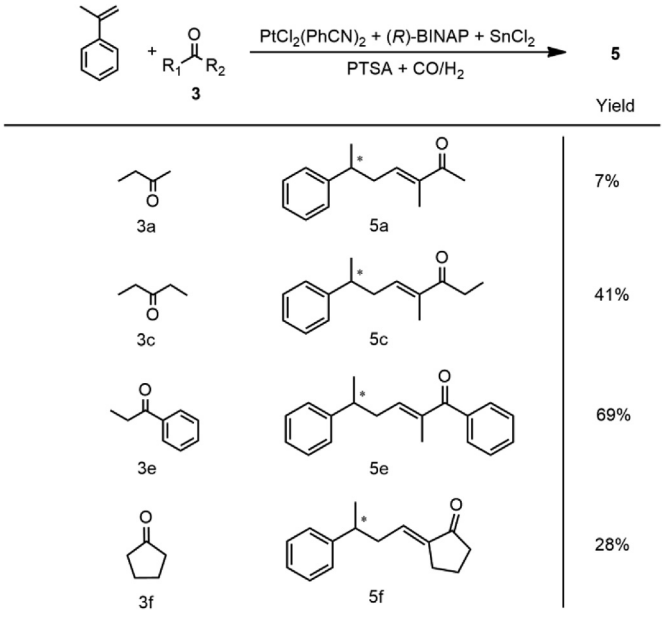
Under regular hydroformylation conditions only ethylbenzene can be found as by-product in the product mixture. Unfortunately, the presence of the acid co-catalyst facilitates the reduction of the formed aldehydes to alcohols, especially at higher temperatures, therefore lower chemoselectivities can be achieved compared to experiments performed in the absence of acids [24].

Most of the experiments were carried out in acetone, used as reactant in the aldol condensation step and solvent as well (method A). Another method was also developed, when toluene was used as solvent and lower amounts of acetone was present in the reaction mixture (method B, details in experimental section) (entries 18, 19). The comparable result provided by the latter process, allows us to extend the scope of the ketones applied in tandem hydroformylation/aldol condensation reactions.

In majority, the reactions were carried out using enantiomerically pure ligands. The enantioselectivity of the hydroformylation step conducted in the presence of acetone and PTSA was comparable to experiments performed earlier in toluene [24]. The e.e of the condensed products was not determined, but we cannot assume significant differences to the aldehyde stereoisomers. Although the optical yield of the aldehydes was moderate (varied in the range of 5–25%), the application of (*R*)-BINAP was still reasonable for further experiments in the view of conversion and the lack of side products (entry 5).




**Scheme 2.** Tandem hydroformylation/aldol condensation reactions of styrene with different ketone. (Reaction conditions: 0.01 mmol of $PtCl_2(PhCN)_2$, 0.01 mmol (*R*)-BINAP, 0.02 mmol $SnCl_2$, 1 mmol styrene, 0.1 mmol PTSA, $p(CO) = p(H_2) = 40$ bar, 100 °C, 24 h).




**Scheme 3.** Tandem hydroformylation/aldol condensation reactions of α-methylstyrene with different ketones (Reaction conditions: 0.01 mmol of $PtCl_2(PhCN)_2$, 0.01 mmol (*R*)-BINAP, 0.02 mmol $SnCl_2$, 1 mmol α-methylstyrene, 0.1 mmol PTSA, $p(CO) = p(H_2) = 40$ bar, 100 °C, 24 h).

To determine the scope, compatibility and limitations of the reaction, domino hydroformylation/aldol condensation reactions were conducted in the presence of various ketones and *in situ* system formed from $PtCl_2(PhCN)_2$, (*R*)-BINAP and $SnCl_2$ under optimised conditions (Scheme 2).

It can be stated, that various aliphatic and aromatic ketones underwent transformation to the corresponding unsaturated ketones in moderate yield and selectivity. Using 2-butanone (**3a**) we observed that the functionalization takes place on the methylene group almost exclusively. Generally, only trace amount of products due to condensation via the methyl group and similar amount of saturated ketones can be detected in the following experiments. The yield of the desired products can be increased to 63% in the presence of 3-pentanone (**3c**) with excellent chemoselectivity. Double functionalization reaction is detected neither on methyl nor on the methylene group of the applied ketones. Methyl functionalization takes place in the case of sterically hindered isobutyl-methyl-ketone (**3b**), however low amount of condensed product was achieved. Transformation of aromatic ketones like acetophenone (**3d**) and propiophenone (**3e**) is favoured compared to aliphatic analogues. Similarly, cyclic aliphatic ketones are also suitable coupling partners for the synthesis of corresponding unsaturated ketones in moderate yield (41% and 39%, respectively).

The linear aldehyde regioisomer, formed in the hydroformylation reaction proved to be more reactive in the aldol condensation step in all cases. The only exception was observed in the presence of acetophenone, where the branched ketone (**4d$^{i}$**) selectivity of 65% was achieved.

In order to eliminate one of the two regioisomers, another set of experiments was conducted in the presence of α-methylstyrene. As it was expected, only the linear ('less branched') aldehyde can be found as hydroformylation product. The formed 3-phenylbutanal proved to be also feasible partner to generate the corresponding ketones in low to moderate yields (Scheme 3).

Comparing the results with previous experiments (summarised in Table 1), it can be seen that only the methylene functionalization takes part and lower conversions can be obtained with α-methylstyrene. After all, in the presence of propiophenone the best yield can be achieved in platinum catalysed tandem hydroformylation/aldol condensation reactions (69%).

## 4. Summary

Tandem hydroformylation/aldol condensation reactions were carried out in the presence of platinum catalysts and acid co-catalysts to synthesize unsaturated ketones with moderate yield. The application of various ligands and ketones led to the target products under optimised reaction conditions. α-Methylene group of the tested ketones proved to be more reactive in aldol condensation step than their methyl group adjacent to the carbonyl functionality. Unlike previous results obtained with different catalytic systems, hydrogenation of the α,β-unsaturated ketones took place to a very low extent, *i.e.*, the saturated ketones could be detected in traces only. Therefore, a potential new methodology for the synthesis of α,β-unsaturated ketones was described.

## Acknowledgement

This work was supported by the ÚNKP-17-4-II New National Excellence Program of the Ministry of Human „Capacities". The authors thank the Hungarian Research Fund (K113177) for the financial support. This work was supported by the GINOP-2.3.2-15-2016-00049 grant. The project has been supported by the European Union, co-financed by the European Social Fund Grant no.: EFOP-3.6.1.-16-2016-00004 entitled by Comprehensive Development for Implementing Smart Specialization Strategies at the University of Pécs. The present scientific contribution is dedicated to the 650$^{th}$ anniversary of the foundation of the University of Pécs, Hungary.

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