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Domino-Hydroformylation/Aldol Condensation Catalysis: Highly Selective Synthesis of α,β-Unsaturated Aldehydes from Olefins

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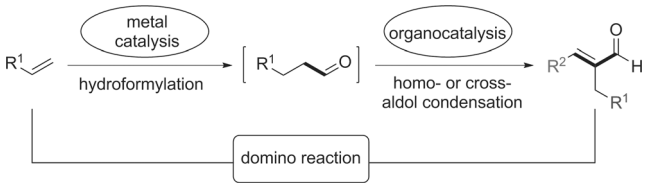
Abstract: A general and highly chemo-, regio-, and stereoselective synthesis of α,β-unsaturated aldehydes by a domino hydroformylation/aldol condensation reaction has been developed. A variety of olefins and aromatic aldehydes were efficiently converted into various substituted α,β-unsaturated aldehydes in good to excellent yields in the presence of a rhodium phosphine/acid–base catalyst system. In view of the easy availability of the substrates, the high atom-efficiency, the excellent selectivity, and the mild conditions, this method is expected to complement current methodologies for the preparation of α,β-unsaturated aldehydes.

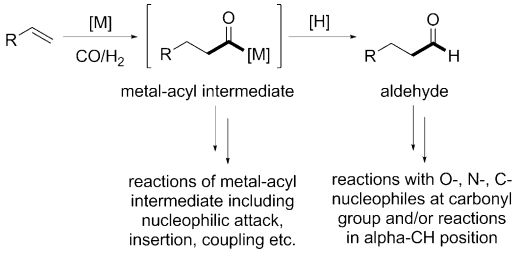
Introduction

α,β-Unsaturated aldehydes represent an important class of fine chemicals possessing a broad spectrum of applications in food, cosmetic, agrochemical, and pharmaceutical industries.[1] Additionally, they also serve as valuable intermediates in numerous organic syntheses.[2] Therefore, many practical methods, including oxidations of allylic alcohols,[3] Peterson olefinations,[4] formylations,[5] Heck reactions,[6] Aldol condensations,[7] Saegusa oxidations,[8] and hydroformylation of alkynes[9] have been developed in this regard. Nevertheless, many of these protocols suffer from drawbacks that include relatively harsh reaction conditions, the use of prefunctionalized substrates, high catalyst loading, generation of halogenated wastes, and limited selectivity (chemo-, regio-, and stereoselectivity). In this respect, the development of more efficient and atom-economic methodologies is of high importance. Obviously, the selective domino-hydroformylation/aldol condensation reaction provides an ideal and straightforward pathway to overcome the above-mentioned difficulties/limitations (Scheme 1).



Scheme 1. Efficient synthesis of α,β-unsaturated aldehydes by a domino-hydroformylation/aldol condensation reaction.

Hydroformylation of olefins to give aldehydes as predominant products, discovered by Otto Roelen in 1938, is an intriguing and extensively studied reaction.[10,11] Owing to its inherent industrial importance, the hydroformylation of aliphatic olefins has been widely explored. Nowadays, major applications of this transformation are used for the production of bulk chemicals.[12] Due to the versatile chemistry of the aldehyde group,[13] the resulting products are further converted by reduction, oxidation, or other reactions to give alcohols, amines, carboxylic acid derivatives, aldol condensation products, and many others. Following a general trend in organic chemistry,[14] hydroformylation can also be integrated in tandem or domino reaction sequences. Thus, many reactions of the metal–acyl intermediates or the final aldehydes can be achieved directly under hydroformylation conditions as collected in Scheme 2.[15] However, the additional reagents, products or variations of reaction conditions optimized for the hydroformylation step, may suppress or hinder the initial hydroformylation step which is not trivial in all cases.



Scheme 2. Selected examples of domino and tandem reactions including hydroformylation reactions.

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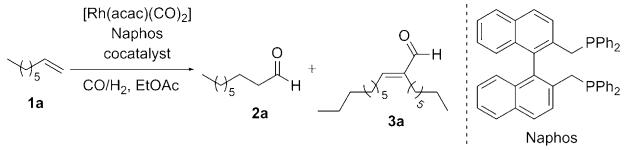
In general, aldol products are only observed as unwanted side products in olefin conversions under hydroformylation conditions. However, for a successful domino hydroformylation aldol condensation sequence efficient and aldol addition of the enolized aldehyde to another aldehyde product has to occur. Even more challenging is the selective cross-aldol reaction of two different aldehydes present under hydroformylation conditions due to the usual problems of chemo- and regioselectivity. Compared to the well-studied domino hydroformylation/reductive amination reactions (the so-called hydroaminomethylation)[16] and hydroformylation/hydrogenation reactions (the so-called hydroxymethylation),[17] the related domino-hydroformylation/aldol condensation reaction of olefins to give α,β-unsaturated aldehydes has received only scarce attention. In early studies, it has been found that hydroformylation/aldol condensation reaction sequences usually suffer from low chemoselectivity and/or low yield of the desired unsaturated aldehyde, primarily because the formation of the corresponding saturated aldehydes and alcohols can be hardly suppressed under the harsh conditions.[18] However, Eilbracht and co-workers reported intramolecular hydroformylation/aldol reactions to synthesize carbocyclic ring products for which unsaturated silyl enol ethers were utilized as substrates to avoid the problems of chemo- and regioselectivity.[19] Furthermore, the same group described a strategy of combining metal catalysis and organocatalysis to realize intermolecular hydroformylation/aldol reactions. In this case cyclic olefins or styrene were used as substrates to avoid regioselectivity problems of the hydroformylation step. Moreover, only acetone and cyclopentanone were used as C-nucleophiles in this case.[20] Interestingly, recently the first enantioselective intermolecular sequential hydroformylation/cross-aldol process has been reported by Breit et al.[21] but this process requires a large excess of olefin or aldehydes and its substrate scope is still limited. In summary, until today there exists no general methodology for intermolecular hydroformylation/aldol condensation reactions to give α,β-unsaturated aldehydes.

Herein, we present the combination of a specific rhodium(I) phosphine complex and pyrrolidinium benzoate as an efficient catalyst system for practical intermolecular domino-hydroformylation/aldol condensation reactions. Both industrially and synthetically important olefins are selectively transformed into the desired products under mild conditions.

Results and Discussion

To develop the catalytic system for a general synthesis of α,β-unsaturated aldehydes from olefins, the reaction of 1-octene **1a** to give 2-heptylundec-2-enal **3a** was chosen as a model system. Initial attempts were carried out in the presence of $[Rh(acac)(CO)_2]$ (acac = acetylacetone) and Naphos (**L6**). This ligand was previously applied by us and allows for highly regioselective rhodium-catalyzed hydroformylation reactions.[22] In general, catalytic experiments were performed at 65 °C in the presence of 0.1 mol% of $[Rh(acac)(CO)_2]$ and 0.2 mol% of **L6** under 10 bar of syngas. To control the aldol condensation step appropriately, several bases and acids were tested under the established hydroformylation conditions. When simple NaOH was used as catalyst for the aldol condensation step, nonanal **2a** was obtained smoothly from 1-octene **1a** but to our surprise no condensation product **3a** was formed (Table 1, entry 1). Unfortunately unlike previous reports,[19–21] the conversion was slightly decreased and only a trace amount of condensation product **3a** was formed using the standard catalyst for aldol reactions, L-proline (entry 2). Changing the co-catalyst to organic base, the addition of pyrrolidine resulted in good yield of nonanal **2a**, but still a very low yield of the desired enal product **3a** was observed (entry 3). Moreover, we investigated the influence of several acids in this reaction step. As an example, benzoic acid showed no activity for the aldol condensation step (entry 4). Since the formation of more reactive enamines is catalyzed by acids,[23] next we applied a combina-

Table 1. Domino hydroformylation/homoaldol condensation of 1-octene **1a**: Cocatalyst effect.[a]



Entry	Cocatalyst	Conversion [%][b]	Yield [%] **2a** (*n*/*iso*)[c]	Yield [%] **3a** (*E*/*Z*)[d]
1	NaOH	99	96 (76:24)	0
2	L-proline	87	76 (93:7)	3 (89:11)
3	pyrrolidine	97	79 (98:2)	4 (99:1)
4	benzoic acid	98	95 (95:5)	0
5	pyrrolidine and benzoic acid	100	3 (66:34)	90 (96:4)
6	piperidine and benzoic acid	98	27 (63:37)	62 (96:4)
7	morpholine and benzoic acid	98	46 (82:18)	30 (92:8)
8	thiomorpholine and benzoic acid	98	52 (82:18)	25 (91:9)
9	diethylamine and benzoic acid	98	27 (93:7)	68 (94:6)
10	*n*-butylamine and benzoic acid	89	26 (65:35)	40 (95:5)
11	pyridine and benzoic acid	99	95 (90:10)	0
12	triethylamine and benzoic acid	98	95 (92:8)	0
13	pyrrolidine and AcOH	100	14 (88:12)	81 (97:3)
14	pyrrolidine and methylsulfonic acid (MSA)	100	91 (76:24)	0
15	pyrrolidine and *p*-toluenesulfonic acid (PTSA)	100	91 (73:27)	0

[a] Reaction conditions: **1a** (1.5 mmol), $[Rh(acac)(CO)_2]$ (0.1 mol%), Naphos (0.2 mol%), cocatalyst (10 mol%), CO/H_2 (10 bar), EtOAc (2 mL), 65 °C, 24 h. [b] Conversion determined by GC analysis using isooctane as the internal standard. [c] Yield and the ratios of linear to branch isomers determined by GC analysis using isooctane as the internal standard. [d] Yield determined by GC analysis using isooctane as the internal standard; the ratios of *E* to *Z* isomers were determined by GCMS analysis.

tion of pyrrolidine and benzoic acid as a co-catalyst system. Gratifyingly, the desired enal product **3a** was obtained in high yield and with high stereoselectivity (90% yield, $E/Z = 96/4$; entry 5). As shown in Table 1, the desired condensation product **3a** was also obtained in the presence of benzoic acid and other amines (entries 6–10). However, the combination of benzoic acid with pyridine and triethylamine did not result in any condensation product (entries 11 and 12). Next, the combination of pyrrolidine with different acids was investigated. While methanesulfonic acid and *p*-toluenesulfonic acid monohydrate provided no condensation product, the use of a weaker acid (i.e. acetic acid) resulted in condensation product **3a** in 81% yield along with 14% of nonanal (entries 13–15).

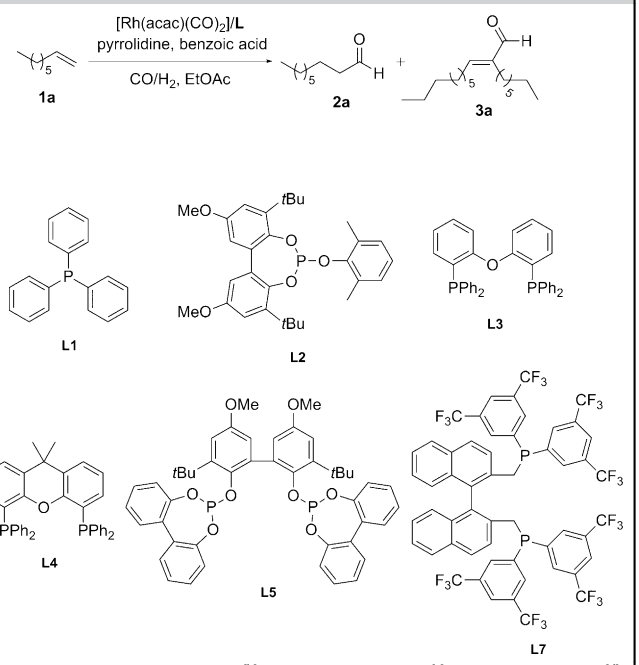
With a suitable catalyst system for the aldol condensation step in hand, we elaborated the influence of different ligands on this domino reaction under the established aldol condensation conditions. Low conversion and no corresponding aldehydes were observed in the absence of phosphine ligands (Table 2, entry 1). When standard monodentate phosphines or phosphites were used, low yields of the desired enal products were obtained, primarily because of the low *n*-regioselectivity of the hydroformylation step (entries 2 and 3). DPEphos **L3** showed low activity for the hydroformylation reaction (entry 4). Moderate yields of enal products were obtained using highly active bidentate phosphite ligands for the hydroformylation reaction (i.e. **L4** and **L5**), which might be explained due to their instability under acidic conditions (entries 5 and 6). Furthermore, the yield of **3a** slightly decreased when a Naphos derivative (Iphos) **L7** was employed (entry 7). Finally, we evaluated the influence of critical reaction parameters, such as the concentration of the organocatalyst, syngas pressure, and reaction temperature, in the presence of **L6** as ligand. As shown in Table 2, using 5 mol% of acid/base catalyst resulted in the same yield of **3a**; however, at lower loading of the co-catalysts the yield of **3a** decreased significantly (entries 8 and 9). Lowering the syngas pressure resulted in nearly full conversion of **1a**, but just a moderate yield of the desired product **3a** was obtained (entry 10). Low conversion was observed when lowering the reaction temperature (entry 11).

The progress of the hydroformylation/homoaldol condensation sequence of 1-octene **1a** was examined under the optimized reaction conditions (Figure 1). Notably throughout the course of the reaction, the initial hydroformylation product **2a** is present as a minor component (<5%). A simultaneous decrease of **1a** and increase of the condensation product, respectively, over the period of 10 h is observed. Apparently, the hydroformylation of 1-octene is the rate-determining step in this hydroformylation/homoaldol condensation reaction.

With the optimized reaction conditions established (Table 2, entry 8), we examined the generality of this process with respect to various olefins (Table 3). Both short- and long-chained terminal olefins **1a**--**g** provided the corresponding α,β-unsaturated aldehydes in good to excellent yields and with high stereoselectivity (*E/Z* ratios: >95/5; entries 1–7). When the organocatalyst loading was increased to 20 mol%, also sterically crowded olefins **1h** and **1i** were smoothly transformed into the corresponding α,β-unsaturated aldehydes in good yields and with high stereoselectivities (Table 3, entries 8 and 9). Gratifyingly, substrates containing different functional groups, such as amine, olefin, halide, and ether were well tolerated and smoothly transformed to the corresponding functionalized α,β-unsaturated aldehydes in good yields with high stereoselectivities (entries 9–12).

Next, we turned our attention to the challenging hydroformylation/cross-aldol reaction of 1-octene **1a** with benzaldehyde **4a**. In general, the difficult task in this reaction is to avoid the formation of the homoaldol product **3a**. Indeed, the developed reaction protocol provided almost equimolar amounts of **5aa** and **3a** (Table 4, entry 1), which prompted us to further control the chemoselectivity. To our delight, chang-

Table 2. Domino-hydroformylation/homoaldol condensation of 1-octene **1a**: Variation of reaction conditions.[a]



Entry	Ligand	Conversion [%][b]	Yield [%] **2a** (*n/iso*)[c]	Yield [%] **3a** (*E/Z*)[d]
1	–	12	0	0
2	**L1**	100	25 (1:99)	15 (>99:1)
3	**L2**	99	31 (1:99)	20 (>99:1)
4	**L3**	36	10 (62:38)	17 (>99:1)
5	**L4**	86	17 (50:50)	39 (94:6)
6	**L5**	99	4 (1:99)	58 (96:4)
7	**L7**	99	0	80 (96:4)
8[e]	**L6**	**98**	**3 (66:34)**	**90 (96:4)**
9[f]	**L6**	100	14 (88:12)	70 (95:5)
10[g]	**L6**	98	0	68 (96:4)
11[h]	**L6**	16	8 (50:50)	7 (>99:1)

[a] Reaction conditions: **1a** (1.5 mmol), $[Rh(acac)(CO)_2]$ (0.1 mol%), monodentate ligand (1.0 mol%), bidentate ligand (0.2 mol%), pyrrolidine (10 mol%), benzoic acid (10 mol%), CO/H_2 (10 bar), EtOAc (2 mL), 65 °C, 24 h. [b] Conversion determined by GC analysis using isooctane as the internal standard. [c] Yield and the ratios of linear to branch isomers determined by GC analysis using isooctane as the internal standard. [d] Yield determined by GC analysis using isooctane as the internal standard; the ratios of *E* to *Z* isomers were determined by GCMS analysis. [e] Pyrrolidine (5 mol%), benzoic acid (5 mol%). [f] Pyrrolidine (2.5 mol%), benzoic acid (2.5 mol%). [g] CO/H_2 (5 bar). [h] Reaction temperature: 50 °C.

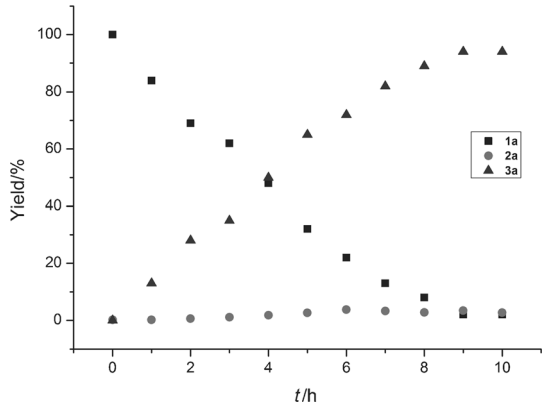


Figure 1. Compound distribution of the domino-hydroformylation/homoaldol condensation sequence. Reaction conditions: 1-octene (7.5 mmol), [Rh(acac)(CO)$_2$] (0.1 mol%), **L6** (0.2 mol%), pyrrolidine (5 mol%), and benzoic acid (5 mol%), CO/H$_2$ (10 bar), EtOAc (10 mL), 65 °C, 10 h. ■: **1a**; ●: **2a**; ▲: **3a**.

ing the solvent from EtOAc to *N*-methyl-2-pyrrolidone (NMP) led to only traces of homoaldol product **3a** and a high yield of the desired crossaldol product **5aa** was observed (entry 2).

Notably, directly using nonanal **2a** with benzaldehyde **4a** as a control experiment in the presence of the acid/base co-catalyst revealed the formation of two equivalents of the homoaldol products compared to the cross-aldol product with moderate conversion (based on nonanal) [Eq. (1)]. In essence, such a general problem of chemoselectivity can easily be resolved by our domino-hydroformylation/cross-aldol protocol, presumably attributed to the low concentration of nonanal **2a** compared to benzaldehyde **4a** during the course of the reaction. Indeed, the kinetic examination of the domino-hydroformylation/cross-aldol condensation of 1-octene **1a** with benzaldehyde **4a** under the optimal reaction conditions revealed in the first 7 h of the reaction a very small concentration of nonanal (<1%). As shown in Figure 2, parallel to the decrease of the concentration of the starting materials (1-octene **1a** and benzaldehyde **4a**) an increase of the desired condensation prod-

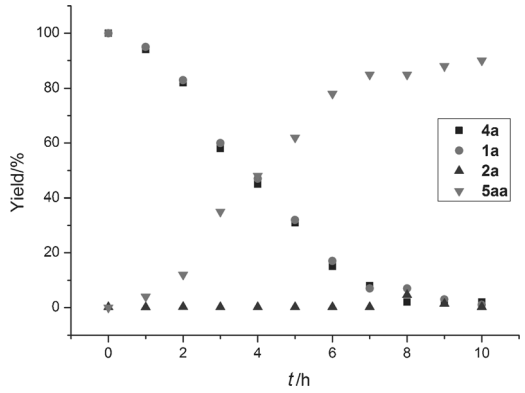
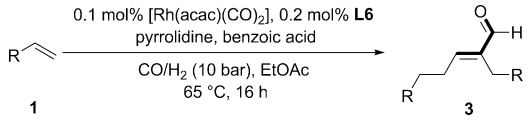
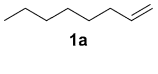
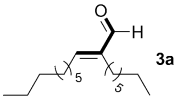
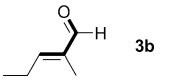
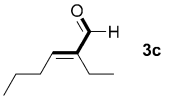
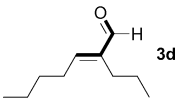
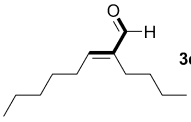
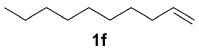
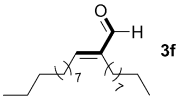
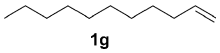
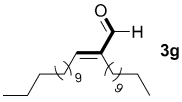
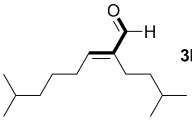
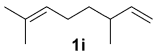
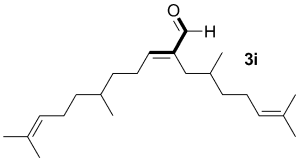
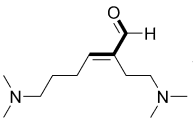
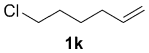
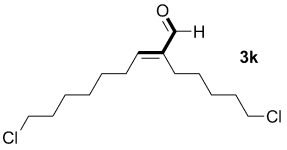
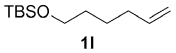
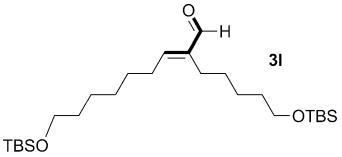


Figure 2. Compound distribution of domino-hydroformylation/cross-aldol condensation. Reaction conditions: 1-octene (7.5 mmol), benzaldehyde (7.5 mmol), [Rh(acac)(CO)$_2$] (0.1 mol%), **L6** (0.2 mol%), pyrrolidine (5 mol%), and benzoic acid (5 mol%), CO/H$_2$ (10 bar), NMP (10 mL), 65 °C, 10 h. ■: **4a**; ●: **1a**; ▲: **2a**; ▼: **5aa**.

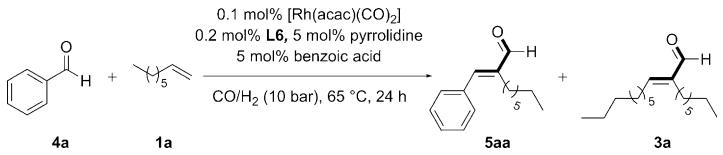
Table 3. Domino-hydroformylation/homoaldol reaction of various olefins **1**.[a]



Entry	1	3	Yield [%] (*E*/*Z*)[b]
1			89 (96:4)
2[c]			96 (>99:1)
3			69 (96:5)
4			81 (97:3)
5			85 (>99:1)
6			91 (97:3)
7			89 (97:3)
8[d]			86 (99:1)
9[d]			75 (97:3)
10[d]			78 (>99:1)
11[d]			69 (97:3)
12			92 (95:5)

[a] Reaction conditions: **1** (15 mmol), [Rh(acac)(CO)$_2$] (0.1 mol%), **L6** (0.2 mol%), pyrrolidine (5 mol%), and benzoic acid (5 mol%), CO/H$_2$ (10 bar), EtOAc (20 mL), 65 °C, 16 h. [b] Isolated yield; the ratios of *E* to *Z* isomers were determined by GCMS analysis. [c] [Rh(acac)(CO)$_2$] (0.01 mol%), **L6** (0.02 mol%), yield determined by GC analysis. [d] Pyrrolidine (20 mol%) and benzoic acid (20 mol%).

Table 4. Domino hydroformylation/cross-aldol reaction of **1a** with **4a**: Solvent effect.[a]

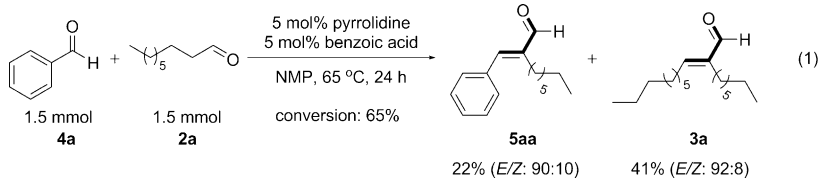


4a 1a 5aa 3a

Entry	Solvent	Conversion [%][b]	Yield [%] **5aa** (*E/Z*)[c]	Yield [%] **3a** (*E/Z*)[c]
1	EtOAc	98	42 (95:5)	36 (97:3)
2	NMP	94	90 (96:4)	trace

[a] Reaction conditions: **1a** (1.5 mmol), **4a** (1.5 mmol), [Rh(acac)(CO)$_2$] (0.1 mol%), **L6** (0.2 mol%), pyrrolidine (5 mol%), and benzoic acid (5 mol%), CO/H$_2$ (10 bar), solvent (2 mL), 65 °C, 24 h. [b] Conversion based on **1a** and determined by GC analysis. [c] Yield determined by GC analysis; the ratios of *E* to *Z* isomers were determined by GCMS analysis.

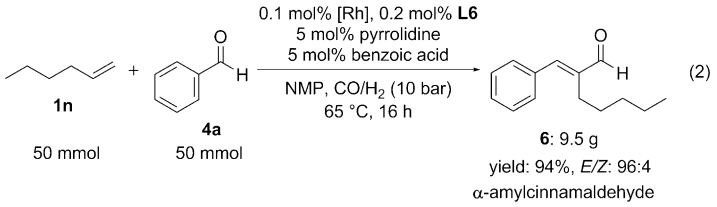
uct **5aa** is observed over the period of 10 h. In agreement with domino-hydroformylation/homoaldol condensation reaction vide supra (Figure 1), hydroformylation of 1-octene **1a** is also established as a rate-determining step in this domino-hydroformylation/cross-aldol condensation reaction.



Notably, directly using nonanal **2a** with benzaldehyde **4a** as a control experiment in the presence of the acid/base co-catalyst revealed the formation of two equivalents of the homoaldol products compared to the cross-aldol product with moderate conversion (based on nonanal) [Eq. (1)]. In essence, such a general problem of chemoselectivity can easily be resolved by our domino-hydroformylation/cross-aldol protocol, presumably attributed to the low concentration of nonanal **2a** compared to benzaldehyde **4a** during the course of the reaction. Indeed, the kinetic examination of the domino-hydroformylation/cross-aldol condensation of 1-octene **1a** with benzaldehyde **4a** under the optimal reaction conditions revealed in the first 7 h of the reaction a very small concentration of nonanal (<1%). As shown in Figure 2, parallel to the decrease of the concentration of the starting materials (1-octene **1a** and benzaldehyde **4a**) an increase of the desired condensation product **5aa** is observed over the period of 10 h. In agreement with domino hydroformylation/homoaldol condensation reaction vide supra (Figure 1), hydroformylation of 1-octene **1a** is also established as the rate-determining step in this domino-hydroformylation/cross-aldol condensation reaction.

With the optimal conditions in hand (Table 4, entry 2), we examined the generality of the domino-hydroformylation/cross-aldol condensation sequence with respect to aromatic aldehydes and olefins (Table 5). Generally, various benzaldehydes with electron-neutral, -deficient, and -rich substituents underwent efficient transformation to afford the corresponding α,β-unsaturated aldehydes in good to excellent yields with high *E* stereoselectivities (**5aa**–**ai**; Table 5). Meanwhile, aldehydes containing different functional groups such as halide, nitrile, and nitro, were well tolerated, too (**5ab**–**ad** and **5ag**–**ah**). Moreover, heterocyclic aldehydes proved also to be efficient coupling partners to generate the corresponding products in good yields (**5aj**–**al**). From a synthetic point of view, the synthesis of functionalized α,β-unsaturated aldehydes from functionalized olefins and aromatic aldehydes is important, which is reflected in products **5ka** and **5ia**, which are obtained in good yield when using our protocol. A point to note is that all the yields of the corresponding homoaldol byproducts are less than 5% according to GC analysis.

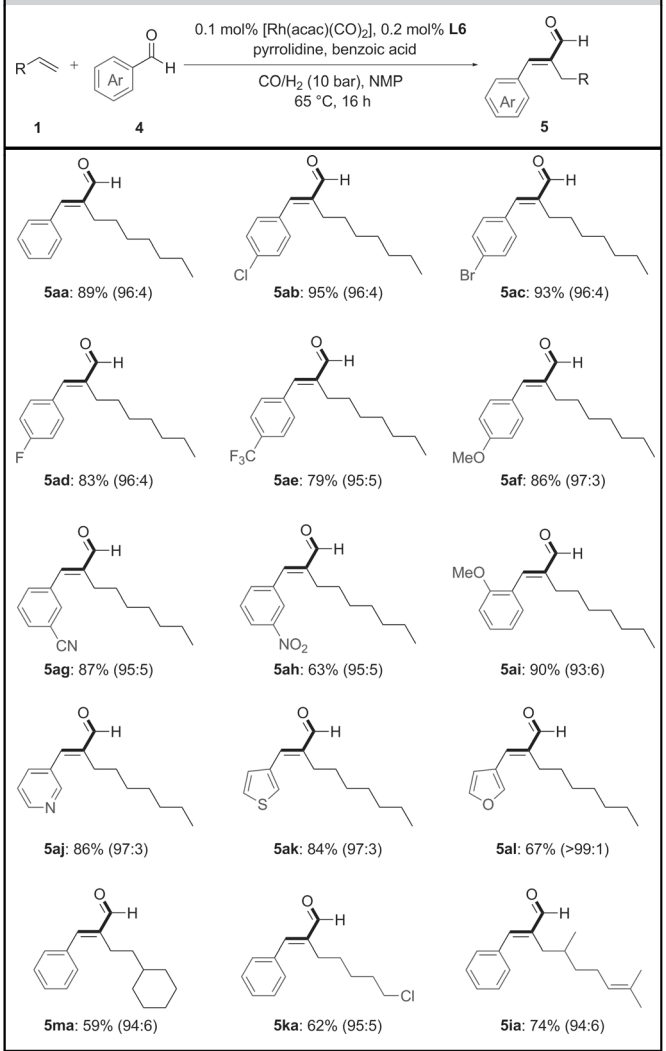
Finally, we were interested in demonstrating the usefulness of our procedure for the synthesis of industrially relevant fine chemicals. Hence, the synthesis of **6** was performed, which is a very popular fragrance substance for creating jasmine notes in the fragrance industry.[24] The product is stable to alkali and long-lasting and large quantities are used, particularly in soap perfumes. To our delight, our domino sequence is conveniently scaled up to a 50 mmol scale resulting in a 94% yield of the desired α-amylcinnamaldehyde [Eq. (2)].



Conclusion

Here, we present an efficient and highly selective intermolecular domino-hydroformylation/aldol reaction sequence that allows for the synthesis of α,β-unsaturated aldehydes. Various olefins and aromatic aldehydes underwent efficient transformation in the presence of a cooperative rhodium/phosphine and organocatalyst system to afford the corresponding α,β-unsaturated aldehydes in good to excellent yields with high *E* stereoselectivities. For the first time also excellent chemoselectivity is achieved in intermolecular hydroformylation/cross-aldol condensation reactions and the corresponding α,β-unsaturated aldehydes were obtained effectively by suppressing the unwanted homoaldol condensation side reactions. Key to success is

Table 5. Domino-hydroformylation/cross-aldol reaction of **1** with **4**.



[a] Reaction conditions: **1** (1.5 mmol), **4** (1.5 mol), $[Rh(acac)(CO)_2]$ (0.1 mol%), **L6** (0.2 mol%), pyrrolidine (5 mol%), benzoic acid (5 mol%), CO/H_2 (10 bar), NMP (2 mL), 65 °C, 16 h; yield of isolated product; the ratios of *E* to *Z* isomers were determined by GCMS analysis; cases of **5 ad–ia** by using pyrrolidine (15 mol%) and benzoic acid (15 mol%).

the inherently low concentration of the aldehyde formed in the hydroformylation step.[25]

Our synthetic protocol is straightforward, atom-efficient, and does not need stoichiometric amounts of additives or base. Because of the importance of α,β-unsaturated aldehydes in bulk and fine chemical industries, we believe this practical synthetic strategy has the potential to be used frequently.

Experimental Section

General procedure for the preparation of 3

A 100 mL steel autoclave was charged under an argon atmosphere with $[Rh(acac)(CO)_2]$ (3.87 mg, 0.1 mol%), Naphos **L6** (19.52 mg, 0.2 mol%), and benzoic acid (91.5 mg, 5 mol%). Then, EtOAc (20 mL), pyrrolidine (62.5 μL, 5 mol%), and olefin **1** (15 mmol) were added under an argon atmosphere. The autoclave was pressurized with 10 bar CO/H_2 (1:1) and heated to 65 °C for 16 h. After the reaction time, the autoclave was cooled with ice water and the pressure was released. The stereoselectivity was measured by GC analysis of the crude reaction mixture. After removing the solvent by vacuum, the residue was directly purified by flash chromatography on silica gel (eluent: heptane/ethyl acetate = 30:1) to give the desired product **3** (**3 j** was purified by bulb-to-bulb distillation).

General procedure for the preparation of 5

A 25 mL Schlenk flask was charged with $[Rh(acac)(CO)_2]$ (3.1 mg, 0.1 mol%), Naphos **L6** (15.62 mg, 0.2 mol%), pyrrolidine (50 μL, 5 mol%), benzoic acid (73.2 mg, 5 mol%), and NMP (16 mL). A 4 mL glass vial was charged with **4** (1.5 mmol) and a stirring bar was added. Then, this clear light yellow solution (2 mL) and **1** (1.5 mmol) were injected by syringe. The vial was placed in an alloy plate, which was transferred into an autoclave (300 mL) of the 4560 series from Parr Instruments under argon atmosphere. After flushing the autoclave three times with nitrogen, the pressure of CO/H_2 (1:1) was increased to 10 bar. The reaction was performed for 16 h at 65 °C. After the reaction finished, the autoclave was cooled to room temperature and the pressure was carefully released. The stereoselectivity was measured by GC analysis of the crude reaction mixture. The reaction mixture quenched by water and extracted with ethyl acetate (3×15 mL). The combined organic layer was washed with brine (1×45 mL) and dried over anhydrous $MgSO_4$. After the evaporation, the residue was purified by flash chromatography on silica gel (eluent: heptane/ethyl acetate = 30:1) to give the desired product **5**.

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Keywords: catalysis · domino reactions · hydroformylation · olefins · unsaturated aldehydes

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