Homogeneous Catalysis

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Remote Control of Regio- and Diastereoselectivity in the Hydroformylation of Bishomoallylic Alcohols with Catalytic Amounts of a Reversibly Bound Directing Group**

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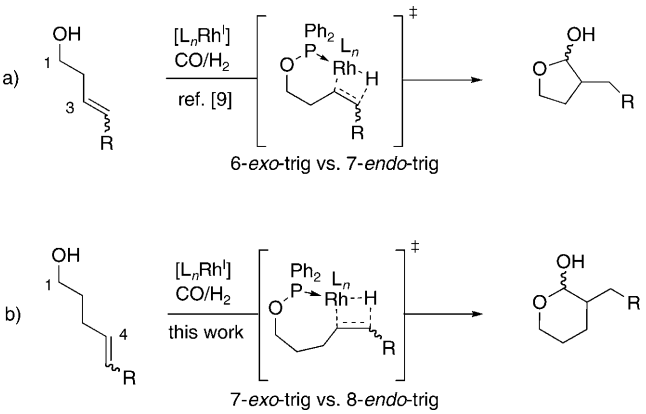
The hydroformylation of olefins is the largest volume application of homogeneous catalysis in industry with about 9 million tons of oxo products produced worldwide each year.[1,2] In this transformation alkenes are reacted with synthesis gas in the presence of a metal catalyst to furnish the homologated aldehydes—a conversion in complete accord with the criteria of atom economy.[3] The aldehydes formed are useful functional groups suitable for further skeleton-expanding transformations, which may be performed even as tandem processes.[4] Despite these obvious advantages, the hydroformylation of olefins is still not commonly employed in the course of a complex synthesis, because of the difficulty in controlling regio- and stereoselectivity simultaneously. A number of catalysts exist today that allow the hydroformylation of terminal aliphatic alkenes to give linear products selectively (linear-selective).[5] Conversely, no catalyst is known for a general hydroformylation of terminal and internal alkenes to give branched products selectively (branched-selective).[6] One solution to this problem has been the use of removable catalyst-directing groups covalently bound to the substrate that facilitate both regiocontrol and acyclic stereocontrol in reactions of allylic and homoallylic alcohols.[7] However, an obvious drawback of this approach is the requirement of additional steps for introduction and removal of the directing group as well as the need for stoichiometric amounts. More preferable would be the use of catalytic amounts of the directing group, as we have recently shown in a supramolecular approach based on complementary hydrogen bonding between the substrate and the catalyst system.[8] Alternatively, we and others have reported on the use of catalyst-directing groups which bind covalently but reversibly to the substrate.[9,10,11] Thus, we identified diphenylphosphinites as ideal systems for the reversible transesterification of alcohols under hydroformylation conditions. Hence, a highly regioselective hydroformlyation of homoallylic alcohols could be realized using this catalyst system to furnish γ-lactols in excellent yields (Scheme 1 a).[9] The basis for the observed high regioselectivity is the preference for the transition state of an intramolecular 6-*exo*-trig hydrometallation over that of the 7-*endo*-trig alternative. Here, the



Scheme 1. Remote control of regioselectivity in the hydroformylation of homoallylic and bishomoallylic alcohols.

functional hydroxy group to which the directing group is bound has a 1,3-relation to the reacting functional group; this is the maximum distance ever reported in directed hydroformylation to achieve efficient substrate control.[2]

We herein report that it is possible to shift the hydroxy function to which the directing group becomes bound yet one more atom further away from the reacting functional alkene group into a remote 1,4-relation (Scheme 1 b) and still get excellent levels of both regioselectivity and diastereoselectivity in the course of the hydroformylation. This can serve in the atom-economical preparation of a wide range of δ-lactols and lactones and even structural units of polypropionate natural products, all of which are important building blocks in organic synthesis.

We began our studies on hydroformylation of pent-4-en-1-ol (**1**) employing the reaction conditions we developed previously for the position-selective hydroformylation of homoallylic alcohols (Table 1). To our surprise, a smooth hydroformylation reaction was observed with excellent levels of regioselectivity in favor of the branched product, the δ-lactol **2** (Table 1, entry 1). However, the reaction was slower than in the case of homoallylic alcohols, and thus conversion

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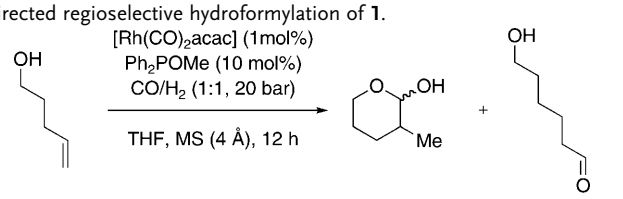
Table 1: Optimization of the reaction conditions for the phosphinite-directed regioselective hydroformylation of **1**.



1 **2** **3**

Entry	*T* [°C]	Conv. [%][a]	**2**/**3**[a]
1	40	71	95:5
2	60	Quant.	97:3

[a] Determined by ^{1}H NMR spectroscopy. acac = acetylacetonate

was incomplete under these conditions. Finally, when the reaction temperature was increased to 60 °C, complete conversion was attained after 12 hours with even improved regioselectivity (Table 1, entry 2).

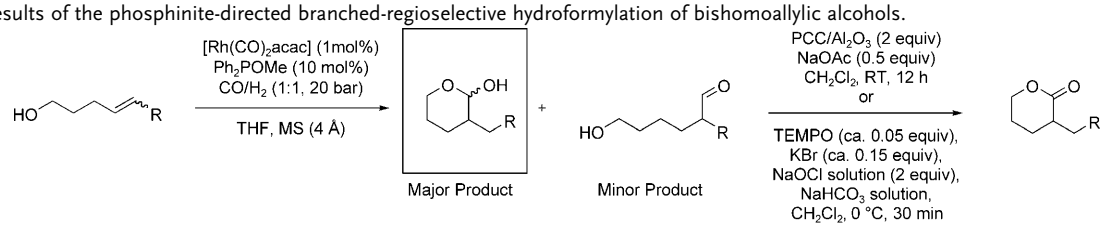
Next, we turned our attention to bishomoallylic alcohol derivatives with 1,2-disubstituted alkene functions. It should be noted that the regioselective hydroformylation of 1,2-disubstituted alkene units is one of the major challenges in hydroformylation chemistry, and only a few special solutions have been reported.[12] For the hydroformylation of bishomoallylic alcohol substrates with internal alkene units the reaction temperature had to be raised further to 80 °C and the reaction time had to be extended to 16 hours to compensate for the reduced reactivity of the internal double bond and to achieve full conversion. With these optimized conditions in hand we were pleased to find that in all cases the reaction proceeded smoothly to furnish (after oxidation) the corresponding δ-lactones in good to excellent yields (Table 2).

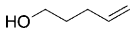
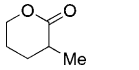
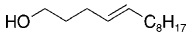
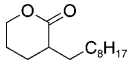
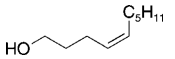
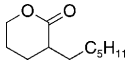
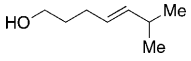
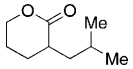
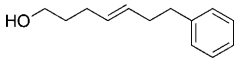
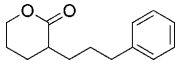
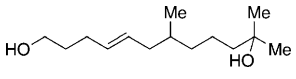
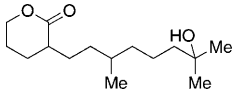
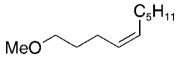
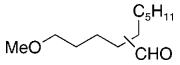
Substrates with *Z*- and *E*-configured alkene functions gave similar results (Table 2, entries 2 and 3). A sterically more demanding secondary alkyl substituent in 5-position was tolerated as well (Table 2, entry 4). Even an unprotected hydroxy function in the side chain did not affect the reaction selectivity (Table 2, entry 6).

To simplify product analysis, the primary δ-lactol products were oxidized in all cases to the corresponding δ-lactones by employing either the convenient reagent pyrdinium chlorochromate (PCC) or by using the more environmentally benign 2,2,6,6-tetramethyl-1-piperinoxyl radical (TEMPO) (Tables 2 and 3). It should be noted that the intermediate δ-lactols are not just substrates for oxidation reactions yielding lactones; they also represent valuable starting materials for further skeleton expansions that proceed on the aldehyde oxidation level, for example, the Wittig olefination.[13]

To highlight the directing effect of the phosphinite ligand system we conducted a second hydroformylation with each substrate employing the standard rhodium/triphenylphosphine system. As expected, in each case we observed the

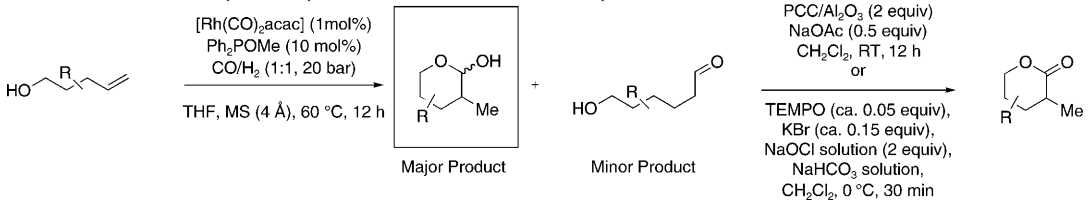
Table 2: Results of the phosphinite-directed branched-regioselective hydroformylation of bishomoallylic alcohols.

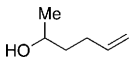
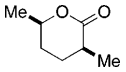
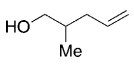
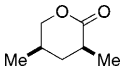
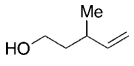
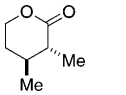
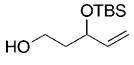
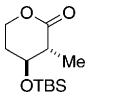


Entry	Substrate	Major product	Hydroformylation conditions	Oxidation conditions	Yield lactone [%]	r.r.[a]
1			60 °C, 12 h	PCC	86	97:3 (31:69)[b]
2			80 °C, 16 h	PCC	84	99:1 (53:47)
3			80 °C, 16 h	PCC	87	99:1 (53:47)
4			80 °C, 16 h	PCC	77	99:1 (70:30)
5			80 °C, 16 h	TEMPO	88	98:2 (50:50)
6			80 °C, 16 h	PCC	69	97:3 (53:47)
7			80 °C, 16 h	–	n.i.[d]	51:49[c] (51:49)[c]

[a] r.r. = Regioisomer ratio. Regioselectivity of the hydroformylation reaction determined by ^{1}H NMR spectroscopy at the stage of the lactol and open-chain aldehyde. In brackets: Regioselectivity of the hydroformylation with 10 mol% PPh_3 as the ligand under otherwise identical conditions. [b] Detection of additional lactol peaks, probably arising from isomerization and hydroformylation. [c] Determined by GC methods. Assignment of the two aldehydes is exchangeable. [d] Not isolated.

Table 3: Acyclic stereocontrol in the hydroformylation of substituted bishomoallylic alcohols.

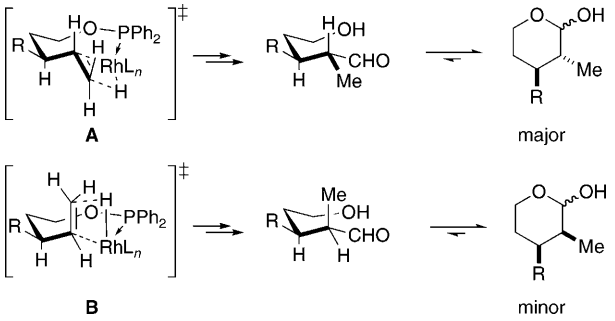


Entry	Substrate	Major product	Oxidation conditions	Yield lactone [%]	r.r.[a]	*cis*/*trans*[b]
1			TEMPO	99	97:3 (27:73)[c]	68:32
2			PCC	78	99:1 (38:62)[c]	61:39
3			TEMPO	82	99:1 (22:78)[c]	4:96
4			TEMPO	99	99:1 (32:68)[c]	6:94

[a] Regioselectivity of the hydroformylation reaction determined by ^{1}H NMR spectroscopy at the stage of the lactol and open-chain aldehyde. In brackets: Regioselectivity of the hydroformylation with 10 mol% PPh_3 as the ligand under otherwise identical conditions. [b] Diastereoselectivity was determined at the stage of the lactone by ^{1}H NMR spectroscopy. [c] Detection of additional lactol peaks, probably arising from isomerization and hydroformylation.

formation of mixtures of the two possible regioisomers and no regioselectivity (Table 2, regioselectivity values in parentheses). To test the function of the phosphinite as an exchangeable catalyst-directing group, we blocked the free hydroxy group by formation of the corresponding methyl ether (Table 2, entry 7). Thus, subjection of the methyl ether of *cis*-4-decene-1-ol to the optimized conditions for the phosphinite-directed hydroformylation gave a dramatically reduced conversion (3% by GC analysis) and furnished a mixture of regioisomers. Thus, both observations—the dramatic rate acceleration and the high regioselectivity in the phosphinite/bishomoallylic alcohol system—indicate that this reaction proceeds by a directed pathway through covalent but reversible substrate binding.

Next, we were interested in whether we could induce additional diastereoselectivity in the course of this directed regioselective hydroformylation reaction. Therefore, we investigated bishomoallylic alcohol substrates with a methyl-group-bearing tertiary stereogenic center either in the 1-, 2-, or 3-position (Table 3, entries 1–3). A stereogenic center in the 1- or 2-position does not result in any significant stereoinduction; however, when the stereogenic center was adjacent to the alkene function, high levels of acyclic stereocontrol (Table 3, entry 3) in favor of the *trans* diastereomer were observed.[14,15] A rational for the observed stereodiscrimination is provided in Scheme 2. Thus, the transition state for the 7-*exo*-trig hydrometallation, in which allylic 1,3-strain is minimized (**A**), is preferred over the competing transition state, in which allylic 1,2-strain is minimized (**B**). We also examined a substrate with a sterically less demanding 3-*tert*-butyldimethylsilyloxy (OTBS) substituent. Here, too, high levels of regio- and stereocontrol were achieved (Table 3, entry 4). Noteworthy, the resulting product



Scheme 2. Rational for acyclic stereocontrol in the directed hydroformylation of 3-substituted bishomoallylic alcohols.

is an interesting building block for the construction of polypropionates, which are now available through this method; this synthetic approach exploits all the advantages of the hydroformylation reaction such as atom efficiency and low loadings of the transition-metal catalyst.

In conclusion we have documented the first highly regio- and diastereoselective hydroformylation of terminal and internal bishomoallylic alcohols in which only a catalytic amount of a catalyst-directing group is employed. To our knowledge the distance between the double bond and the functional group to which the directing group is bound is the longest ever reported. The described method is mild, highly selective, and tolerant of many functional groups. The new method allows for atom-economical preparation of a wide range of δ-lactols and lactones and even structural units of polypropionate natural products—all of which are important building blocks in organic synthesis. Future studies will address the problem of enantioselectivity as well as the

application of similar directing systems to other catalytic reactions.

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Keywords: diastereoselectivity · homogeneous catalysis · hydroformylation · regioselectivity · synthetic methods

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[13] For example: R. W. Hoffmann, H.-J. Zeiss, W. Ladner, S. Tabche, *Chem. Ber.* **1982**, *115*, 2357 – 2370.

[14] An additional interesting observation of the experiment described in Table 2, entry 1 is that even secondary hydroxyl functions can undergo the phosphinite transesterification process as exemplified by the high levels of regioselectivity obtained.

[15] While diastereoselectivity for substrates with stereogenic centers in the 1- or 2-position was low, it should be noted that a subsequent adjustment of the stereocenter in α-position to the lactone carbonyl group is readily achievable under basic conditions. See for example: S. Takano, K. Masuda, K. Ogasawara, *J. Chem. Soc. Chem. Commun.* **1980**, 887 – 888.

