

Combined Transition-Metal- and Organocatalysis: An Atom Economic C3 Homologation of Alkenes to Carbonyl and Carboxylic Compounds

Susanne T. Kemme, Tomáš Šmejkal, and Bernhard Breit^{*[a]}

Abstract: A combination of regioselective room-temperature/ambient-pressure hydroformylation (transition-metal catalysis) and decarboxylative Knoevenagel reactions (organocatalysis) allowed for the development of an efficient, one-pot C3 homologation of terminal alkenes to (*E*)- α,β -unsaturated acids and esters, (*E*)- β,γ -unsaturated acids, (*E*)- α -cyano acrylic acids, and

α,β -unsaturated nitriles. All reactions proceed under mild conditions, tolerate a variety of functional groups, and furnish unsaturated carbonyl compounds

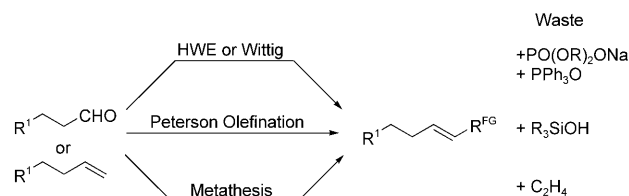
Keywords: atom economy • hydroformylation • Knoevenagel condensation • organocatalysis • supramolecular catalysis

in good yields and with excellent regio- and stereocontrol. Further, an iterative C2 homologation of (*E*)- α,β -unsaturated carboxylic acids is possible through a combination of decarboxylative hydroformylation employing a supramolecular catalyst followed by decarboxylative Knoevenagel condensation with an organocatalyst.

Introduction

An ideal target-oriented synthesis should consist of skeleton-constructing reactions while avoiding unnecessary functional-group interconversions and protection and deprotection steps.^[1] If a synthetic target contains functional groups, those should be directly introduced in the course of the skeleton-expanding operation without the need for further manipulation.^[2] This requires carbon–carbon bond-forming reactions that proceed under mild conditions and tolerate the typical reactive functional groups of natural target structures, such as alcohols, amines, carboxylic acids, etc. Furthermore, if such reactions would satisfy the criteria of atom economy, a highly efficient synthetic methodology should be the result.^[3] In this context we became interested in the functional subunit of unsaturated carboxylic acid derivatives. These moieties represent an interesting and important class of functionalities. Typical synthetic procedures to access these product classes employ Wittig-type olefinations,^[4] cross-alkene metathesis,^[5] and the Peterson olefination

(Scheme 1).^[6] Unfortunately these reactions suffer either from a bad atom economy, the necessity for special reagents, or additional steps. Accordingly, a clean byproduct-free and



Scheme 1. Common homologation methodologies for the preparation of unsaturated compounds.

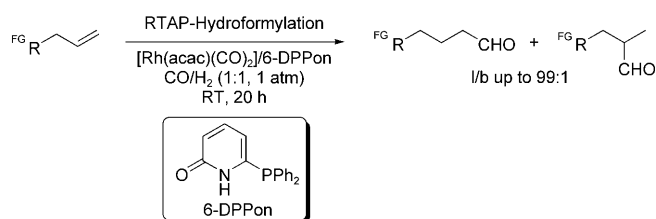
selective methodology for the synthesis of α,β -unsaturated carboxylic acid derivatives from aldehydes would be highly desirable. However, due to their intrinsic reactivity, aldehydes are usually not particularly stable and isolation can be troublesome. We reasoned that a solution to this problem could be a process combining aldehyde generation in situ with a subsequent decarboxylative Knoevenagel reaction as a nearly atom-economic olefination process with water and carbon dioxide being the only byproducts.^[7]

In this context, we recently reported on the development of a supramolecular self-assembly catalyst that allows for regioselective hydroformylation of terminal alkenes under mild reaction conditions. Employing the self-assembling 6-

[a] S. T. Kemme, T. Šmejkal, Prof. B. Breit
Institut für Organische Chemie und Biochemie
Freiburg Institute for Advanced Studies (FRIAS)
Albert-Ludwigs-Universität Freiburg, Albertstrasse 21
79104 Freiburg (Germany)
Fax: (+49) 761-203-8715
E-mail: bernhard.breit@chemie.uni-freiburg.de

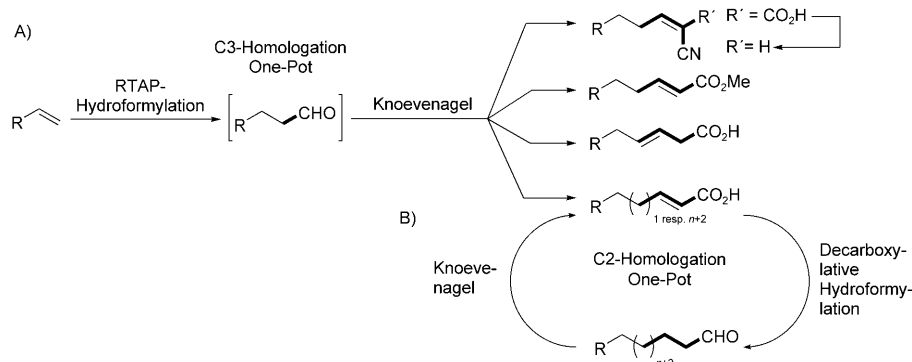
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200903223>.

diphenyl-phosphanylpyridone (6-DPPon)/Rh^I catalyst the reaction can be performed even at room temperature under ambient pressure, thus avoiding the use of special pressure-vessel equipment (Scheme 2).^[8]



Scheme 2. RTAP hydroformylation–atom-economic C1 homologation.

Herein, we report in full detail on the development of a combined regioselective room-temperature/ambient-pressure hydroformylation (RTAP, transition-metal catalysis) employing our self-assembly 6-DPPon/Rh^I-catalyst and a decarboxylative Knoevenagel condensation (organocatalysis) in a one-pot procedure (Scheme 3).^[9] Thus, by starting from



Scheme 3. Combined transition-metal- and organocatalysis—a new approach to carbonyl and carboxylic compounds.

simple terminal alkenes this process allows for a formal hydroalkenylation of an alkene leading to a C3 homologation to furnish a wide range of unsaturated carbonyls, such as α,β -unsaturated carboxylic acids, esters, nitriles, and β,γ -unsaturated carboxylic acids. Both catalytic processes tolerate a variety of functional groups, proceed under mild conditions, give the unsaturated products in good yields and with excellent regio- and stereocontrol, and produce carbon dioxide and water as the only stoichiometric byproducts (Scheme 3A).

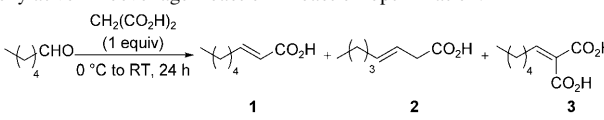
Additionally, inspired by the biosynthesis of fatty acids a new two-carbon homologation procedure of aldehydes and α,β -unsaturated carboxylic acids has been developed by a combination of supramolecular transition-metal catalysis and decarboxylative Knoevenagel condensation (Scheme 3B).

Results and Discussion

Synthesis of α,β -unsaturated carboxylic acids: α,β -Unsaturated carboxylic acids represent a structural motif found in many natural products, such as pheromones.^[10] In spite of their widespread occurrence in synthetic targets, to the best of our knowledge there is no direct catalytic method for the construction of the α,β -unsaturated carboxylic acid motif meeting the criteria of atom economy. Common synthetic methodology relies on a two-step procedure resulting from the construction of a corresponding ester that is subsequently saponified to liberate the carboxylic acid.^[11] The standard method for the synthesis of the α,β -unsaturated carboxylic ester is a two-carbon chain elongation of an aldehyde by the Wittig or related Horner–Wadsworth–Emmons olefination.^[4c–f] An interesting alternative is the cross-metathesis between terminal alkenes and acrylic esters with ethylene as the sole byproduct.^[5b–e] However, the reaction is incompatible with a free carboxylic acid, and hence an additional ester hydrolysis step has to be employed. A significantly improved atom economy shows the decarboxylative Knoevenagel condensation because only water and carbon dioxide

are formed as byproducts. However, the application of the decarboxylative Knoevenagel condensation (Knoevenagel–Doebner) for the synthesis of α,β -unsaturated carboxylic acids is described as limited. Yields for enolizable aliphatic aldehydes are low, the *E/Z*-selectivity varies, and, most importantly, not α,β -, but rather β,γ -unsaturated acids are obtained.^[11,22,40] Hence, our first goal was to identify a useful protocol for the decarboxylative Knoevenagel reaction to obtain α,β -unsaturated carboxylic acids from enolizable aldehydes.

For this reason the influence of various reaction conditions on the reaction of capronaldehyde and malonic acid was studied (Table 1). Thus, preliminary experiments revealed that a combination of pyridine and a secondary amine catalyst gave the most promising results. When employing catalytic amounts of pyridine (0.1 equiv) and pyrrolidine (1 mol %) the chemoselectivity was high ($\alpha,\beta/\beta,\gamma$ 96:4), but decarboxylation of the unsaturated carboxylic diacid **3** (11 %) was incomplete (Table 1, entry 1). Originally, DMF was used as the solvent, which made the isolation of the reaction products troublesome. Interestingly, when pyridine (2 equiv) was used as the solvent and reagent in the presence of catalytic amounts of pyrrolidine (1 mol %), (*E*)-oct-2-enoic acid was obtained in an excellent yield (93 %) and with high chemo- and stereoselectivity ($\alpha,\beta/\beta,\gamma$ > 98:2, *E/Z* > 99:1) (Table 1, entry 2). Other secondary amines were also effective as catalysts (Table 1, entries 3–5). Interestingly,

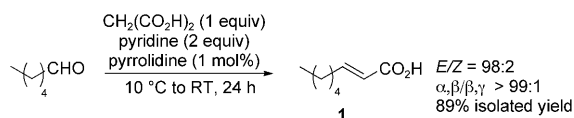
Table 1. Synthesis of α,β -unsaturated carboxylic acids by using a decarboxylative Knoevenagel reaction—reaction optimization.


Entry	Base 1 (equiv)	Base 2 (mol %)	NMR yield [%] ^[a]	Ratio 1/2
1 ^[b]	pyridine (0.1)	pyrrolidine (1)	1 (85), 2 (4), 3 (11)	96:4
2	pyridine (2)	pyrrolidine (1)	1 (93), 2 (1.6)	>98:2
3	pyridine (2)	piperidine (1)	1 (91), 2 (1.2)	>99:1
4	pyridine (2)	L-proline (1)	1 (88), 2 (1.8)	98:2
5	pyridine (2)	Et ₃ NH (1)	1 (74), 2 (4.5)	94:6
6	pyridine (2)	–	1 (50)	>99:1
7	–	pyrrolidine (1)	3 (98)	–
8 ^[c]	DMAP (2)	pyrrolidine (1)	1 (22), 2 (11), 3 (66)	67:33

[a] ¹H NMR spectra detected, trimethoxybenzene as standard. [b] DMF (6 M solution of the aldehydes) was added. [c] THF (1 M solution of the aldehyde) was added. Formation of a precipitate was observed.

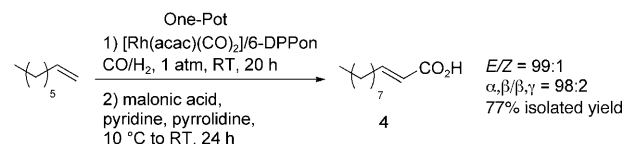
with pyridine alone product **1** was formed with high selectivity, but in low yield (50 %, Table 1, entry 6). By using pyrrolidine alone, we observed full conversion of the aldehyde, but diacid **3** was the only product (Table 1, entry 7). Hence, there is cooperativity between these two base catalysts (vide infra). Dimethylaminopyridine, which has been described as an excellent catalyst for the synthesis of α,β -unsaturated esters, was not effective for this reaction (Table 1, entry 8).^[11]

With optimized conditions in hand, α,β -unsaturated carboxylic acid **1** was prepared on a preparative scale (50 mmol) and isolated in excellent yield and selectivity (Scheme 4). In the next step, we explored whether this de-

Scheme 4. Knoevenagel reaction for the preparation of α,β -unsaturated acids.

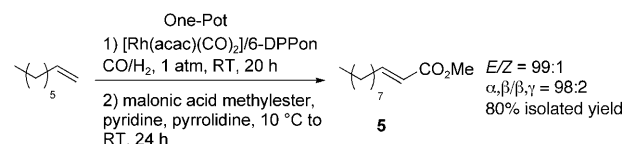
carboxylative Knoevenagel reaction could be coupled with an atom-economic in situ generation of the required aldehyde. For this purpose we chose our recently developed regioselective room-temperature/ambient-pressure (RTAP) hydroformylation by employing the self-assembling 6-DPPon/Rh^I catalyst. Such a one-pot regioselective hydroformylation/decarboxylative Knoevenagel reaction would install a C3 extension of a terminal alkene, and would thus correspond to a formal and hitherto unknown cross-hydroalkenylation of a terminal alkene with acrylic acid.^[12] Initial experiments showed that the reaction conditions of the decarboxylative Knoevenagel are incompatible with the conditions of RTAP-hydroformylation protocol, which precluded a Tandem process. However, a very efficient and practical one-pot process was developed. Thus, first hydroformylation was performed with [Rh(acac)(CO)₂]/6-DPPon (acac = acetylacetonate) as the catalyst precursor in a flat-bottomed

Schlenk tube under ambient pressure of the synthesis gas at room temperature. The reaction occurs with high regioselectivity (99:1) in favor of the linear aldehyde. After 20 h, the synthesis gas was replaced with argon and the base catalyst and malonic acid were added. After an additional 20 h at 10 °C and 4 h at room temperature, the reaction was complete and the α,β -unsaturated carboxylic acid **4** was isolated by chromatography on silica in good overall yield (77 %) (Scheme 5). The procedure turned out to be very reliable

Scheme 5. An example of a one-pot RTAP hydroformylation/Knoevenagel reaction to α,β -unsaturated carboxylic acid **4**.

and general for terminal alkenes. Many functional groups including free-alcohol functionalities, acetals and carbamates were tolerated (for the substrate scope see Table 5).

Synthesis of α,β -unsaturated carboxylic esters: To explore whether such a one-pot process consisting of RTAP-hydroformylation and a decarboxylative Knoevenagel reaction can be employed for the synthesis of other classes of unsaturated carbonyl derivatives, we looked at the preparation of α,β -unsaturated carboxylic esters^[13] by starting from malonic acid half esters. Their decarboxylative Knoevenagel reaction with aldehydes was reported in 2005 by List et al. The reaction has been performed in DMF at room temperature over 5 to 48 h by using 4-dimethylaminopyridine (DMAP) (10–20 mol %) and piperidine (10 mol %) as organocatalysts.^[11,14] The drawback is indeed the formation of the aldehyde starting material in a separate step. Conversely, a wide range of functionalized alkenes are commercially available and allow for a rapid formylation by employing our RTAP-hydroformylation protocol. Thus, transferring the conditions of the one-pot process developed for malonic acid to the corresponding methyl half ester furnished the desired α,β -unsaturated ester **5** in 80 % yield with high chemo- and stereoselectivity (l/b 99:1, $\alpha,\beta/\beta,\gamma$ > 98:2, *E/Z* > 99:1, Scheme 6). Again,

Scheme 6. An example of a one-pot RTAP hydroformylation/Knoevenagel reaction to α,β -unsaturated carboxylic ester **5**.

many functional groups including free-alcohol functionalities as well as acetals and carbamates were tolerated (for substrate scope see Table 5).

Synthesis of β,γ -unsaturated carboxylic acids: Simple linear β,γ -unsaturated carboxylic moieties are found in natural products, identified among volatile constituents, isolated from various fruits and food, and have also been reported as pheromones and as important synthetic intermediates.^[15] Those can be easily transformed into lactones,^[16] homoallylic alcohols,^[17] and unsaturated macrolides.^[18] Therefore, the preparation of β,γ -unsaturated carboxylic acids is attractive and interesting in organic synthesis. A variety of methods, such as the cross-alkene metathesis, have been reported for preparing β,γ -unsaturated carboxylic acids, which give the desired products in good yield but with moderate stereoselectivity. In many cases, specific reagents and catalysts had to be used or the reaction suffered from severe reaction conditions and a limited substrate tolerance.^[5b,f,19] None of these methods is as simple and atom economic as the decarboxylative Knoevenagel reaction. In 1998 Ragoussis et al. reported a synthesis of β,γ -unsaturated carboxylic acids in good yields and with good selectivity by employing the decarboxylative Knoevenagel reaction. The reaction proceeded in DMF (or DMSO) at 100 °C with piperidinium acetate (1–4 mol %) as the sole catalyst.^[20] However, under these conditions, the substrate scope is limited. To overcome these limitations we were interested to identify milder reaction conditions, which would allow us to run the deconjugative and decarboxylative Knoevenagel reaction at lower temperatures. When we used our optimized standard conditions and exchanged pyridine by the less nucleophilic base 2,6-lutidine, the reaction of capronaldehyde with malonic acid furnished a 57:43 mixture of α,β - versus β,γ -unsaturated carboxylic acid **2** (Table 2, entry 2). Increasing the reaction temperature to 40 °C led to an increased amount of the deconjugative product ($\alpha,\beta/\beta,\gamma$ 8:92, entry 4). When using 2,6-di-*tert*-butylpyridine no improvement was observed ($\alpha,\beta/\beta,\gamma$ 31:69, entry 6). Interestingly, employing the stronger base tetramethylguanidine (TMG) gave excellent chemoselectivity towards the deconjugated product, albeit the conversion was low ($\alpha,\beta/\beta,\gamma$ 1:99, entry 7). Changing towards 1,8-

diazabicyclo[5.4.0]undec-7-ene (DBU) gave both excellent chemoselectivity and conversion ($\alpha,\beta/\beta,\gamma$ 1:99, entry 8).

Interestingly, under these reaction conditions, the presence of pyrrolidine is no longer essential (Table 2, entry 9), which suggests that these reactions proceed by a different reaction mechanism (vide infra). Optimized reaction conditions require two equivalents of DBU and a reaction temperature of 40 °C (compare entries 9–11). With these conditions in hand we again combined them with RTAP-hydroformylation in a one-pot operation, and thus prepared a wide variety of functionalized β,γ -unsaturated acids in good yields and with high selectivities (see Scheme 7 and Table 5).



Scheme 7. An example of a one-pot RTAP hydroformylation/Knoevenagel reaction to β,γ -unsaturated carboxylic acid **6**.

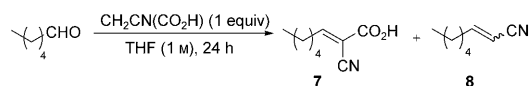
Synthesis of (*E*)- α -cyano acrylic acids: Our next objective was the use of nitrile acetic acid as a methylene-active reagent to prepare α -cyano acrylic acids, which are interesting intermediates for the synthesis of β^2 -amino acids^[21] (which are important building blocks in medicinal chemistry),^[22] and find applications as organocatalysts.^[23] The most frequently used access towards α -cyano acrylic acids is provided by the Knoevenagel condensation, which employs an excess of pyridine or piperidine with heating.^[24] Reports on reaction conditions employing catalytic amounts of a base are rare.^[25] To the best of our knowledge, there is no report on a Knoevenagel condensation of nitrile acetic acid, which occurs without heating in the presence of a catalytic amount of an amine base. Thus, subsection of nitrile acetic acid and capronaldehyde to our optimized conditions for the decar-

Table 2. Variation of the bases to furnish β,γ -unsaturated carboxylic acids by starting from capronaldehyde by using a decarboxylative Knoevenagel reaction.

Entry	Base 1 (equiv)	Base 2 (mol %)	<i>T</i> [°C]	NMR yield [%] ^[a]	Ratio 1/2
1 ^[b]	pyridine (2)	pyrrolidine (1)	10	1 (93), 2 (1.6)	98:2
2 ^[b]	2,6-lutidine (2)	pyrrolidine (1)	10	1 (4), 2 (3)	57:43
3 ^[c]	2,6-lutidine (2)	pyrrolidine (1)	RT	1 (12), 2 (88)	12:88
4	2,6-lutidine (2)	pyrrolidine (1)	40	1 (5), 2 (90)	8:92
5	2,6-lutidine (1)	pyrrolidine (1)	40	1 (18), 2 (82)	18:82
6	2,6-di- <i>t</i> -Bu-pyridine (2)	pyrrolidine (1)	40	1 (22), 2 (50)	31:69
7	TMG (2)	–	40	1 (0), 2 (57)	1:99
8	DBU (2)	pyrrolidine (1)	40	1 (0), 2 (93)	1:99
9	DBU (2)	–	40	1 (0), 2 (94)	1:99
10	DBU (2)	–	RT	1 (0), 2 (0)	–
11	DBU (1)	–	40	1 (0), 2 (30)	1:99

[a] ¹H NMR spectra detected, trimethoxybenzene as standard. [b] 0 °C/10 min, 10 °C/20 h, RT/4 h, direct hydroformylation/Knoevenagel one-pot reaction with 1-octene. [c] 4 d reaction time.

boxylative Knoevenagel condensation furnished the α -cyano acrylic acid **7** with excellent *E/Z* selectivity (from >99:1) and a good yield. Hence, under these conditions a decarboxylation did not occur. Thus, the presence of pyridine, which is essential for the decarboxylation process, should be unnecessary to provide the Knoevenagel condensation product **7**. Indeed running the same reaction in the absence of pyridine led to Knoevenagel condensation product **7** in a similar yield (Table 3, entries 1 and 2). On the other hand, when employing pyridine alone,

Table 3. Synthesis of α,β -unsaturated nitrile acetic acids by starting from capronaldehyde—reaction optimization.

Entry	Base 1 (equiv)	Base 2 (mol %)	<i>T</i> [°C]	NMR yield ^[a] 7 [%]	Ratio 7/8
1	pyridine (2)	pyrrolidine (1)	RT	98	> 99:1
2	—	pyrrolidine (1)	RT	97	> 99:1
3	pyridine (2)	—	RT	no reaction	—

[a] ¹H NMR spectra detected, trimethoxybenzene as standard.

the Knoevenagel condensation did not occur at all (Table 3, entry 3).

By using these optimized Knoevenagel condensation conditions, a one-pot procedure with our RTAP-hydroformylation by starting with 1-octene furnished the corresponding α -cyano acrylic acid derivative **9** with the best selectivity and in good yield ($\alpha,\beta/\beta,\gamma$ 1:99, *E/Z* 99:1, 75 %, Scheme 8).

Scheme 8. One-pot RTAP hydroformylation/Knoevenagel reaction towards the α -cyano acrylic acid derivative **9**.

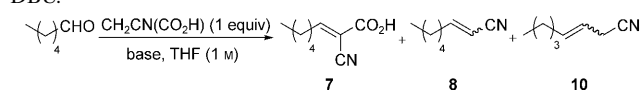
Alkene geometry was confirmed by NOESY experiments (see the Supporting Information). Also here, the reaction conditions could be applied to a wide range of functionalized alkenic substrates (see Scheme 8 and Table 5).

Development of a hydroformylation/decarboxylative Knoevenagel one-pot protocol for the synthesis of α,β -unsaturated nitriles: α,β -Unsaturated nitriles are found as a structural motif in pheromones,^[26] but they also represent versatile bi-functional building blocks for organic synthesis. Standard methods for the preparation of α,β -unsaturated nitriles are Wittig and analogous olefination protocols, the Peterson olefination and related elimination reactions, and the cross-metathesis reaction.^[5b,27–31] Again, these reactions often suffer from limited substrate tolerance or require special reagents. With the α -cyano acrylic acids in hand we had a closer look at whether a decarboxylative Knoevenagel condensation could be an alternative. Interestingly, to the best of our knowledge, a general decarboxylative Knoevenagel condensation of α -cyano acrylic acids resulting from the Knoevenagel condensation with aliphatic aldehydes is unknown. For the corresponding α -cyano cinnamic acids, resulting from the Knoevenagel condensation with aromatic aldehydes, the decarboxylation has been described to require heating to more than 150 °C.^[32] Surprisingly, we found that by starting from capronaldehyde and nitrile acetic acid a smooth decarboxylative Knoevenagel condensation occurred at room temperature in the presence of 1.5 equivalents

of DBU. The corresponding unsaturated nitriles **8** and **10** were obtained as a 92:8 mixture, both as a mixture of *cis*- and *trans*-alkene isomers, respectively (Table 4, entry 3).

The amount of DBU employed in the course of the reaction had an important influence on the ratio of unsaturated

Table 4. Results of decarboxylative Knoevenagel condensation of capronaldehyde with nitrile acetic acid in the presence of varying amounts of DBU.



Entry	Base (equiv)	<i>T</i> [°C]	<i>t</i> [h]	NMR yield [%]	Ratio 8/10 ^[a]
1	DBU (3.0)	RT	24	7 (–), 8 (78), 10 (10)	89:11
2	DBU (1.5)	RT	24	7 (–), 8 (81), 10 (16)	83:17
3	DBU (1.5)	40	24	7 (–), 8 (77), 10 (7)	92:8
4	DBU (1.0)	40	24	7 (–), 8 (34), 10 (44)	44:56
5	DBU (0.5)	RT	24	7 (–), 8 (78), 10 (22)	78:22
6	DBU (0.5)	40	24	7 (–), 8 (7), 10 (69)	9:91
7	DBU (0.1)	RT	24	7 (50), 8 (0), 10 (0)	–

[a] Both **8** and **10** are a mixture of *cis* and *trans* isomers in a ratio of ca. 1:1, as determined by ¹H NMR spectroscopy.

nitriles **8** and **10**. While 1.5 equivalents of DBU seemed to be the optimum amount to favor the α,β -unsaturated product **8**, decreasing the amount of DBU to 0.5 equivalents allowed the selective preparation of the β,γ -unsaturated nitrile **10** (Table 4, entry 6). Other bases, such as 2,6-lutidine (no reaction) and 1,4-diazobicyclo[2.2.2]octane (mixture of unknown products) were not efficient.

With these conditions in hand, we again combined them with the RTAP-hydroformylation reaction in a one-pot operation, and thus could prepare a wide variety of functionalized α,β -unsaturated nitriles in good yields (see Table 5).

Two-carbon homologation of aldehydes and α,β -unsaturated carboxylic acids: The two-carbon homologation of the alkyl chain of aldehydes or carboxylic acids (Scheme 9) is a synthetic problem commonly encountered in the literature. Typically Wittig or related Horner–Wadsworth–Emmons reactions and subsequent functional-group interconversions are used.^[33] These methods usually suffer from bad atom economy and relatively low functional-group tolerance.

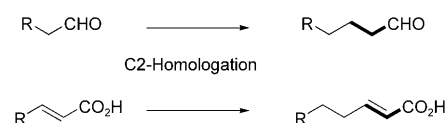
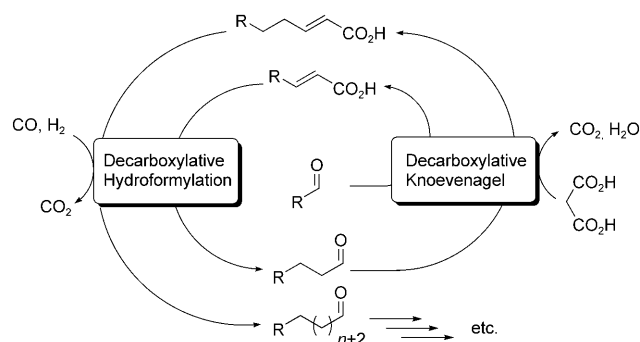
Scheme 9. Two-carbon homologation of aldehydes and α,β -unsaturated carboxylic acids, R = alkyl or aryl.

Table 5. RTAP hydroformylation/decarboxylative Knoevenagel one-pot reaction of functionalized terminal alkenes with the Rh/6-DPPon system and an organocatalyst.

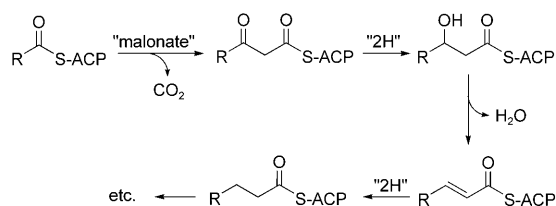
Substrate 1	CH ₂ (CO ₂ H)R'	R'=CO ₂ H ^[b] 4a-e	R'=CO ₂ H ^[c] 6a-e	R'=CO ₂ Me ^[b] 5a-e	R'=CN ^[d] 9a-e	R'=CN ^[e] 11a-e
I/b 99:1 ^[f]	yield [%] ^[g] α,β/β,γ ^[h]	77 98:2	75 1:99	80 98:2	80 99:1	70 85:15
I/b 99:1	yield [%] α,β/β,γ	72 98:2	59 1:99	68 97:3	82 99:1	48 85:15
I/b 99:1	yield [%] α,β/β,γ	75 99:1	89 1:99	80 94:6	57 99:1	60 81:19
I/b 99:1	yield [%] α,β/β,γ	68 99:1	78 1:99	60 92:8	72 99:1	45 88:12
I/b 99:1	yield [%] α,β/β,γ	68 98:2	76 1:99	62 98:2	69 99:1	67 86:14
I/b 99:1	yield [%] α,β/β,γ	69 98:2	53 1:99	69 98:2	63 99:1	55 87:13

[a] Conditions (RTAP hydroformylation): [Rh(acac)(CO)₂] (0.66 mol %), 6-DPPon (3.33 mol %), alkene (1.0 equiv), CO/H₂ (1:1) 1 atm., THF (c₀-alkene)=1.0 M, RT, 20 h. [b] Conditions (decarboxylative Knoevenagel): malonic acid (1.0 equiv), respectively, malonic acid methylester (1.1 equiv), pyridine (2.0 equiv), pyrrolidine (1 mol %), 20 h at 10 °C then 4 h at RT. [c] Conditions (decarboxylative Knoevenagel): malonic acid (1.0 equiv), DBU (2.0 equiv), 24 h at 40 °C. [d] Conditions (Knoevenagel): nitrile acetic acid (1.1 equiv), pyrrolidine (1 mol %), 24 h at RT, no Z isomer was determined in the ¹H NMR spectra. [e] Conditions (decarboxylative Knoevenagel): nitrile acetic acid (1.1 equiv), pyrrolidine (1 mol %), 24 h at RT, DBU (2.0 equiv), 24 h at RT, a mixture of *cis* and *trans* isomers in a ratio of 1:1 was observed, as determined by the ¹H NMR spectra. [f] Ratio of the intermediate aldehyde regioisomers of the hydroformylation, (isomerization to the internal alkene <5%), ¹H NMR spectra detected. [g] Isolated yield of the unsaturated product. [h] Ratio of the two regioisomers of the Knoevenagel reaction, ¹H NMR spectra detected.

In the previous chapters, two-carbon elongation of aldehydes to give α,β-unsaturated carboxylic acid by a decarboxylative Knoevenagel reaction was described. Recently, our group reported a new catalytic transformation of α,β-unsaturated carboxylic acids to aldehydes (decarboxylative hydroformylation).^[34] We envisaged the combination of these two catalytic methods as a homologation process for both aldehydes and α,β-unsaturated carboxylic acids (Scheme 10). Inspiration for this concept came from the biosynthesis of fatty acids carried out by a multifunctional enzyme complex–fatty acid synthase (Scheme 11).^[35] The fatty acid is anchored to the acyl-carrier protein (ACP) and the acyl



Scheme 10. Concept for the homologation of α,β-unsaturated carboxylic acids and aldehydes.



Scheme 11. Biosynthesis of fatty acids.

chain grows by two carbon atoms in each cycle. Two reductions and one dehydration are required to convert the β -keto group to an alkyl group forming a substrate, which can again enter the cycle. Although the synthetic and natural cycle employ completely different chemical reactions and catalysts, the stoichiometric byproducts of both processes are the same (CO_2 and H_2O). Obviously the atom economy is similar in both cases. To explore the synthetic potential of our method, aliphatic aldehydes were subjected to the two-step homologation procedure by using guanidine ligand **13** for the decarboxylative hydroformylation.^[34] Aldehydes (**12a–e**) were obtained in 62–84% yields over two steps (Table 6).

Table 6. Two-carbon homologation of aliphatic aldehydes.^[a]

Reaction scheme showing the synthesis of **12a-e** from an aldehyde (**R-CHO**) via Knoevenagel condensation and decarboxylative hydroformylation.

Knoevenagel: $\text{R-CHO} + \text{CH}_2(\text{CO}_2\text{H})_2$ (pyridine, pyrrolidine) $\rightarrow$ $\text{R-CH=CH-CO}_2\text{H}$

Decarboxylative Hydroformylation: $\text{R-CH=CH-CO}_2\text{H} \xrightarrow{[\text{Rh}]/\mathbf{13}, \text{CO}/\text{H}_2}$ $\text{R-CH}_2\text{CH}_2\text{CHO}$ (**12a-e**)

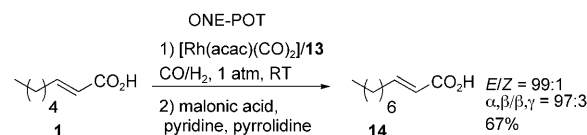
Chemical structure of ligand **13**:

13

Entry	Substrate	Product	Yield [%] ^[b]
1		12a	84 ^[c]
2		12b	76 ^[d]
3		12c	83 ^[d]
4		12d	62 ^[e]
5		12e	73 ^[e,f]

[a] Conditions: (decarboxylative Knoevenagel): malonic acid (1.0 equiv), pyridine (2.0 equiv), pyrrolidine (1–3 mol %), RT to 60 °C, 24 h. Conditions: (decarboxylative hydroformylation): $[\text{Rh}(\text{acac})(\text{CO})_2]/\textbf{13}$ /substrate 1:10:200, $c_0(\text{substrate}) = 0.2 \text{ M}$, CH_2Cl_2 (8 mL), 13 bar CO/H_2 (1:1), 25 °C, 24 h. [b] Yields of aldehyde products over two steps. [c] GC yield. [d] NMR yield. [e] Isolated yield. [f] Over 3 steps by starting from 4-phenylbut-1-ene (RTAP hydroformylation–decarboxylative Knoevenagel–decarboxylative hydroformylation).

Of course, the order of reactions can be also changed giving an efficient two-carbon elongation of α,β -unsaturated carboxylic acids. More interestingly, this transformation could be also performed as a one-pot procedure (Scheme 12). Decarboxylative hydroformylation of (*E*)-oct-2-enoic acid **1** was conducted as described.^[34] After 24 h,

Scheme 12. One-pot C2 homologation of oct-2-enoic acid **1**.

synthesis gas was removed by bubbling argon through the solution. Malonic acid (1 equiv), pyridine (2 equiv), and pyrrolidine (1 mol %) were added and the reaction mixture was stirred for a further 24 h at RT to furnish dec-2-enoic acid **14**.

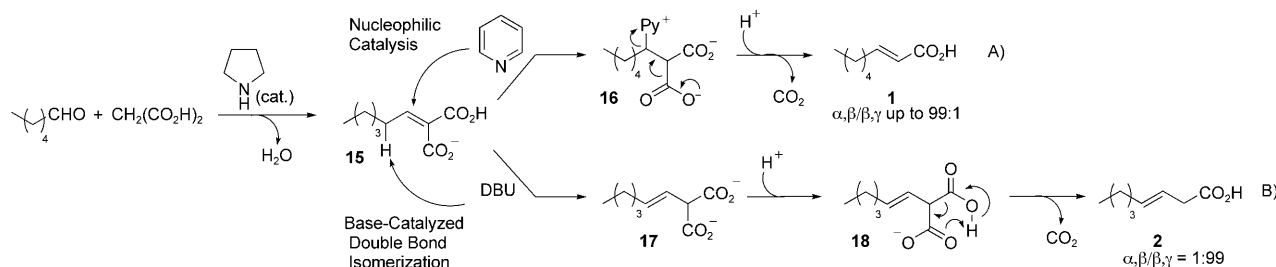
Mechanistic discussion: Accordingly, the decarboxylative condensation of malonic acid derivatives presents an interesting, atom-economic alternative to the more traditional carbon–carbon bond-forming reactions. These and analogous processes are relatively rarely synthetically exploited so far because of the dominating controversy concerning the mechanism.

Our results confirm a correlation between the catalyst nucleophilicity, the basicity, and the chemoselectivity of the decarboxylative Knoevenagel reaction (Table 7).^[36] On the one hand, a weak but nucleophilic base like pyridine afforded the decarboxylation to α,β -unsaturated carboxylic acids (Table 7, entry 1); on the other hand, a rather strong but less nucleophilic base, such as DBU led to the β,γ -isomer selectively (Table 7, entry 4). Bases with $\text{p}K_a$ values between these two bases led either to bad selectivity (Table 7, entry 2, 2,6-lutidine) or low conversion (Table 7, entry 3, TMG). We reasoned that under these conditions two different mechanisms are operating (Scheme 13). The first step is in both cases A and B a classical Knoevenagel condensation that is catalyzed by the secondary amine, which here is pyrrolidine, via the formation of highly electrophilic iminium ion intermediates from the corresponding aldehyde with formation of diacid **15**. The same intermediate, alkylidenmalonic acid **15**, could be isolated when pyrrolidine was used as the sole catalyst. This step is fast and shows over 50% conversion after 30 min at 10 °C. When **15** was treated with pyridine, a smooth decarboxylation occurred and furnished the α,β -unsaturated carboxylic acid **1**.^[9a] Hence, a two-step mechanism is most likely. We propose that pyridine functionalities (see pathway A) as a Lewis basic catalyst that undergoes conjugate addition to Knoevenagel product **15** followed by decarboxylation via the indicated transition-state **16**. In pathway B, diacid **15** undergoes a base-catalyzed double-bond isomerization to the β,γ -unsaturated carboxylate **17**. We assume that more than one equivalent of base is necessary due to the deprotonation of acid **15**. Mechanistic studies by Corey et al. led to the proposal that decarboxylation of α,β -unsaturated malonic acids **1** can only proceed via β,γ -unsaturated intermediate **18**, which then smoothly decarboxylates to the β,γ -unsaturated carboxylic acid **2**.^[37] This mechanism probably also operates during the condensation of malonic acid and aliphatic aldehydes catalyzed by piperi-

Table 7. Correlation between the strength of the base used and the regioselectivity of the Knoevenagel reaction.

$\text{CH}_2(\text{CO}_2\text{H})_2 \xrightarrow[\text{THF (1 M), 24 h}]{\text{CHO}} \text{CH}_2(\text{CO}_2\text{H})_2 \text{ (1 equiv)}$				
Entry	Base	$\text{p}K_{\text{a}}^{[\text{a}]}$	Ratio 1/2 at 10 °C	Ratio 1/2 at 40 °C
1	pyridine	12.3	98:2 full conversion	n.d. ^[b]
2	2,6-lutidine	13.9	57:43 good conversion	8:92 good conversion
3	TMG	23.3	n.d. ^[b]	1:99 low conversion
4	DBU	24.2	no conversion	1:99 full conversion

[a] $\text{p}K_{\text{a}}$ of the conjugated acid in CH_3CN . [b] Not determined.



Scheme 13. Proposed mechanism, which is dependent upon the base used.

dinium acetate in dimethyl sulfoxide at 100 °C as described by Ragoussis et al.^[25,38]

Conclusion

Traditionally, each unit operation advances the synthesis by a single step, which wastes solvents, time, and energy. The efficient synthesis of unsaturated (carboxylic) compounds and the “homologation process” described in this work represent examples of the new paradigm of sustainable chemistry: multiple reactions carried out in a single vessel promoted by compatible catalysts.^[39] Thus, combining our recently developed regioselective room-temperature/ambient-pressure hydroformylation (transition-metal catalysis) with a new variant of the decarboxylative Knoevenagel reaction (organocatalysis) allowed for the development of an efficient, one-pot C3 homologation of terminal alkenes to furnish (*E*)- α,β -unsaturated acids and esters, (*E*)- β,γ -unsaturated acids, (*E*)- α -cyano acrylic acids, and α,β -unsaturated nitriles. All reactions proceed under mild conditions, tolerate a variety of functional groups, and furnish unsaturated carbonyl compounds in good yields and with excellent regio- and stereocontrol. Further, inspired by fatty-acid biosynthesis an iterative two-carbon homologation of the (*E*)- α,β -unsaturated carboxylic acid is possible through a combination of a decarboxylative hydroformylation by employing a supramolecular catalyst system followed by a decarboxylative Knoevenagel condensation, which makes use of an organocatalyst.

Experimental Section

Typical procedure for the synthesis of α,β -unsaturated carboxylic acids (Table 5, 4a–e, (*E*)-undec-2-enoic acid (4)): Under an atmosphere of argon, 1-octene (785 μL , 5.00 mmol, 150 equiv) was added to a solution of 6-DPPon (46.7 mg, 167 μmol , 5.00 equiv) and $[\text{Rh}(\text{acac})(\text{CO})_2]$ (8.50 mg, 33.0 μmol , 1.00 equiv) in THF (5 mL, 1 M according to the alkene) at room temperature in a flat-bottomed Schlenk tube. The argon atmosphere was replaced by synthesis gas (balloon). The reaction mixture was stirred at room temperature and ambient pressure for 20 h. Subsequently, the synthesis gas was removed over 20 min by bubbling argon through the solution. The solution was cooled to 0 °C and malonic acid (520 mg, 5.00 mmol, 150 equiv), pyridine (809 μL , 10.0 mmol, 300 equiv), and pyrrolidine (4.00 μL , 50.0 μmol , 1.50 equiv) were added. The reaction mixture was warmed to 10 °C and stirred for 20 h at this temperature, and then an additional 4 h at room temperature. The reaction was finished by the addition of aqueous H_3PO_4 (20 %, 10 mL). After phase separation, the aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over MgSO_4 . The solvent was removed in vacuo. Purification by flash chromatography (silica gel, petroleum ether/diethyl ether/acetic acid 100:20:1) furnished 710 mg (77 %) of the acid as a colorless oil. ^1H NMR (400.132 MHz, CDCl_3): δ = 0.88 (t, J = 7.0 Hz, 3H), 1.20–1.36 (m, 10H), 1.43–1.50 (m, 2H), 2.23 (tdd, J = 7.2, 7.2, 1.6 Hz, 2H), 5.82 (dt, J = 15.6, 1.6 Hz, 1H), 7.09 (dt, J = 15.6, 7.0 Hz, 1H), 11.9 ppm (brs, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.626 MHz, CDCl_3): δ = 14.1, 22.7, 27.9, 29.2, 29.4, 31.9, 32.3, 120.6, 152.5, 172.3 ppm; MS (CI, NH_4Cl , 130 eV): m/z (%): calcd for $\text{C}_{11}\text{H}_{20}\text{O}_2$: 184.15; found: 202.1 (100) $[\text{M}+\text{NH}_4]^+$; elemental analysis calcd (%) for: C 71.20, H 10.94; found: C 71.53, H 10.98.

Typical procedure for the synthesis of α,β -unsaturated carboxylic esters (Table 5, 5a–e, (*E*)-methyl-2-undecenoate (5)): Under an atmosphere of argon, 1-octene (785 μL , 5.00 mmol, 150 equiv) was added to a solution of 6-DPPon (64.7 mg, 167 μmol , 5.00 equiv) and $[\text{Rh}(\text{acac})(\text{CO})_2]$ (8.50 mg, 33.0 μmol , 1.00 equiv) in THF (5 mL, 1 M according to the alkene) at room temperature in a flat-bottomed Schlenk tube. The argon atmosphere was replaced by synthesis gas (balloon). The reaction mixture was stirred at room temperature and ambient pressure for 20 h. Subsequently, the synthesis gas was removed over 20 min by bubbling argon through the solution. The solution was cooled to 0 °C and malonic acid methyl ester (556 μL , 5.50 mmol, 165 equiv), pyridine (809 μL ,

10.0 mmol, 300 equiv), and pyrrolidine (2.00 μ L, 24.0 μ mol, 1.50 equiv) were added. The reaction mixture was warmed to 40 °C and stirred for 20 h at this temperature, and then an additional 4 h at room temperature. The reaction was finished by the addition of aqueous H_3PO_4 (20%, 10 mL). After phase separation, the aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over MgSO_4 . The solvent was removed in vacuo. Purification by flash chromatography (silica gel, short column with CH_2Cl_2) furnished 793 mg (80%) of the ester **5** as a colorless oil. ^1H NMR (400.132 MHz, CDCl_3): δ = 0.88 (t, J = 6.9 Hz, 3H), 1.24–1.31 (m, 10H), 1.41–1.48 (m, 2H), 2.20 (m, 2H), 3.72 (s, 3H), 5.79–5.84 (dt, J = 15.7, 7.0 Hz, 1H), 6.93–7.01 ppm (dt, J = 15.7, 1.5 Hz, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.626 MHz, CDCl_3): δ = 24.2, 72.7, 28.1, 29.2, 29.3, 29.4, 31.9, 32.3, 51.5, 65.9, 120.9, 150.0, 167.3 ppm; the analytical data match with those reported in literature.^[40]

Typical procedure for the synthesis of β,γ -unsaturated carboxylic acids (Table 5, 6a–e, (E)-2-cyanoundec-2-enoic acid (6)): Under an atmosphere of argon, 1-octene (785 μ L, 5.00 mmol, 150 equiv) was added to a solution of 6-DPPon (64.7 mg, 167 μ mol, 5.00 equiv) and $[\text{Rh}(\text{acac})(\text{CO})_2]$ (8.50 mg, 33.0 μ mol, 1.00 equiv) in THF (5 mL, 1 M according to the alkene) at room temperature in a flat-bottomed Schlenk tube. The argon atmosphere was replaced by synthesis gas (balloon). The reaction mixture was stirred at room temperature and ambient pressure for 20 h. Subsequently, the synthesis gas was removed over 20 min by bubbling argon through the solution. At room temperature malonic acid (520 mg, 5.00 mmol, 150 equiv) and DBU (1.50 g, 10.0 mmol, 300 equiv) were added. The reaction mixture was stirred for 24 h at room temperature. The reaction was finished by the addition of aqueous NaOH (1 M, up to pH 11). After phase separation, the aqueous phase was extracted three times with ethyl acetate and the aqueous phase was acidified by adding aqueous H_3PO_4 (20%, down to pH 2). This aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over MgSO_4 . The solvent was removed in vacuo to furnish 688 mg (75%) of the acid **6** as a colorless solid. M.p. 48–50 °C; ^1H NMR (400.132 MHz, CDCl_3): δ = 0.88 (t, J = 5.8 Hz, 3H), 1.22–1.32 (m, 10H), 2.00–2.05 (m, 2H), 3.05–3.08 (m, 2H), 5.46–5.62 ppm (m, 2H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.613 MHz, CDCl_3): δ = 14.1, 22.7, 27.8, 29.1, 29.2, 29.3, 31.8, 32.4, 109.4, 113.1, 166.3, 166.4 ppm; MS (EI, 70 eV, 500 μ A): m/z (%): calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$: 209.14; found: 210.1 (19) $[\text{M}+\text{H}]^+$, 166.1 (35) $[\text{M}-\text{CN}-\text{OH}]^+$, 164.1 (25) $[\text{M}-\text{CO}_2\text{H}]^+$, 138.0 (58) $[\text{M}-\text{COOH}-\text{CN}]^+$; HRMS (CI, $\text{Cl}(\text{NH}_3)$, 130 eV, 300 μ A): m/z : calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2+\text{NH}_4$: 227.17595; found: 277.17580.

Typical procedure for the synthesis α -cyano acrylic acids (Table 5, 9a–e, (E)-undec-3-enoic acid (9)): Under an atmosphere of argon, the alkene (5.00 mmol, 150 equiv) was added to a solution of 6-DPPon (167 μ mol, 5 equiv) and $[\text{Rh}(\text{acac})(\text{CO})_2]$ (33.0 μ mol, 1 equiv) in THF (5 mL, 1 M according to the alkene) at room temperature. The argon atmosphere was replaced by synthesis gas (balloon). The reaction mixture was stirred at room temperature and ambient pressure for 20 h. Subsequently, the synthesis gas was removed over 20 min by bubbling argon through the solution. At room temperature, nitrile acetic acid (486 mg, 5.5 mmol, 165 equiv) and pyrrolidine (4.00 μ L, 50.0 μ mol, 1.5 equiv) were added and the reaction mixture was stirred at room temperature for 24 h. The reaction was finished by the addition of aqueous NaOH (1 M, up to pH 11). After phase separation, the aqueous phase was extracted three times with ethyl acetate and the aqueous phase was acidified by adding aqueous H_3PO_4 (20%, down to pH 2). This aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over MgSO_4 . The solvent was removed in vacuo to furnish 640 mg (77%) of the acid **9** as a colorless solid. M.p. 63–65 °C; ^1H NMR (400.132 MHz, CDCl_3): δ = 0.88 (t, J = 6.6 Hz, 3H), 1.27–1.36 (m, 10H), 1.53–1.61 (tt, J = 7.2, 7.2 Hz, 2H), 2.57–2.62 (td, J = 7.5, 7.5 Hz, 2H), 7.74 (t, J = 7.9 Hz, 1H), 10.74 ppm (brs, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.613 MHz, CDCl_3): δ = 14.1, 22.7, 27.8, 29.1, 29.2, 29.3, 31.8, 32.4, 109.4, 113.1, 166.3, 166.4 ppm; MS (EI, 70 eV, 500 μ A): m/z (%): calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$: 209.14; found: 210.1 (19) $[\text{M}+\text{H}]^+$, 166.1 (35) $[\text{M}-\text{CN}-\text{OH}]^+$, 164.1 (25) $[\text{M}-\text{CO}_2\text{H}]^+$, 138.0 (58) $[\text{M}-\text{COOH}-\text{CN}]^+$; HRMS (CI, $\text{Cl}(\text{NH}_3)$, 130 eV, 300 μ A): m/z : calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2+\text{NH}_4$: 227.17595; found: 277.17580.

Typical procedure for the synthesis of α,β -unsaturated nitriles (Table 5, 11a–e, undec-2-enenitrile (11)): Under an atmosphere of argon, 1-octene (314 μ L, 2.00 mmol, 150 equiv) was added to a solution of 6-DPPon (18.6 mg, 66.6 μ mol, 5.00 equiv) and $[\text{Rh}(\text{acac})(\text{CO})_2]$ (3.40 mg, 13.3 μ mol, 1.00 equiv) in THF (2 mL, 1 M according to the alkene) at room temperature in a flat-bottomed Schlenk tube. The argon atmosphere was replaced by synthesis gas (balloon). The reaction mixture was stirred at room temperature and ambient pressure for 20 h. Subsequently, the synthesis gas was removed over 20 min by bubbling argon through the solution. At room temperature, nitrile acetic acid (187 mg, 2.20 mmol, 165 equiv) and pyrrolidine (2.00 μ L, 0.02 mmol, 1.5 equiv) were added and the reaction mixture was stirred at room temperature for 24 h. Then DBU (450 μ L, 3.00 mmol, 225 equiv) was added and the reaction mixture was stirred for an additional 24 h at room temperature. The reaction was finished by the addition of aqueous NaOH (1 M, up to pH 11). After phase separation, the aqueous phase was extracted three times with ethyl acetate and the combined organic phases were dried over MgSO_4 . The solvent was removed in vacuo. Purification by flash chromatography (silica gel, cyclohexane/ethyl acetate 20:1, R_f = 0.45) furnished 233 mg (70%) of the nitrile **11** as a colorless liquid. ^1H NMR (400.132 MHz, CDCl_3): δ = 0.88 (t, J = 6.9 Hz, 3H), 1.27–1.4 (m, 10H), 1.49–1.51 (m, 2H), 2.21 (tdd, J = 7.0, 7.0, 1.7 Hz, 2H; *trans*), 2.42 (tdd, J = 7.4, 7.4, 1.4 Hz, 2H; *cis*), 5.31 (dt, J = 11.0, 1.4 Hz, 1H; *cis*), 5.31 (dt, J = 16.3, 1.7 Hz, 1H; *trans*), 6.47 (dt, J = 10.9, 7.7 Hz, 1H; *cis*), 6.72 ppm (dt, J = 16.3, 7.0 Hz; *trans*); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.626 MHz, CDCl_3): δ = 14.2, 22.7, 27.7, 28.3, 29.1, 29.2, 29.3, 31.9, 32.0, 33.4, 99.5, 116.2, 117.7, 155.4, 156.3 ppm; MS (EI, 70 eV): m/z (%): calcd for $\text{C}_{11}\text{H}_{19}\text{N}$: 165.28; found: 164.2 (23) $[\text{M}-\text{H}]^+$, 150.1 (46) $[\text{M}-\text{NH}]^+$, 136.1 (100) $[\text{M}-\text{CH}_3\text{N}]^+$, 122.1 (92) $[\text{M}-\text{C}_3\text{H}_7]^+$, 108.1 (32) $[\text{M}-\text{C}_4\text{H}_9]^+$, 94.1 (47) $[\text{M}-\text{C}_5\text{H}_{11}]^+$, 94.1 (47) $[\text{M}-\text{C}_6\text{H}_{13}]^+$, 80.1 (53) $[\text{M}-\text{C}_6\text{H}_{13}]^+$; HRMS: m/z : (CI, $\text{Cl}(\text{NH}_3)$, 130 eV, 300 μ A): calcd for $\text{C}_{11}\text{H}_{19}\text{N}$: 164.1440; found: 164.1439.

Procedure for the one-pot decarboxylative hydroformylation/decarboxylative Knoevenagel reaction to (E)-dec-2-enoic acid (14) (Scheme 12): Decarboxylative hydroformylation of (E)-oct-2-enoic acid (227 mg, 1.60 mmol) was carried out according to the literature procedure.^[34] Subsequently, the autoclave was depressurized and the synthesis gas was removed over 20 min by bubbling argon through the solution. The solution was cooled to 0 °C and malonic acid (167 mg, 1.60 mmol), pyridine (259 μ L, 253 mg, 3.20 mmol), and pyrrolidine (1.30 mg, 16.0 μ mol) were added. The reaction mixture was warmed to RT and stirred for 24 h at this temperature (76% conversion of the Knoevenagel reaction). The reaction was finished by the addition of aqueous H_3PO_4 (20%, 10 mL) at 0 °C. It was extracted three times with CH_2Cl_2 , the combined organic phases were dried (Na_2SO_4), and the solvent was removed in vacuo. Purification by chromatography (silica gel, petroleum ether/ Et_2O /AcOH 100:20:1) furnished 183 mg (67%) of the acid **14** as a colorless liquid. ^1H NMR (400.132 MHz, CDCl_3): δ = 0.88 (t, J = 7.0 Hz, 3H); 1.17–1.38 (m, 8H); 1.41–1.56 (m, 2H); 2.23 (tdd, J = 7.0, 7.0, 1.5 Hz, 2H), 5.82 (dt, J = 15.7, 1.5 Hz, 1H), 7.09 (dt, J = 15.7, 7.0 Hz, 1H), 12.0 ppm (brs, 1H); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.626 MHz, CDCl_3): δ = 14.0, 22.5, 27.8, 29.0, 29.6, 31.6, 32.2, 120.5 (s, 1C; C2), 152.4 (s, 1C; C3), 172.3 ppm (s, 1C; COOH); the analytical data match with those reported in the literature.^[19f]

Acknowledgements

This work was supported by the DFG (International Research Training Group: “Catalysts and Catalytic Reactions for Organic Synthesis”, GRK 1038) and the Alfred Krupp Foundation.

- [1] R. W. Hoffmann, *Synthesis* **2006**, 3531–3541.
- [2] a) J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, 97, 5763–5784; J. B. Hendrickson, *J. Am. Chem. Soc.* **1975**, 97, 5784–5800; b) J. B. Hendrickson, *Angew. Chem.* **1990**, 102, 1328–1338; *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1286–1295.

- [3] a) B. M. Trost, *Science* **1991**, 254, 1471–1477; b) B. M. Trost, *Angew. Chem.* **1995**, 107, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, 34, 259–281.
- [4] For Horner–Wadsworth–Emmons or Wittig reactions, see: a) D. R. Brittelli, *J. Org. Chem.* **1981**, 46, 2514–2520; b) E. G. McKenna, B. J. Walker, *J. Chem. Soc. Chem. Commun.* **1989**, 568–569; c) D. Ok, C. Li, T. L. Shih, S. Salva, M. B. Ayer, S. L. Colletti, P. K. Chakravarty, M. J. Wyratt, M. H. Fisher, L. Gregory, M. Zakson-Aiken, W. L. Shoop, D. M. Schmatz, P. T. Meinke, *Bioorg. Med. Chem. Lett.* **2002**, 12, 1751–1754; d) H. J. Bestmann, R. Dostalek, R. Zimmermann, *Chem. Ber.* **1992**, 125, 2081–2084; e) D. R. Brittelli, *J. Org. Chem.* **1981**, 46, 2514–2520; f) P. Coutrot, M. Snoussi, P. Savignac, *Synthesis* **1978**, 133–134.
- [5] For metathesis reactions, see: a) T.-L. Choi, C. W. Lee, A. K. Chatterjee, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, 123, 10417–10418; b) S. BouzBouz, R. Simmons, J. Cossy, *Org. Lett.* **2004**, 6, 3465–3467; c) T.-L. Choi, C. W. Lee, A. K. Chatterjee, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, 123, 10417–10418; d) F. Thorstensson, I. Kvarnström, D. Mussil, I. Nioleson, B. Samuelsson, *J. Med. Chem.* **2003**, 46, 1165–1179; e) B. H. Lipshutz, S. Ghorai, Z. V. Bošković, *Tetrahedron* **2008**, 64, 6949–6954; f) S. Hilf, R. H. Grubbs, A. F. M. Kilbinger, *J. Am. Chem. Soc.* **2008**, 130, 11040–11048.
- [6] a) D. J. Peterson, *J. Org. Chem.* **1968**, 33, 780–784; b) D. J. Ager, *Synthesis* **1984**, 384–398; c) A. Barbero, Y. Blanco, C. García, F. J. Pulido, *Synthesis* **2000**, 1223–1228.
- [7] a) E. Knoevenagel, *Chem. Ber.* **1898**, 31, 2596–2619; b) O. Doebner, *Chem. Ber.* **1900**, 33, 2140–2142.
- [8] For RTAP-hydroformylation reactions, see: a) W. Seiche, A. Schuschowski, B. Breit, *Adv. Synth. Catal.* **2005**, 347, 1488–1494; for hydroformylation reactions in general, see: b) O. Roelen (Chemische Verwertungsgesellschaft mbH), German Patent DE 849,548, **1938/1952**; c) O. Roelen (Chemische Verwertungsgesellschaft mbH), U.S. Patent 1,327,066, **1943**; [*Chem. Abstr.* **1944**, 38, 5501]; for reviews about hydroformylation, see: d) B. Breit, W. Seiche, *Synthesis* **2001**, 1–36; e) B. Breit, *Acc. Chem. Res.* **2003**, 36, 264–275; f) M. Beller, C. Bolm, *Transition Metals for Organic synthesis, Vol. 1*, 2nd ed., **2004**, Wiley-VCH, Weinheim; g) P. W. N. M. van Leeuwen, C. P. Casey, G. T. Whiteker, *Rhodium-Catalyzed Hydroformylation* (Eds.: P. W. N. M. van Leeuwen, C. Claver), Kluwer Academic Publishers, Dordrecht, **2000**, Chapter 4; for hydroformylation tandem reactions, see: h) P. Eilbracht, L. Bärfacker, C. Buss, C. Hollmann, B. E. Kitsos-Rzychon, C. L. Kranemann, T. Rische, R. Roggenbuck, A. Schmidt, *Chem. Rev.* **1999**, 99, 3329–3365; i) M. D. Keränen, K. Kot, C. Hollmann, P. Eilbracht, *Org. Biomol. Chem.* **2004**, 2, 3379–3384; j) S. Chercheja, T. Rothenbücher, P. Eilbracht, *Adv. Synth. Catal.* **2009**, 351, 339–344; k) P. Köhling, A. M. Schmidt, P. Eilbracht, *Org. Lett.* **2003**, 5, 3213–3216; l) B. Breit, S. K. Zahn, *Angew. Chem.* **2001**, 113, 1964–1967; *Angew. Chem. Int. Ed.* **2001**, 40, 1910–1913; m) B. Breit, S. K. Zahn, *Tetrahedron* **2005**, 61, 6171–6179.
- [9] a) S. T. Kemme, T. Šmejkal, B. Breit, *Adv. Synth. Catal.* **2008**, 350, 989–994; for the first domino hydroformylation/Knoevenagel/hydrogenation reaction with dimethyl malonate, see: b) B. Breit, S. K. Zahn, *Angew. Chem.* **2001**, 113, 1964–1967; *Angew. Chem. Int. Ed.* **2001**, 40, 1910–1913; c) B. Breit, S. K. Zahn, *Tetrahedron* **2005**, 61, 6171–6179; for some other syntheses, see: d) C. D. Vanderwal, E. N. Jacobsen, *Sci. Synth.* **2006**, 20, 551–565; for the Peterson olefination, see: e) P. A. Grieco, C. L. J. Wang, S. D. Burke, *J. Chem. Soc. Chem. Commun.* **1975**, 537–538; aldehyde reactions with dibromacetic acid promoted by SmI₂: f) J. M. Concellón, C. Concellón, *J. Org. Chem.* **2006**, 71, 1728–1731; for the reaction of trimethylsilylketene acetal and aldehydes see: g) M. Bellassoued, M. Gaudemar, *Tetrahedron Lett.* **1988**, 29, 4551–4554.
- [10] a) M. S. Blum, R. Boch, R. E. Doolittle, M. T. Tribble, J. G. Traynham, *J. Insect Physiol.* **1971**, 17, 349–364; b) “The Chemistry of Pheromones and other Semiochemicals”: S. Schulz in *Topics in Current Chemistry*, Springer, Heidelberg, **2004**, p. 154; c) A. Brockmann, D. Dietz, J. Spaethe, J. Tautz, *J. Chem. Ecol.* **2006**, 32, 657–667.
- [11] a) B. List, A. Doebling, M. T. Hechavarria Fonseca, A. Job, R. R. Torres, *Tetrahedron* **2006**, 62, 476–482; b) B. List, A. Doebling, M. T. Hechavarria Fonseca, K. Wobser, H. van Thienen, R. R. Torres, P. L. Galilea, *Adv. Synth. Catal.* **2005**, 347, 1558–1560.
- [12] For some examples of hydroalkenylation, see: a) T. V. Rajan Babu, T. Koike, *Chem. Rev.* **2003**, 103, 2845–2860; b) G. Takahashi, E. Shirakawa, T. Tsuchimoto, Y. Kawakami, *Adv. Synth. Catal.* **2006**, 348, 837–840; c) N. Tsukada, H. Setoguchi, T. Mitsuboshi, Y. Inoue, *Chem. Lett.* **2006**, 35, 1164–1166; d) A. K. Gupta, K. S. Kim, C. H. Oh, *Synlett* **2005**, 457–461; e) C. H. Oh, J. H. Ryu, *Bull. Korean Chem. Soc.* **2003**, 24, 1563; f) T. Fujii, T. Koike, A. Mori, K. Osaka-da, *Synlett* **2002**, 295–298.
- [13] a) M. S. Blum, R. Boch, R. E. Doolittle, M. T. Tribble, J. G. Traynham, *J. Insect Physiol.* **1971**, 17, 349–364; b) R. J. Bartelt, L. L. Jackson, A. M. Schaner, *J. Chem. Ecol.* **1985**, 11, 1197–1208; c) M. S. Blum, R. Boch, R. E. Doolittle, M. T. Tribble, J. G. Traynham, *J. Insect Physiol.* **1971**, 17, 349–364.
- [14] For other syntheses, see: Wittig and Horner–Wadsworth–Emmons reactions: a) B. E. Maryanoff, A. B. Reitz, *Chem. Rev.* **1989**, 89, 863–927; b) R. J. K. Taylor, M. Reid, J. Foot, S. A. Raw, *Acc. Chem. Res.* **2005**, 38, 851–869; c) D. R. Brittelli, *J. Org. Chem.* **1981**, 46, 2514–2520; for metathesis: d) T. L. Choi, C. W. Lee, A. K. Chatterjee, R. H. Grubbs, *J. Am. Chem. Soc.* **2001**, 123, 10417–10418; e) B. H. Lipshutz, S. Ghorai, Z. V. Bošković, *Tetrahedron* **2008**, 64, 6949–6954; For other synthesis by hydrogentransfer, see: f) M. I. Hall, S. J. Pridmore, J. M. J. Williamsa, *Adv. Synth. Catal.* **2008**, 350, 1975–1978; g) Heck coupling with pincer Pd–carbene complex: T. Tua, J. Malineni, K. H. Dötz, *Adv. Synth. Catal.* **2008**, 350, 1791–1795; h) boronic acid-catalyzed condensation: R. Manzano, L. Ozores, A. Job, L. Rodefeld, B. List, *Beilstein J. Org. Chem.* **2009**, 5, 3; i) by a Heck reaction D. Song, W.-B. Yi, *J. Mol. Catal. A* **2008**, 280, 20–23.
- [15] a) V. Ragoussis, E. Vamvak, M. Kolymbadi, *J. Chem. Res.* **2002**, 398–399; b) A. Oritz, A. Quesada, A. Sanchez, *J. Chem. Ecol.* **2004**, 30, 991–1000; c) H. Maarse, C. A. Visscher, M. H. Boelens, *Volatile Compounds in Food, Qualitative and Quantitative Data*, TNO-CIVO Food Analysis Institute, The Netherlands, **1989**.
- [16] J. Klein, *J. Am. Chem. Soc.* **1959**, 81, 3611–3614.
- [17] C. U. Grünanger, B. Breit, *Angew. Chem.* **2008**, 120, 7456–7459; *Angew. Chem. Int. Ed.* **2008**, 47, 7346–7349.
- [18] G. Hidalgo-Del Vecchio, A. C. Oehlschlager, *J. Org. Chem.* **1994**, 59, 4853–4857.
- [19] For other syntheses, see: a) alkene isomerization: Y. Ikeda, J. Ukai, N. Ikeda, H. Yamamoto, *Tetrahedron* **1987**, 43, 743–753; b) with allylbarium reagents: A. Yanagisawa, S. Habaue, K. Yasue, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, 116, 6130–6141; c) zirconoxycarbene-complex-mediated: G. Erker, F. Sosna, *Organometallics* **1990**, 9, 1949–1953; d) by Cr oxidation: L. Schmieder-van de Vondervoort, S. Bouttemy, J. M. Padrón, J. Le Bras, J. Muzart, P. L. Alsters, *Synlett* **2002**, 243–246; e) through Co-oxidation: J.-C. Folest, J. M. Duprilot, J. Perichon, *Tetrahedron Lett.* **1985**, 26, 2633–2636.
- [20] N. Ragoussis, V. Ragoussis, *J. Chem. Soc. Perkin Trans. 1* **1998**, 3529–3533.
- [21] a) J. Lee, D. Gauthier, R. A. Rivero, *J. Org. Chem.* **1999**, 64, 3060–3065; b) R. Hoen, T. Tiemersma-Wegman, B. Procuranti, L. Lefort, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2007**, 5, 267–275.
- [22] K. Gademann, M. Ernst, D. Hoyer, D. Seebach, *Angew. Chem.* **1999**, 111, 1302–1304; *Angew. Chem. Int. Ed.* **1999**, 38, 1223–1226.
- [23] S. G. Davies, A. J. Russell, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Org. Biomol. Chem.* **2007**, 5, 3190–3200.
- [24] a) M. E. Jung, P. Yuk-Sun Lam, M. M. Mansuri, L. M. Speltz, *J. Org. Chem.* **1985**, 50, 1087–1105; b) T. Kametani, H. Kondoh, M. Tsubuki, T. Honda, *J. Chem. Soc. Perkin Trans. 1* **1990**, 5–10; c) Q. Wang, W. M. Campbell, E. E. Bonfantani, K. W. Jolley, D. L. Officer, P. J. Walsh, K. Gordon, R. Humphry-Baker, M. K. Nazeeruddin, M. Graetzel, *J. Phys. Chem. B* **2005**, 109, 15397–15409; for other synthesis, see: d) condensation with ion-exchange catalysis: M. J. Astle, W. C. Gergel, *J. Org. Chem.* **1956**, 21, 493–496; e) condensation of

- acetals with nitrile acetic acid: J. Klein, A. Y. Meyer, *J. Org. Chem.* **1964**, 29, 1035–1037; f) water-mediated: R. V. Hangarge, S. A. Sonwane, D. V. Jarikote, M. S. Shingare, *Green Chemistry* **2001**, 3, 310–312.
- [25] a) G. E. Stokker, A. W. Alberts, J. L. Gilfillan, J. W. Huff, R. L. Smith, *J. Med. Chem.* **1986**, 29, 852–855; b) A. Gazit, P. Yaish, C. Gilon, A. Levitzki, *J. Med. Chem.* **1989**, 32, 2344–2352.
- [26] G. Ohloff, *Scent and Fragrances: The Fascination of Odors and their Chemical Perspective*, **1994**, Springer, Heidelberg, pp. 9–11.
- [27] a) M. Rivard, S. Blechert, *Eur. J. Org. Chem.* **2003**, 2225–2228; b) S. Randl, S. Gessler, H. Wakamatsu, S. Blechert, *Synlett* **2001**, 430–432; c) W. E. Crowe, D. R. Goldberg, *J. Am. Chem. Soc.* **1995**, 117, 5162–5163.
- [28] a) E. G. McKenna, B. J. Walker, *J. Chem. Soc. Chem. Commun.* **1989**, 568–569; b) G. Etemad-Elohadam, J. Seyden-Penne, *Synth. Commun.* **1984**, 14, 565–573; c) J. Villieras, M. Rambaud, B. Kirschleger, *Phosphorous and Sulphur* **1983**, 14, 385–391; d) B. Deschamps, G. Lefebvre, J. Seyden-Penne, *Tetrahedron* **1972**, 28, 4209–4222; e) W. S. Wadsworth, *Synthetic Applications of Phosphoryl-stabilized Anions*, Brookings, **1977**, p. 25; f) H. Y. Lo, J. Bentzien, R. W. Fleck, S. S. Pullen, H. H. Khine, J. R. Woska, Jr., S. Z. Kugler, M. A. Kashem, H. Takahashi, *Bioorg. Med. Chem. Lett.* **2008**, 18, 6218–6221.
- [29] For other reactions, see: a) by water elimination: R. B. Boers, Y. Pazos Randulfe, H. N. S. van der Haas, M. van Rossum-Baan, J. Lugtenburg, *Eur. J. Org. Chem.* **2002**, 2094–2108; b) by sulfide elimination: M. Kimura, S. Matsubara, Y. Sawaki, H. Iwamura, *Tetrahedron Lett.* **1986**, 27, 4177–4178; c) by ammonia water transformation: S. Talukdar, J.-L. Hsu, T.-C. Chou, J.-M. Fang, *Tetrahedron Lett.* **2001**, 42, 1103–1105; d) Y.-Z. Huang, Y. Shen, C. Chen, *Synth. Commun.* **1989**, 19, 83–90; e) by organo-silicon compounds: Y. Yamakado, M. Ishiguro, N. Ikeda, H. Yamamoto, *J. Am. Chem. Soc.* **1981**, 103, 5568–5570; f) by a Heck reaction: D. Song, W.-B. Yi, *J. Mol. Catal. A* **2008**, 280, 20–23.
- [30] a) R. Latouche, F. Texier-Boullet, J. Hamelin, *Tetrahedron Lett.* **1991**, 32, 1179–1182; b) C. Palomo, J. M. Aizpurua, J. M. Garcia, I. Ganboa, F. P. Cossio, B. Lecea, C. López, *J. Org. Chem.* **1990**, 55, 2498–2503.
- [31] Y. Okamoto, T. Nitta, H. Sakurai, *Bull. Chem. Soc. Jpn.* **1969**, 42, 543–545.
- [32] a) J. H. Babler, K. P. Spina, *Tetrahedron Lett.* **1983**, 24, 3835–3838; b) H. Maehr, J. M. Smallheer, *J. Org. Chem.* **1981**, 46, 1752–1755; c) R. A. Hann, *J. Chem. Soc. Perkin Trans. 1* **1974**, 1379–1380.
- [33] a) R. J. Petroski, *Synth. Commun.* **2007**, 37, 3841–3854; b) A. Lindenschmidt, *Science of Synthesis, Vol. 25*, Thieme, Stuttgart, **2006**, p. 237; c) A. Dondoni, G. Fantin, M. Fogagnolo, P. Merino, *Tetrahedron* **1990**, 46, 6167–6184; d) I. J. P. De Esch, A. Gaffar, W. M. P. B. Menge, H. Timmerman, *Bioorg. Med. Chem.* **1999**, 7, 3003–3009.
- [34] For mechanistic details of the reaction with guanidine ligand **13**, see: T. Šmejkal, B. Breit, *Angew. Chem.* **2008**, 120, 4010–4013; *Angew. Chem. Int. Ed.* **2008**, 47, 3946–3949.
- [35] D. Voet, J. G. Voet, *Biochemistry*, 2nd ed., Wiley, New York, **1995**.
- [36] pK_a values: T. Rodima, I. Kaljurand, V. Mäemets, I. Leito, I. A. Koppel, *J. Org. Chem.* **2002**, 67, 1873–1881.
- [37] a) E. J. Corey, *J. Am. Chem. Soc.* **1952**, 74, 5897–5905; b) E. J. Corey, *J. Am. Chem. Soc.* **1953**, 75, 1163–1167; c) E. J. Corey, G. Fraenkel, *J. Am. Chem. Soc.* **1953**, 75, 1168–1172; d) E. J. Corey, *J. Am. Chem. Soc.* **1953**, 75, 1172–1174.
- [38] J. K. Augustine, Y. A. Naik, A. B. Mandal, N. Chowdappa, V. B. Praveen, *J. Org. Chem.* **2007**, 72, 9854–9856.
- [39] D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev.* **2004**, 248, 2365–2379.
- [40] R. C. Larock, *J. Org. Chem.* **1975**, 40, 3237–3242.

Received: November 25, 2009
Published online: February 3, 2010