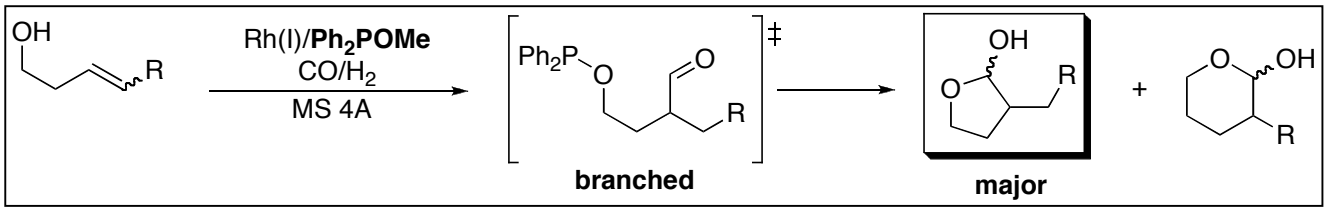
Branched-Regioselective Hydroformylation with Catalytic Amounts of a Reversibly Bound Directing Group



by Christian U. Grünanger and Bernhard Breit

Angew. Chem. Int. Ed. **2008**, *47*, *early view*

Karla Bravo

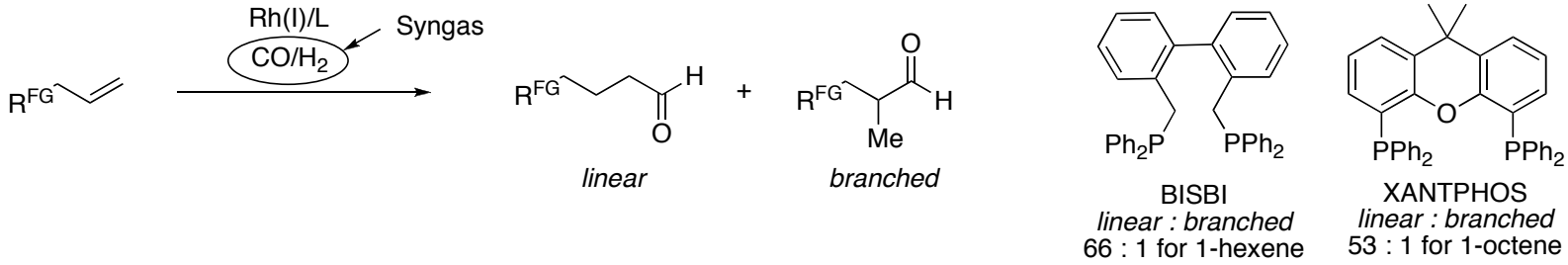
Current Literature

08/30/2008

Hydroformylation of olefins. *An industrial atom-economic C/C-bond forming reaction*

Important industrial process for the production of aldehydes and ketones: **> 7 million tons of oxo products/year.** Based on homogeneous catalysis: $HCo(CO)_4$ (Otto Roelen, 1938), rhodium(I)complexes, $RhH(CO)(PPh_3)_3$ (Wilkinson, 1968).

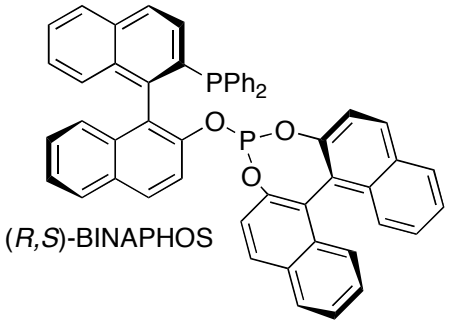
✓ *Linear-selective hydroformylation of terminal alkenes, Ligands (L): BISBI, XANTPHOS.*

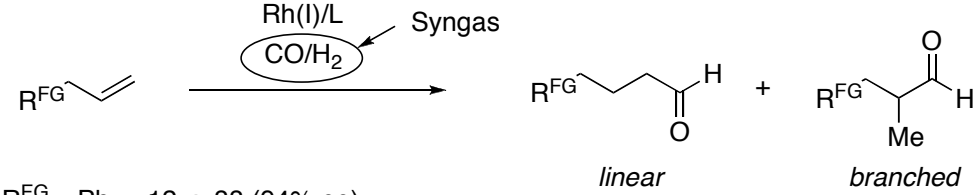


Synthetic challenge: *Control of Branched*-Regioselectivity

- *N*o catalyst is known for a general branched-selective hydroformylation of terminal and internal alkenes.
- Simultaneous control of both, enantio- and regioselectivity in enantioselective hydroformylations has not yet been achieved.

Ligand:





R^{FG} = Ph, 12 : 88 (94% ee)
R^{RG} = Et, 79 : 21 (83% ee)
R^{FG} = OAc, 14 : 86 (92% ee)

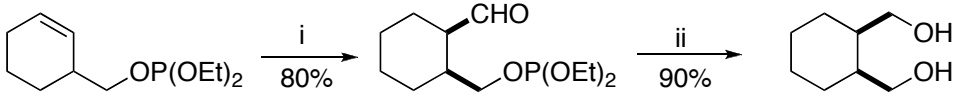
➡ *Efforts have been directed towards the development of a* ***Substrate-Directed Reaction***

Breit, B. *Acc. Chem. Res.* **2003**, *36,* 264-275

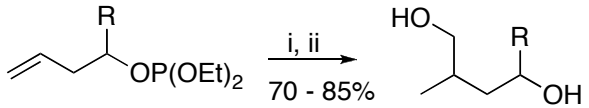
Towards the development of a branched-regioselective hydroformylation reaction…

Use of substrate-bound directing groups (stoichiometric amounts): phosphite and phosphine groups

- Chelation-control by phosphite esters in cyclic and acyclic homoallylic systems.



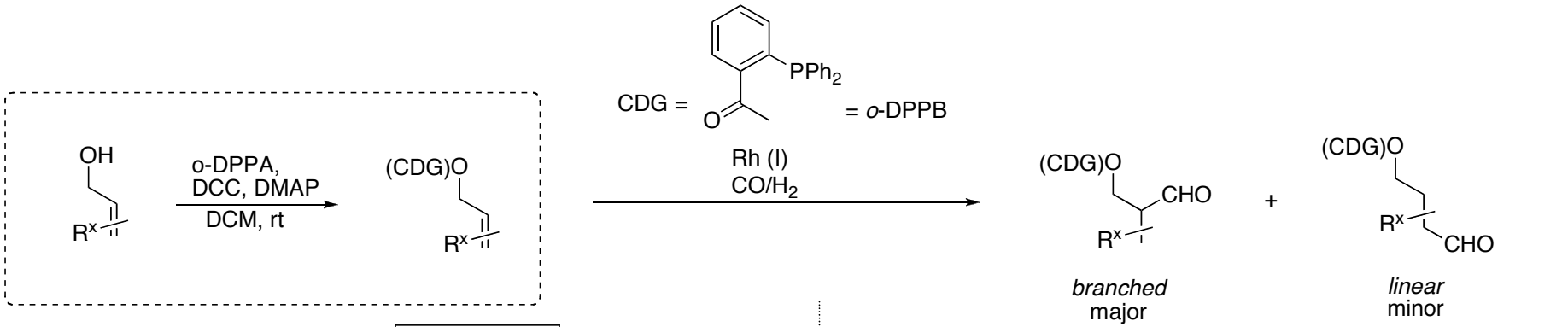
i. H_2/CO (1:1, 500 psi), $[Rh(OAc)_2]_2$ (alkene:Rh, 50:1), benzene, 100°C, 44h, ii. LAH, Et_2O

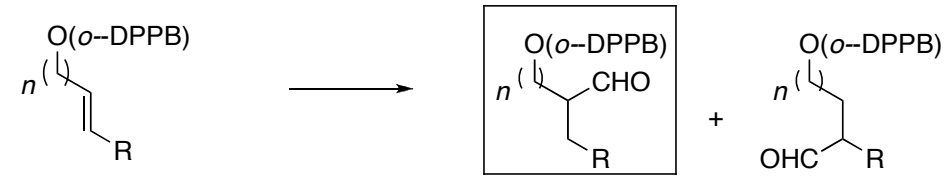


R = H, Me, Ph

Jackson, W. R. et al., *J. Chem. Soc. Chem. Commun.* **1990**, 763 – 764.

- Identification of *o*-DPPB esters (*ortho-(diphenylphosphanyl) benzoyl*) as efficient catalyst-directing groups (CDG) in the branched-selective hydroformylation of allylic esters.

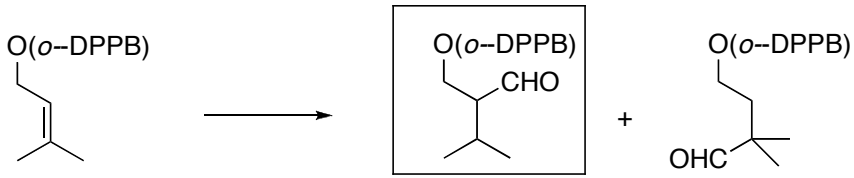




n = 1

R = H,	quant.,	97 : 3
R = *c*Hex,	84%,	81 : 19
R = TBDPS,	87%,	90 : 10

n = 2	**R = H,**	**89%,**	**58 : 42**



96 : 4 (quant.)

Breit ,B. *et. al. Eur. J. Org. Chem.* **2007**, 2497 – 2503.

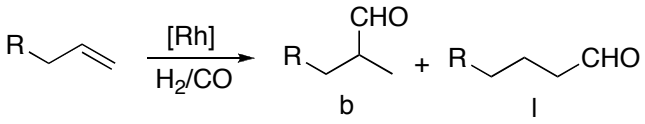
The concept of using catalytic amounts of a directing group to control regioselectivity

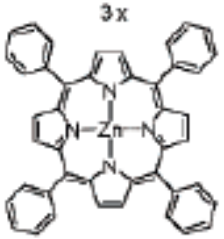
Use of catalytic amounts of a directing group

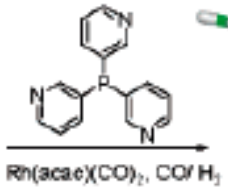
- *Supramolecular catalyst strategies*

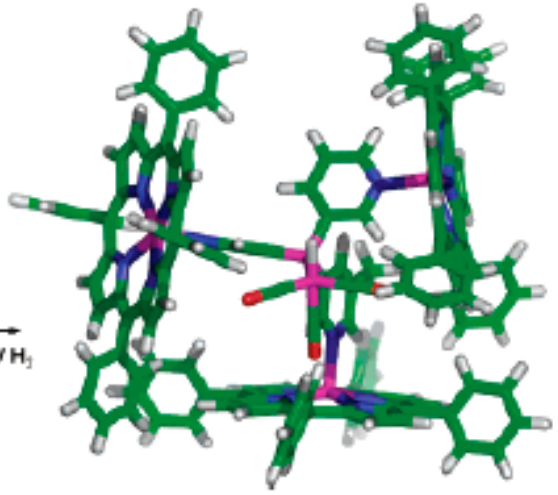
By Self-Assembly

(a) Encapsulated rhodium catalyst







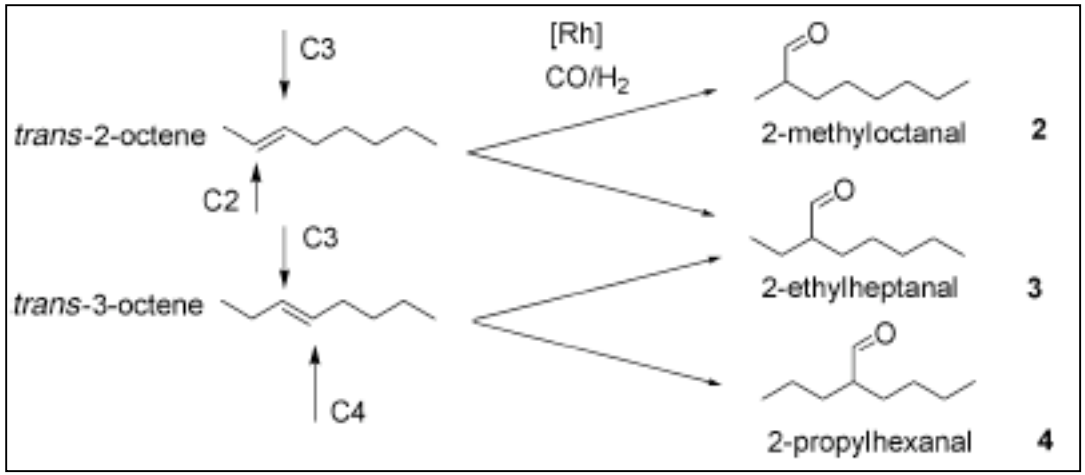


non-encansulapted cat. (l/b = 2.8)
encansulapted cat. (l/b = 0.6, 63% b)

non-encapsulated cat. **(25 °C): 17% conv., 2 (55.6%), 3 (43.8%)**
(80°C): 61% conv., **2** (53.3%), **3** (22.4%)

encapsulated cat. **(25 °C): 32% conv., 2 (9.4%), 3 (87.8%)**
(80°C): 88% conv., **2** (35.2%), **3** (20.9%)

Conditions: [Rh(acac)$(CO)_2$] = 0.7 mmol/L, toluene, P(H_2/CO) =10 bar, substrate/Rh = 1052, [phosphorus] = 6.4 mmol/L h



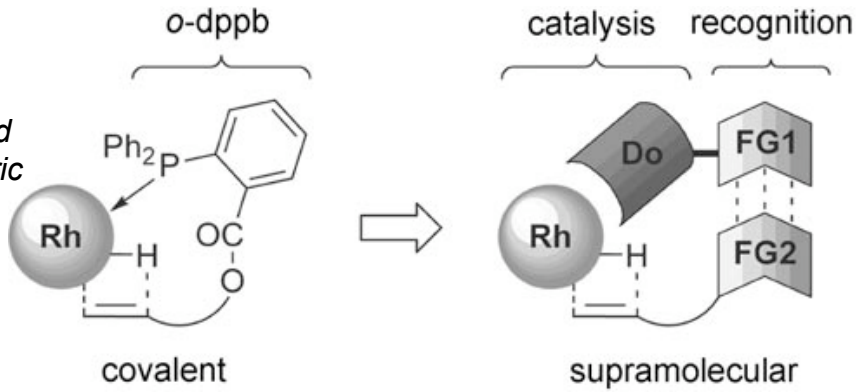
Reek, J. N. H. *et al. J. Am. Chem. Soc.* **2006**, 128, 11344-11345. Reek, J. N. H. *et al. Chem. Eur. J.* **2006**, *12*, 4218 – 4227.

The concept of using catalytic amounts of a directing group to control regioselectivity

(b) Mix. guanidine-phosphine based supramolecular ligand

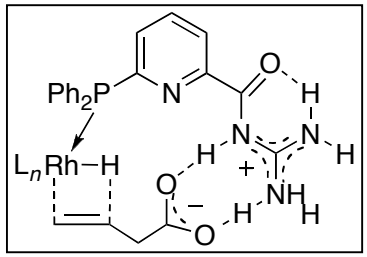
o-dppb

• Covalent ligand-substrate bond prevents use of substoichiometric amounts of the ligand.

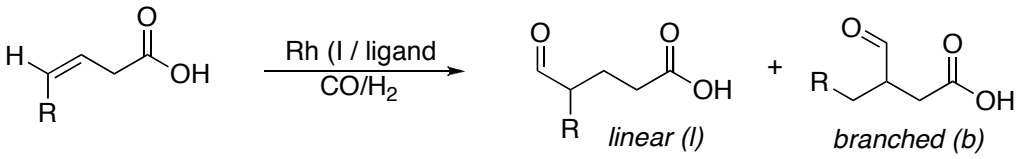


receptor-based ligand

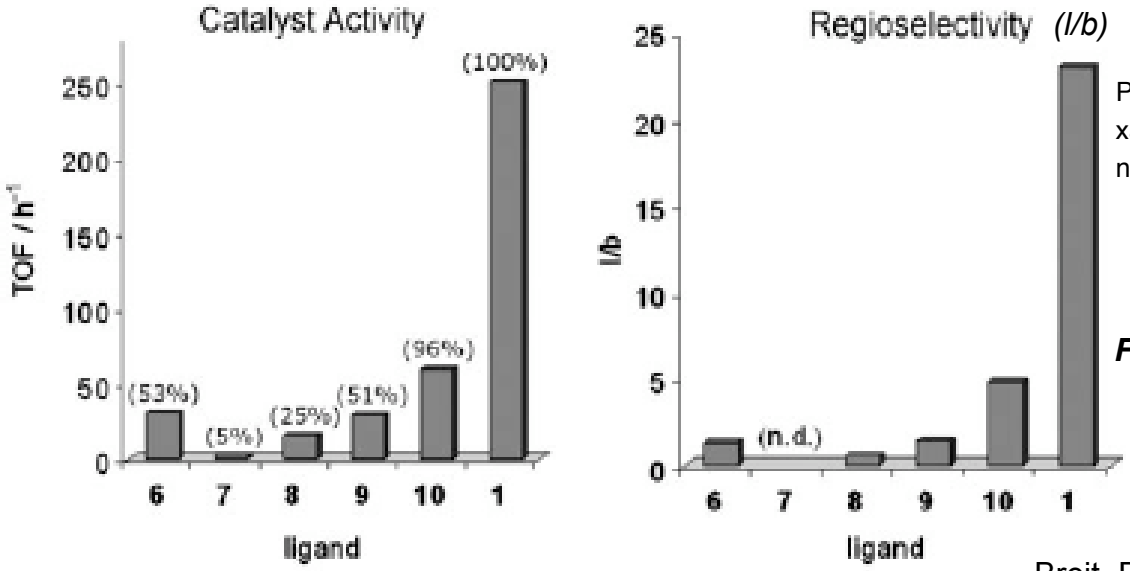
• Combination of phosphine ligand & guanidinium-bases recognition unit for carboxylic acid substrates



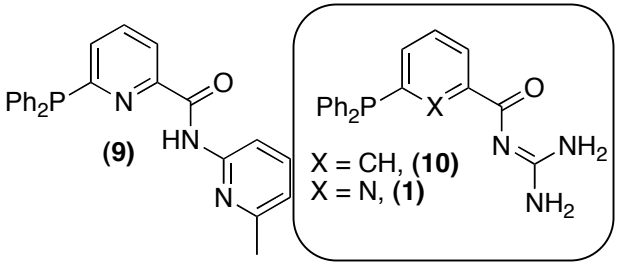
For R = H



For R = Me : a b



PPh_3 **(6)**
xantphos **(7)**
no ligand **(8)**



For an internal alkene, R=Me

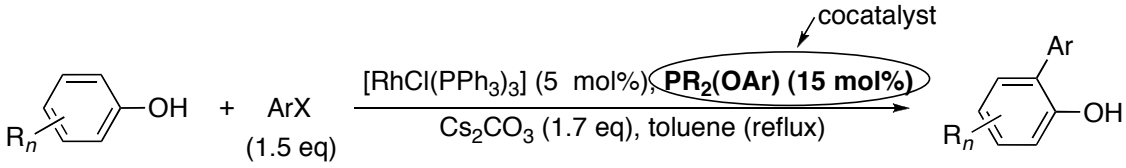
Ligand: **1**, 80.5% conv., **11:1 (a/b)**

Breit, B. *et. al. Angew. Chem. Int. Ed.* **2008**, *47*, 311 –315.

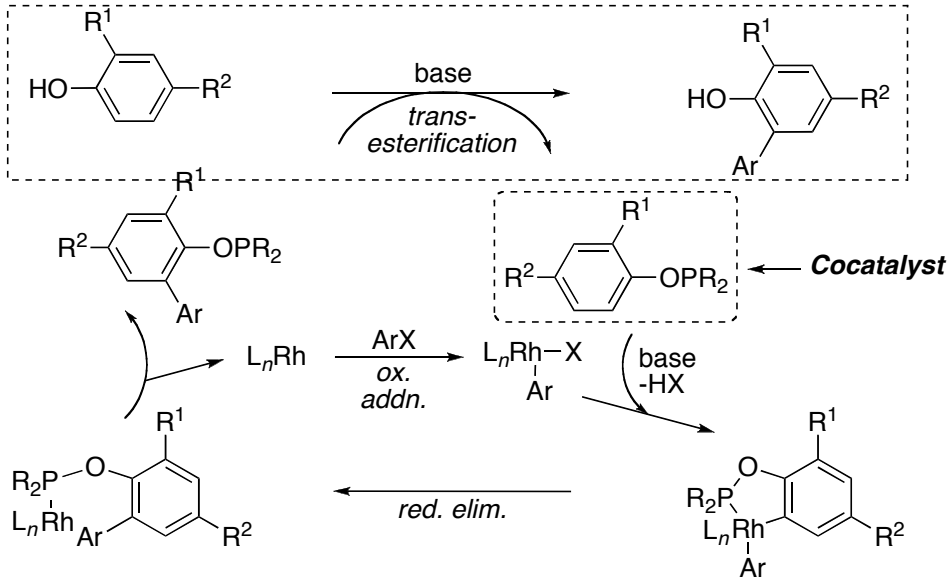
Title Paper: *"Use of catalytic amounts of phosphinites as reversible-bound directing groups for the branched regioselective hydroformylation of homoallylic alcohols"*

Why phosphinites?

o Reversible exchange with phenols and alcohols in the presence of basic or acidic catalysts.



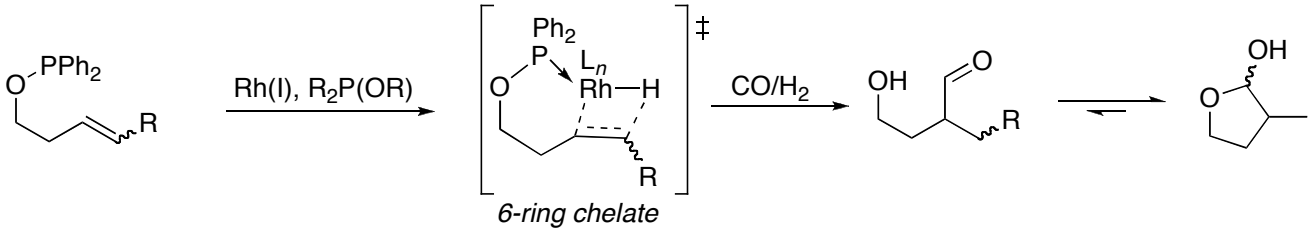
Bedford



Bedford, R. B. *et al. Angew. Chem. Int. Ed.* **2003**, *42*, 112-114.

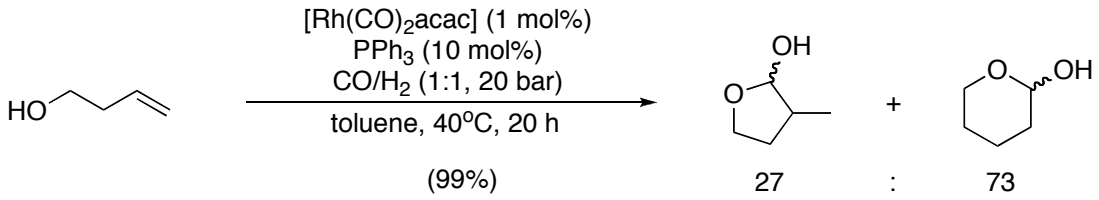
Title Paper: *Phosphinites do the trick …*

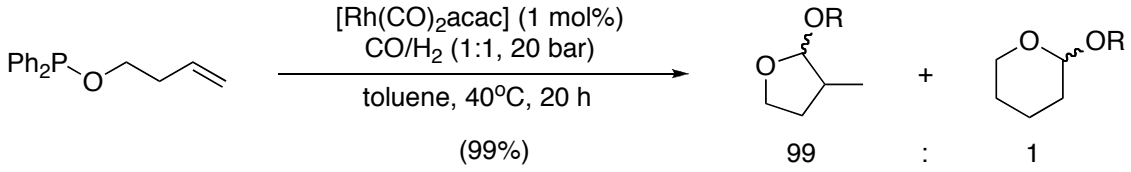
Hypothesis: *"Attachment of a PR_2 group to the OH group of an homoallylic alcohol might alllow the formation of a six- versus seven-memebered chelate, which should favor the branched aldehyde product."*

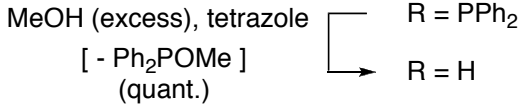


6-ring chelate

Proof of concept:



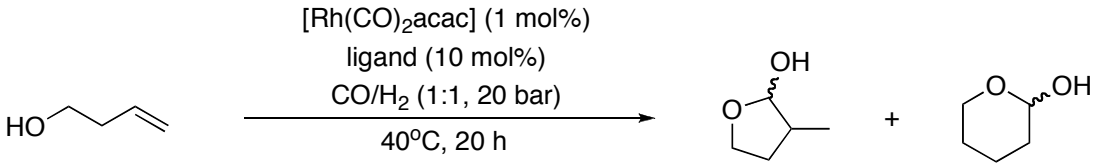




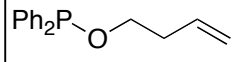
acac = acetylacetonate

Title Paper: *Phosphinites do the trick …*

Optimization of the branched-regioselective hydroformylation using catalytic amounts of phosphinites as CDG (CDG = catalyst directing group).



Ligands:



(2)

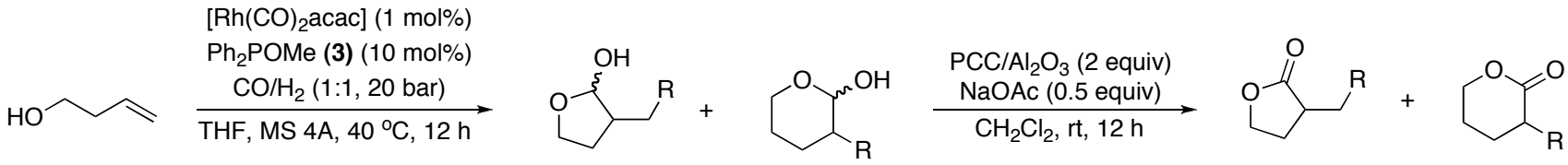
Ph_2POMe **(3)**

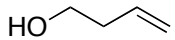
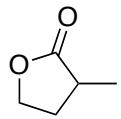
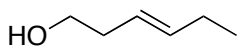
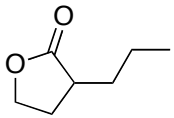
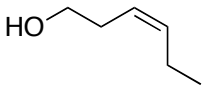
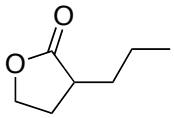
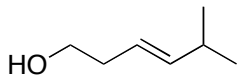
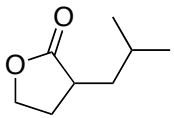
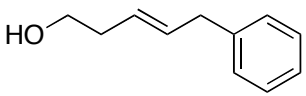
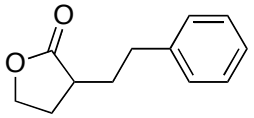
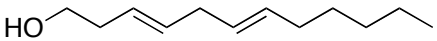
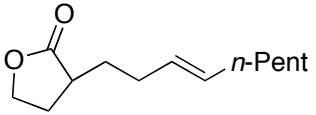
Entry	Ligand	Additive	Solvent	Conv. [%][a]	Regioselectivity[a] (γ:δ)
1	**2**	tetrazole 10 mol%	toluene	66[b]	46:54
2	**2**	Cs_2CO_3 10 mol%	toluene	24	45:55
3	**2**	K_3PO_4 10 mol%	toluene	36	41:59
4	**2**	LiCl 10 mol%	toluene	62	99:1
5	**2**	LiCl 1 mol%	THF	11	99:1
6	**2**	LiCl 0.1 mol% MS (4 Å)[d]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

Title Paper: *Phosphinites do the trick …*

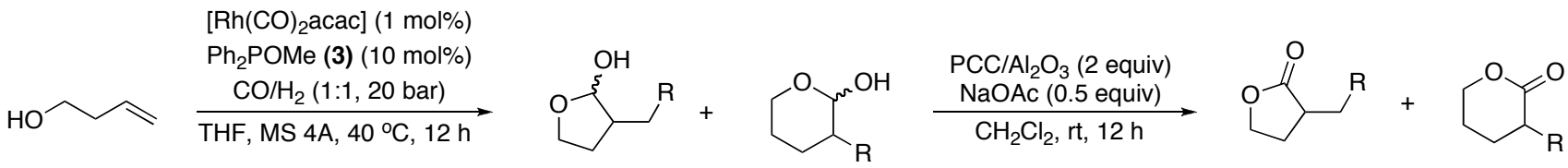
Development of the position-selective hydroformylation of homoallylic alcohols using a catalytic amount of a CDG

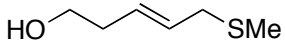
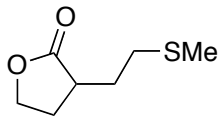
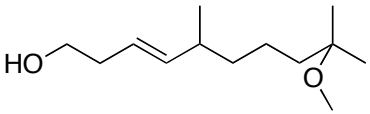
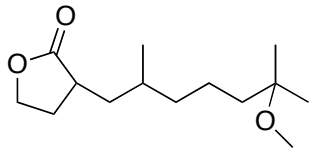
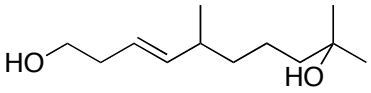
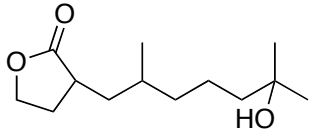
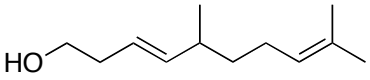
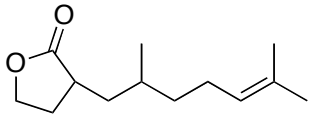
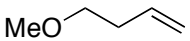
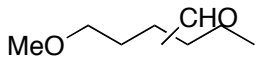


entry	substrate	major product	conv. [%][a]	yield lactones [%][b]	regioselectivity[c] (γ:δ)
1			100	91	99 : 1 (27 : 73)
2			100	85	>99 : < 1 (54 : 46)
3			100	88	>99 : < 1 (52 : 48)
4			98	84	97 : 3 (65 : 35)
5			84	92	99 : 1 (45 : 55)
6		 *n*-Pent	81	83	97 : 3 (28: 72)

[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% PPh3 as the ligand under otherwise identical conditions.

Title Paper: *Phosphinites do the trick …*



entry	substrate	major product	conv. [%][a]	yield lactones [%][b]	regioselectivity[c] (γ:δ)
7			75	42	97 : 3 (48 : 52)
8			98	88	99 : 1
9			85	99	99 : 1
10			93	99	99 : 1
11			6	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% PPh3 as the ligand under otherwise identical conditions.

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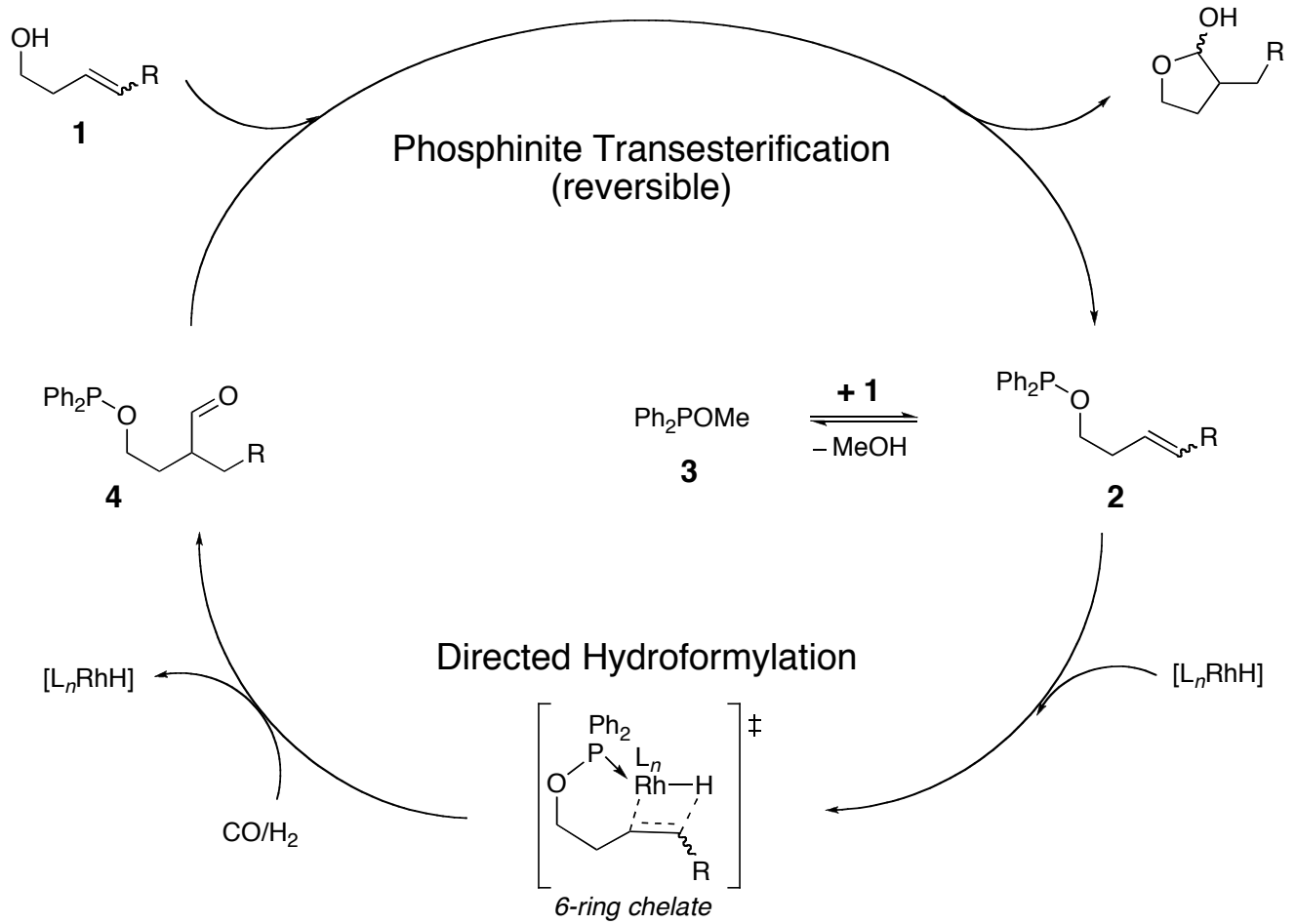
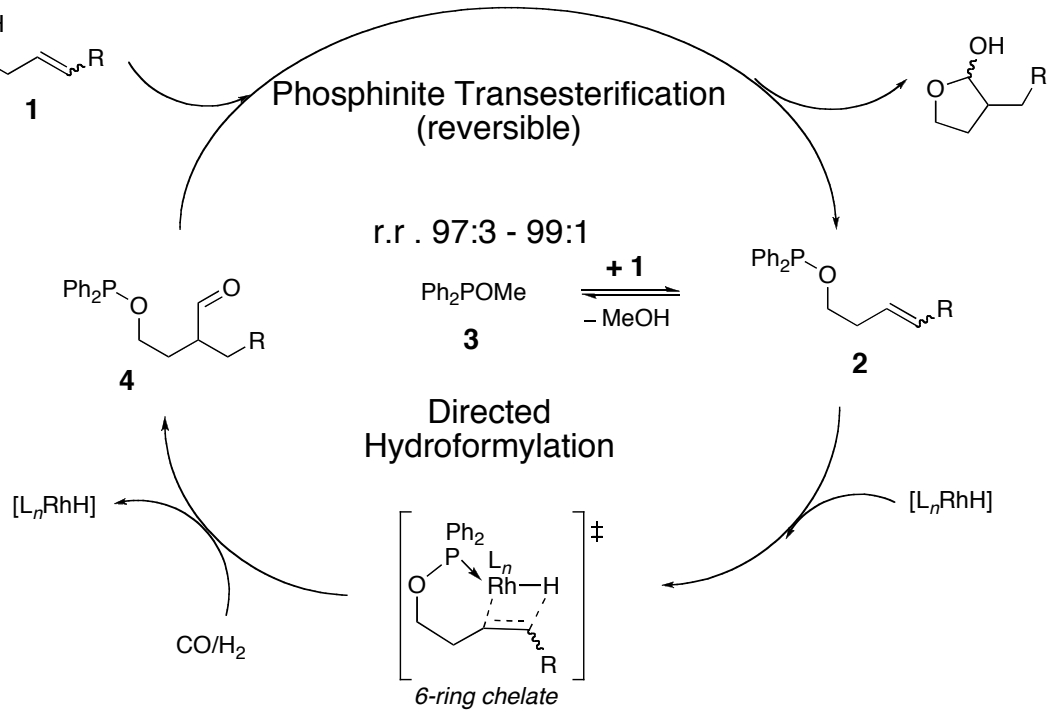


3 is a catalyst-directing group (CDG) operating through reversible substrate- and catalyst-binding

Summary and Conclusions

✓ Phosphinites work as reversibly bound catalyst-directing groups in catalytic amounts for the branched-regioselective hydroformylation of homoallylic alcohols with terminal alkenes, and position-selective hydroformylation of internal alkenes.



✓ The present methodology provides an efficient entry to γ-lactols and -lactones, which are useful synthetic building blocks.

x Limited to a particular functionality (O-heteroatom): homoallylic alcohols.

• Future work:
- Control of diastereo- and enantioselectivity in branched-regioselective hydroformylation reactions.