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Selective Isomerization–Hydroformylation Sequence: A Strategy to Valuable α-Methyl-Branched Aldehydes from Terminal Olefins

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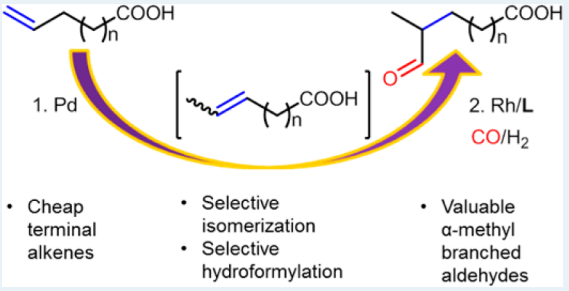
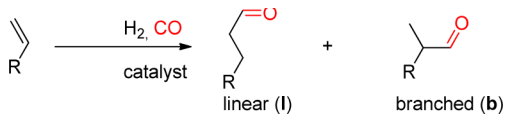
Supporting Information

ABSTRACT: For the first time, an original selective isomerization-hydroformylation sequence to convert terminal olefins bearing an anionic moiety to α-methyl-branched aldehydes with unprecedented selectivities is reported. This opens up new synthetic avenues to these valuable building blocks from inexpensive and bioavailable substrates. The catalytic system involves a suitable selective monoisomerization catalyst and a selective supramolecular catalyst that preorganizes a substrate molecule prior to the hydroformylation reaction via hydrogen bonding. In principle, the strategy can be extended to other classes of substrates, providing suitable catalysts for the hydroformylation of internal alkenes.



KEYWORDS: *isomerization–hydroformylation sequence, branched-regioselective hydroformylation, catalytic cascade reactions, supramolecular chemistry, transition metals*

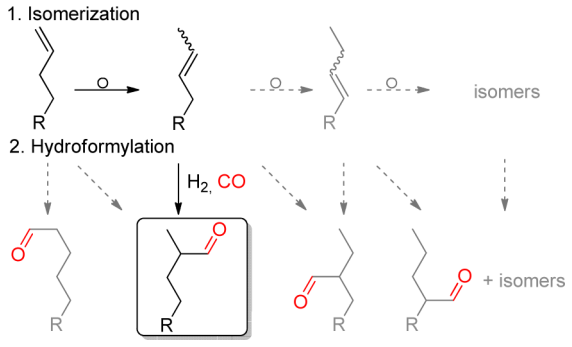
Alkene hydroformylation, the addition of the formyl group (CHO) to a C=C double bond to form an aldehyde using syngas as the reagent, is key to various industrial processes and results in a total production capacity of 10^7 ton/year.[1] Hence, this transformation has attracted considerable research interest over the past decades.[2] This brought a myriad of examples of highly active and selective catalysts[2,3] as well as detailed knowledge of the reaction mechanism.[2a,4] The regioselectivity of the reaction, that is, the ratio between regioisomeric products that can form, is a crucial parameter that should be controlled. For aliphatic olefins, such as 1-octene and 1-hexene, rhodium catalysts generally produce the linear aldehyde preferentially. The selectivity for the linear product can be increased by using bulky ligands[5] and is especially high (*l*/*b* product ratio 50–100) when ligands with a wide bite angle,[6] such as BISBI and Xantphos, are applied.



In contrast, traditional catalysts that form dominantly branched aldehyde products from aliphatic olefins are very scarce,[7] and rather moderate selectivities (*b*/*l* ratio up to 3 and up to 10 for unfunctionalized and functionalized olefins, respectively) have thus far been obtained.[7b] Access to branched aldehydes by catalytic conversion of alkenes is highly desired, considering the synthetic value of these building blocks for the fine chemical and pharma industries.[7a,8] As demonstrated, this selectivity can be realized for the hydroformylation of specific functionalized alkenes using reversible directing groups: catalytic auxiliaries (with *b*/*l* up to 99)[9] or for unfunctionalized alkenes using a capsulary catalyst approach (*b*/*l* up to 1.7).[10]

We aimed at a new alternative approach that bypasses the challenges imposed by the inherent properties of the terminal double bond by combining a selective monoisomerization of the terminal double bond and its subsequent C-2 regioselective hydroformylation (Scheme 1). Herein, we report first examples of such one-pot tandem reactions, using an isomerization catalyst and a supramolecular hydroformylation catalyst recently developed in our group,[15a] to convert terminal alkenes with anionic groups to C-2 aldehyde products with

Scheme 1. Selective Isomerization-Hydroformylation Sequence for a Terminal Olefin to Access the α-Methyl-Branched Aldehyde, And Possible Undesired Side Reaction Pathways



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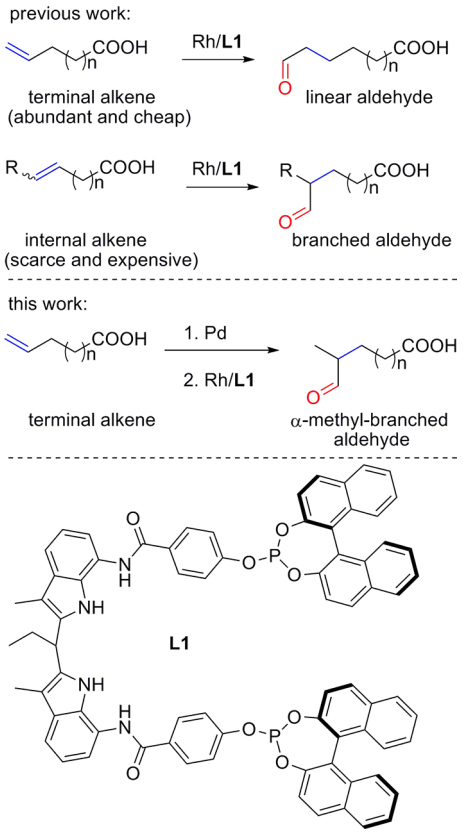
unprecedented selectivities: branched/linear ratios of up to 28 and with up to 85% yields of the α-methyl-branched products.

Our strategy for α-methyl-branched selective hydroformylation of terminal olefins is based on a two-catalyst system involving a single isomerization step followed by a regioselective hydroformylation (Scheme 1). The isomerization of the terminal double bond to the internal alkene product is driven by the higher thermodynamic stability of the latter;[11] however, the primary product can, in principle, enter further isomerization cycles, leading to a mixture of alkenes,[11] which would be detrimental for the overall selectivity of the two-step process. Recent studies reported that a Pd^{II} catalyst[12] and a Ru^{II} "zipper" catalyst[13] are rather selective for monoisomerization of a few terminal alkenes. In contrast, common Ir^{I} and Ru^{II} catalysts[14] led to the formation of mixtures of products with the double bond scrambled along the alkyl chain.[12] The terminal alkene substrates of the current study also contain a carboxylic group at the other terminal end of the alkyl chain because these are the typical functional groups that are required to control the regioselectivity in the subsequent hydroformylation step (Scheme 2). In principle, the anionic group

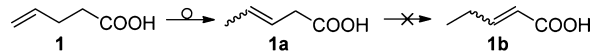
Scheme 2



of the substrate is involved in hydrogen bonding with the supramolecular catalyst used, allowing for precise substrate preorganization at the catalytic center. The restricted freedom of the reactive double bond allows for its highly regioselective hydroformylation (Scheme 2).[15] In addition, this class of substrates is easily accessible, also via isomerizing olefin cross-metathesis of bioavailable fatty acids.[16] The carboxylic group is also one of the most common functional groups in organic molecules, and as such, it can be useful in further product synthesis. Indeed, the targeted α-methyl-branched aldehydes with a carboxylic group represent a class of important building blocks in synthesis of some pharmaceuticals and natural products.[17]

We first optimized the isomerization reaction before attempting the cascade reaction. Initial experiments revealed that both the Pd^{II} and Ru^{II} "zipper"catalysts are active in the isomerization of the carboxyl-containing substrates, showing that the carboxylic group does not interfere with the alkene isomerization. Interestingly, the activity of the Pd catalysts can be readily switched off at the optimal alkene product distribution by the addition of base (e.g., triethylamine), and the Ru catalyst remains active under these conditions. For one-pot cascade reactions this turning off the isomerization activity is important because it allows one to limit the formation of later isomerization products that are detrimental for the overall selectivity, and as such, the Pd catalytic system was used in further studies. Further experiments reveal that a mixture of $[(allyl)PdCl]_2$, PPh_3, and AgOTf provides a catalytically active system already at room temperature in CH_2Cl_2 without the necessity of using any activating additives (e.g., ethylene or diallyl ether).[12] 4-Pentenoic acid (**1**) is smoothly isomerized to 3-pentenoic acid (**1a**), reaching a 3:97 substrate-to-product ratio (Scheme 3). The reverse reaction, that is, starting from

Scheme 3. Isomerization of 4-Pentenoic Acid (1) by the Pd-PPh_3 Catalyst



pure 3-pentenoic acid, leads to the same product distribution, confirming that this is the equilibrium. The catalyst loading can be significantly lowered (see Supporting Information Figure S1), although the equilibrium is reached after a longer reaction time, that is, 20 h with 0.5 mol % Pd catalyst. Importantly, in none of these experiments is overisomerization to 2-pentenoic acid (**1b**) observed, even upon prolonged reaction time and high catalyst loadings.

Next, we studied the isomerization of longer substrates for which the primary products can also be expected to tend to undergo subsequent isomerization steps as a result of the unsubstituted allylic and homoallylic positions in the substrate carbon chain.[11−14] Indeed, the isomerization of 5-hexenoic acid (**2**) leads to a mixture of isomeric products, 4-hexenoic (**2a**) and 3-hexenoic (**2b**) acids (Figure 1). However, double isomerization is observed only after most of the 5-hexenoic acid (**2**) was converted. From the plot of product distribution versus time, a clear window is visible in which **2a** is the dominant product in the mixture, with the best ratio of 1:22:2 for components **2** to **2a** to **2b**. Similarly, isomerization of 6-heptenoic acid (**3**) leads to a mixture of components, yet it can be stopped at 92% of the primary product, 5-heptenoic acid (**3a**), with only 6% of the secondary product, 4-heptenoic acid (**3b**), and 2% of the substrate left (Supporting Information Figure S2). This clearly shows that the primary isomerization of the terminal double bond is much faster than the subsequent one (around 60 times faster in the case of substrate **2**). Such a high relative reaction rate, in principle, allows for the kinetic control of the monoisomerized product formation.

With optimized conditions for alkene monoisomerization in hand, we approached the hydroformylation of a series of terminal alkenes with a carboxylic group, **1**−**5**. In a typical reaction, we stir a 1 M solution of the substrate with 0.5 mol %

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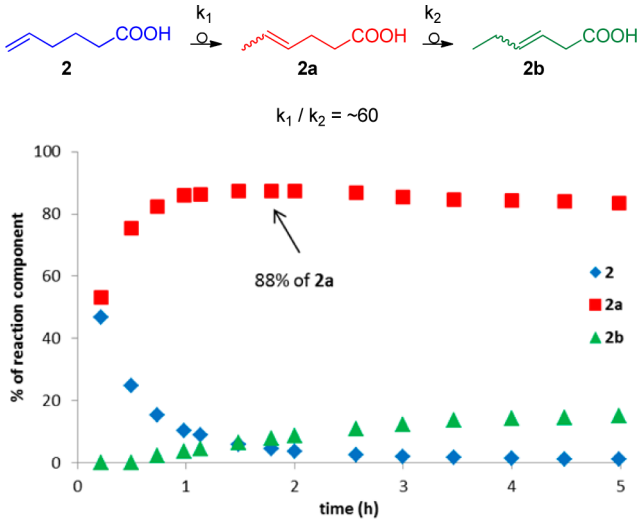
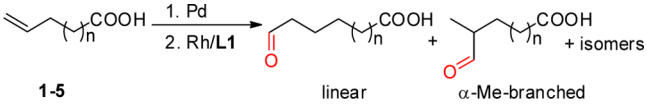


Figure 1. Isomerization of 5-hexenoic acid (**2**) by the Pd-PPh_3 catalyst (10 mol %).

of palladium catalyst for 24 h, after which we add triethylamine (90 mol %) as the base to stop the isomerization reaction. Next, we add a solution of $Rh(acac)CO_2$ (1 mol %) and the ligand **1** (1.1 mol %) and pressurize the autoclave with 10 bar of syngas (H_2/CO 1:1) to initiate the hydroformylation reaction performed at 50 °C. Under these conditions, in the case of all the substrates studied, the α-methyl-branched aldehyde was the major product after the cascade reaction, confirming the feasibility of the developed strategy (Table 1).[18] Substrates **1**–**3**, 4-pentenoic through 6-heptenoic acids, are hydroformylated to the α-methyl-branched aldehydes with unprecedented regioselectivities between 85 and 88%, and yields up to 85%. Longer substrates **4**–**5**, 7-octenoic and 8-nonenoic acids, react with lower regioselectivites, 69 and 48%, respectively. The diminished selectivity can be attributed to the inherent lower regiocontrol of the catalyst used for the longer substrates in the second (hydroformylation) step.[15a] Notably, for all substrates **1**–**5**, the linear aldehyde product that would be typically formed from the terminal alkene is identified as a minor product, (3–12%).

Table 1. Isomerization–Hydroformylation Sequence for Substrates 1-5 with the Pd-PPh_3 and Rh-L1 Catalysts[a]



		regioselectivity			
subs	*n*	% linear	% α-Me-branched	% isomers	% conv. to aldehydes
1	1	7	**88**[b]	5	92
2	2	3	**85**[b]	12	100
3	3	5	**85**	10	81
4	4	6	**69**	26	56
5	5	12	48	40	29

[a]Reagents and conditions: (1) $[(allyl)PdCl]_2/PPh_3$/AgOTf/substrate = 1:2:2:200, [Pd] = 5 mM, CH_2Cl_2, at room temp, 24 h, OTf^- = $CF_3SO_3^-$. (2) $[Rh(acac)(CO)_2]$/**L1**/substrate/TEA = 1:1.1:100:90; [Rh] = 2 mM, 10 bar CO/H_2 (1:1), CH_2Cl_2, 50 °C, 72 h, TEA = triethylamine. Chemo- and regioselectivity (%) were determined by ^{1}H NMR analysis of the reaction mixture. [b]The major product was isolated, and its structure was confirmed by comparison with the actual sample. For full experimental details see the Supporting Information.

In conclusion, we report here a new strategy for the synthesis of α-methyl-branched aldehydes via a one-pot stepwise selective isomerization-hydroformylation protocol. Whereas the more classic one-pot simultaneous isomerization-hydroformylation gives access to the linear aldehydes from internal alkenes,[19] the current strategy leads to branched aldehydes from terminal alkenes. The two transformations, the terminal alkene isomerization and the regioselectively hydroformylation, need to be done sequentially because of the much higher reactivity of the terminal alkenes in hydroformylation. For the hydroformylation step, we have applied our previously developed supramolecular DIMPhos ligand that preorganizes the substrate on the metal complex such that only one of the two possible regioisomers forms. The overall selectivity for the α-methyl-branched aldehyde from the terminal alkene is the highest reported in the literature to date,[7] which makes this in combination with the accessibility of the starting materials from renewable resources an attractive route to these valuable intermediates for synthetic targets.[7a,8] In principle, this strategy can also give access to the C-3 branched aldehydes utilizing appropriate hydroformylation catalysts.[3d,20] It can also be combined with reactions of alkenes other than hydroformylation. Current efforts will include the extension of the cascade protocol to other selective olefin transformations.

■ ASSOCIATED CONTENT

Supporting Information

Details concerning materials and methods, catalytic and kinetic experiments. This information is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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(18) Although both ligand **L1** and the branched aldehyde products are chiral, the enantiomeric excess (ee) was not determined because in the original study on Rh−ligand **L1** catalyst, no enantioselectivity was observed for analogues products; see ref 15a.

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