Homogeneous Catalysis

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Branched-Regioselective Hydroformylation with Catalytic Amounts of a Reversibly Bound Directing Group**

*Christian U. Grünanger and Bernhard Breit**

Selectivity in a synthetic transformation can be controlled either by the reagent or, alternatively, by the substrate. The latter is particularly efficient if attractive substrate–reagent interactions are involved, since it allows the formation of a highly ordered cyclic or polycyclic transition state, which in turn, if properly designed, enables efficient energetic discrimination of competing reaction pathways, resulting in high levels of selectivity. Reactions relying on this principle are termed substrate-directed reactions,[1] and, as a result of their ability to reliably install new functionality and stereochemistry in a predictable manner, they represent important tools in organic synthesis. More recently, the specific installation of substrate-bound removable directing groups has been shown to specifically enforce the desired substrate–reagent interaction, and has extended the range of possible directed reactions towards many synthetically important transition-metal-catalyzed and mediated reactions, including C–H activation.[2–4] However, an obvious drawback of this approach is the requirement for stoichiometric amounts of the directing group, which has to be installed and removed in extra synthetic steps. One way to render this approach more efficient is the multiple use of one directing group in a sequence of reactions, as demonstrated in a recent total synthesis of α-Tocopherol.[5] However, yet more preferable is the use of catalytic amounts of the directing group, as has been achieved recently using supramolecular approaches, such as hydrogen bonding between suitable functional groups within the substrate and complementary functions in the directing ligand.[6] Alternatively, one might design a catalyst-directing group (CDG) that could bind the substrate in a covalent but reversible fashion (Figure 1). First steps towards this goal have been made in special cases of C–H activation.[7,8] However, the principle is more general and should be applicable to a wide range of catalytic reactions, such as the industrially important rhodium-catalyzed hydroformylation.[9]

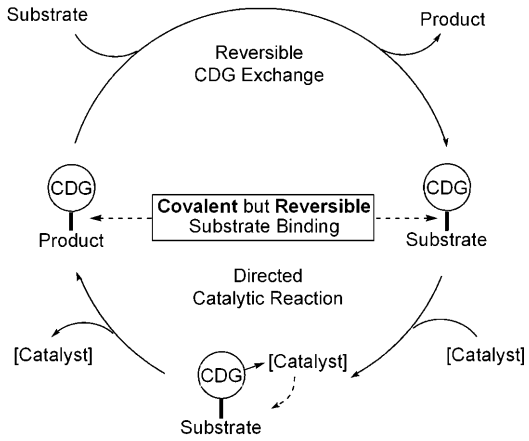

Figure 1. The concept of a catalyst-directing group (CDG) needed only in catalytic amounts through reversible covalent substrate binding.

We report herein on the application of phosphinites as reversibly bound catalyst-directing groups for the highly branched-regioselective hydroformylation of homoallylic alcohols with terminal and internal alkene functions to furnish synthetically attractive γ-lactol and γ-lactone building blocks.

Regiocontrol in the course of the hydroformylation is a difficult problem of industrial and academic importance.[10] Many catalysts exist which allow for linear selective hydroformylation of terminal alkenes. Conversely, no catalyst is known for a general branched-selective hydroformylation of terminal and internal alkenes.[11] However, substrate-bound directing phosphite and phosphine groups can alter the regiochemical outcome of the hydroformylation in favor of the branched aldehyde product.[12]

We thus began our studies with the identification of an efficient covalently bound directing group, which would have the potential for a reversible exchange with a hydroxy function. For this purpose we focused on phosphinites, which might be ideal candidates for two reasons. Firstly, the reversible exchange with phenols and alcohols in the presence of basic or acidic catalysts is known.[8,13] Secondly, attachment of a PR_2 group to the hydroxy function of a homoallylic alcohol might allow for a favorable six- versus seven-membered chelate, which should favor the branched aldehyde product, which cyclizes immediately to the corresponding γ-lactol (see below, Scheme 1).

Thus, homoallylic alcohol **1** and the corresponding phosphinite **2** were subjected to the conditions of hydroformylation employing a standard rhodium catalyst. As

[*] Dipl.-Chem. C. U. Grünanger, Prof. Dr. B. Breit
Institut für Organische Chemie und Biochemie
Freiburg Institute for Advanced Studies (FRIAS)
Albert-Ludwigs-Universität Freiburg
Albertstrasse 21, 79104 Freiburg i. Brsg. (Germany)
Fax: (+49) 761-203-8715
E-mail: bernhard.breit@chemie.uni-freiburg.de

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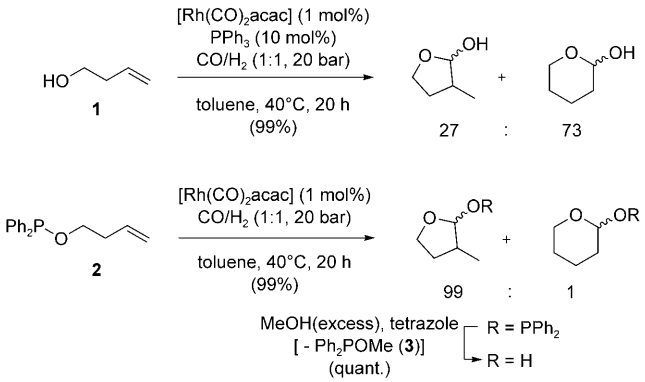
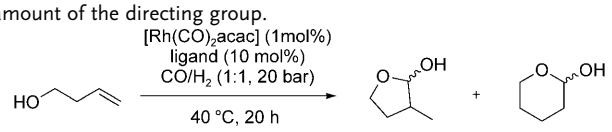


Scheme 1. Hydroformylation of homoallylic alcohol **1** with and without a covalently bound catalyst-directing phosphinite group (**2**). acac = acetylacetonoate.

expected, the alcohol substrate **1** reacted with the standard triphenylphosphine/rhodium catalyst to give a mixture of the regioisomeric γ- and δ-lactols (27:73). Once more this result illustrates that a hydroxy group is unsuited to function as a directing group in the course of the hydroformylation.[14] Conversely, the reaction of phosphinite **2** proceeded completely regioselectively, in favor of the branched regioisomer. The primary reaction products were the lactol phosphinites. Liberation of the lactols was easily achieved upon reaction with methanol in the presence of catalytic amounts of tetrazole.[15] Hence, a transesterification of a phosphinite from the reaction product to another alcohol substrate is possible, and may work under hydroformylation conditions.

Hydroformylation of homoallylic alcohol **1** was probed using catalytic amounts (10 mol%) of phosphinite **2** in the presence of potential transesterification catalysts tetrazole, cesium carbonate, potassium phosphate, and lithium chloride (Table 1).

Table 1: Development of the hydroformylation procedure with a catalytic amount of the directing group.



Entry	Ligand	Additive	Solvent	Conv. [%][a]	Regioselectivity[a] (γ:δ)
1	**2**	tetrazole 10 mol%	toluene	66[b]	46:54
2	**2**	Cs_2CO_3 10 mol%	toluene	24	45:55
3	**2**	K_3PO_4 10 mol%	toluene	36	41:59
4	**2**	LiCl 10 mol%	toluene	62	99:1
5	**2**	LiCl 1 mol%	THF	11	99:1
6	**2**	LiCl 0.1 mol% MS (4 Å)[d]	THF	99	97:3
7	**3**	MS (4 Å)	THF	99[c]	99:1

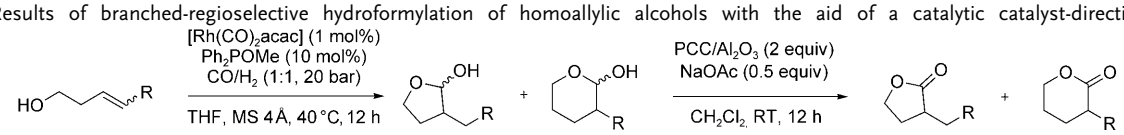
[a] Determined by GC. [b] Conversion after 6 h. [c] Complete conversion was reached after 6 h. [d] MS = molecular sieve.

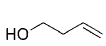
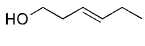
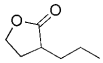
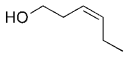
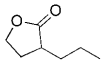
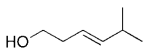
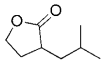
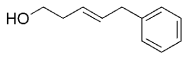
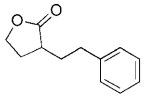
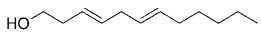
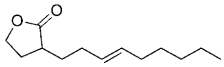
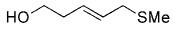
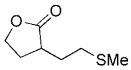
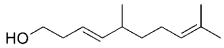
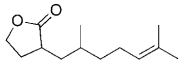
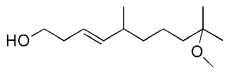
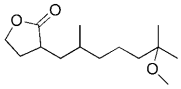
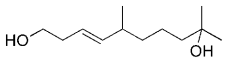
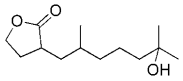
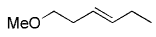
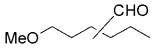
Thus, while addition of tetrazole provided an active hydroformylation catalyst system, the regioselectivity was low (Table 1, entry 1). Previous studies on C–H activation employing phosphinites had identified Cs_2CO_3 and K_3PO_4 as efficient promoters for transesterification.[8] Unfortunately, under the conditions of hydroformylation, low activity and poor regioselectivity were detected (Table 1, entries 2,3). We wondered whether a mild Lewis acid, such as LiCl, could promote transesterification. Thus, addition of 10 mol% LiCl furnished a reasonably active catalyst which proceeded with excellent regioselectivity (99:1, Table 1, entry 4). Lowering the amount of LiCl to 1 mol% and changing the solvent to THF to increase the solubility of the lithium salt led to a decreased catalyst activity while the regioselectivity remained high (Table 1, entry 5). Lowering the amount of LiCl further and addition of molecular sieves to remove traces of water furnished a very active catalyst, albeit with a slightly reduced regioselectivity (97:3, Table 1, entry 6). Interestingly, the reaction proceeded even in the absence of LiCl furnishing the best catalyst system. Thus, employing 1 mol% of rhodium catalyst and 10 mol% of the directing ligand **3**, in THF solvent at 40 °C and with a syngas pressure of 20 bar, were found to be the optimal conditions. After 6 h, complete conversion was reached and a perfect regioselectivity towards the branched regioisomer, the γ-lactol, was detected (Table 1, entry 7).[16]

With these optimized conditions in hand we next checked whether this catalyst system would allow also for regioselective hydroformylation of an internal alkene, which is one of the great challenges in hydroformylation chemistry.[17] We were pleased to find that in all cases the reaction proceeded smoothly with exceptional levels of regiocontrol to afford (after oxidation) the corresponding γ-lactones in good-to-excellent yields. Either *Z*- or *E*-configured alkenes could thus be employed with similar results (Table 2, entries 2 and 3). A sterically more demanding secondary alkyl substituent in 4-position was tolerated as well (Table 2, entry 4). Remarkably, reaction of a substrate functionalized with an additional 1,2-disubstituted alkene function (Table 2, entry 6) displayed a completely regioselective hydroformylation of the homoallylic alkene function. Furthermore, the reaction tolerates functional groups, such as thioethers, ethers, and free hydroxy groups (Table 2, entries 7, 9, and10).

Hydroformylation of the homoallylic alcohols with the standard rhodium/triphenylphosphine catalyst were also performed for comparison purposes, to give an insight into the role of the phosphinite ligand. In all cases mixtures of regioisomers were obtained (see Table 2, regioselectivity values in parentheses). Furthermore, hydroformylation of the methyl ether of (*E*)-3-hexenol with the phosphinite **3**/rhodium catalyst was studied (Table 2, entry 11). In this case the reaction was very slow (6% conversion after 12 h) while under the same conditions the corresponding homoallylic alcohol was quantitatively consumed after 8 h (Table 2, entry 2). Furthermore, the methyl ether furnishes a mixture of regiosomers (53:47, Table 2, entry 11) while in the case of the corresponding homoallylic alcohol, the γ-lactols were formed exclusively (Table 2, entry 2). These results are in accord with a directed reaction, and suggest that the role of **3**

Table 2: Results of branched-regioselective hydroformylation of homoallylic alcohols with the aid of a catalytic catalyst-directing group.



Entry	Substrate	Major Product	Conv. [%][a]	Yield lactones [%][b]	Regioselectivity[c] (γ:δ)
1			100	91	99:1 (27:73)
2			100[d]	85	>99 : <1 (54:46)
3			100[d]	88	>99 : <1 (52:48)
4			98	84	97:3 (65 :35)
5			84	92	99:1 (45:55)
6			81	83	97:3[e] (28:72)[e]
7			75	42	97:3 (48 :52)
8			93	99	99:1[f]
9			98	88	99:1[f]
10			85	99	99:1[f]
11			6[g]	not isolated	53:47 (54:46)

[a] Conversion determined by GC after hydroformylation. [b] Yields based on conversion of hydroformylation step. [c] Regioselectivity of the hydroformylation reaction determined at the stage of the lactols by GC and reconfirmed by NMR spectroscopy after oxidation to the corresponding lactones. In brackets: Regioselectivity of the hydroformylation with 10 mol% PPh_3 as the ligand under otherwise identical conditions. [d] Complete conversion after 8 h. [e] Regioselectivity of the major lactol vsersus all other products including double hydroformylated substrate. [f] Owing to the complexity of the GC trace (4 diastereomers of each lactol) the regioselectivity was determined by NMR spectroscopy of the corresponding lactones. Conversions of the hydroformylation with 10 mol% PPh_3 as the ligand under otherwise identical conditions were too low to allow for determination of regioselectivities. [g] Conversion after 12 h.

is as a catalyst-directing group, operating through reversible substrate- and catalyst-binding. A plausible catalytic cycle is given in Figure 2.

The first step of the reaction is the transesterification of homoallylic alcohol **1** by methyl phosphinite **3**, to furnish phosphinite **2**[18], which undergoes a regioselective directed hydroformylation, favoring the six-membered cyclic hydrometalation transition state to give aldehyde **4**. Subsequent transesterification with the substrate liberates the γ-lactol product, and furnishes phosphinite **2**, which enters a new hydroformylation catalysis cycle.

In summary, we have documented the first highly branched-regioselective hydroformylation of homoallylic alcohols with terminal and internal alkene functions employing catalytic amounts of a directing group. Thus, phosphinites were identified as ideal catalyst-directing groups undergoing transesterification with hydroxy functions under hydroformy-

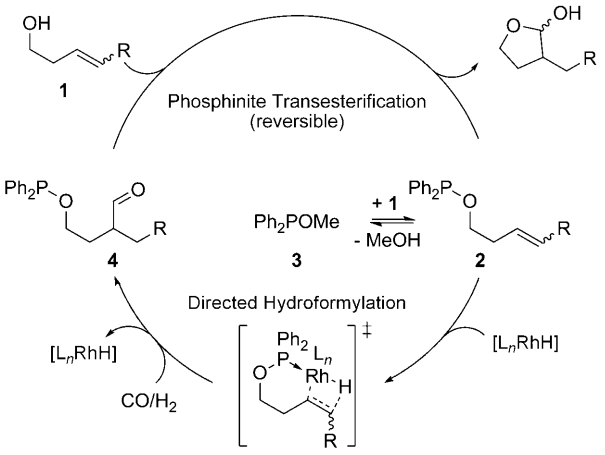


Figure 2. Proposed reaction scheme.

lation conditions without the need for additional transesterification catalysts. The method is mild, selective, and allows for the preparation of a wide range of γ-lactols and lactones which are useful building blocks for organic synthesis.

Future studies will address the problems of diastereo- and enantioselectivity as well as the application of similar directing systems to other catalytic reactions.

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[16] The presence of molecular sieve proved crucial. In its absence only low conversion, albeit with high regioselectivity, was detected.
[17] For regioselective hydroformylation of internal alkenes employing supramolecular catalyst strategies see: a) M. Kuil, T. Soltner, P. W. N. M. van Leeuwen, J. N. H. Reek, *J. Am. Chem. Soc.* **2006**, *128*, 11344 – 11345; and b) ref. [6].
[18] Preliminary mechanistic investigations indicate that the presence of rhodium(I) salts is essential for phosphinite transesterification under these conditions. For more details see the Supporting Information.

