Tandem hydroformylation reactions

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Trieste, May 2024

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- Definition of tandem / cascade / domino reactions

- Tandem hydroformylation–hydrogenation
- Tandem hydroformylation- *CC* bond formations
- Tandem hydroformylation-elimination reactions
- Tandem hydroformylation in the presence of N-nucleophiles
- Tandem hydroformylation–acetalization

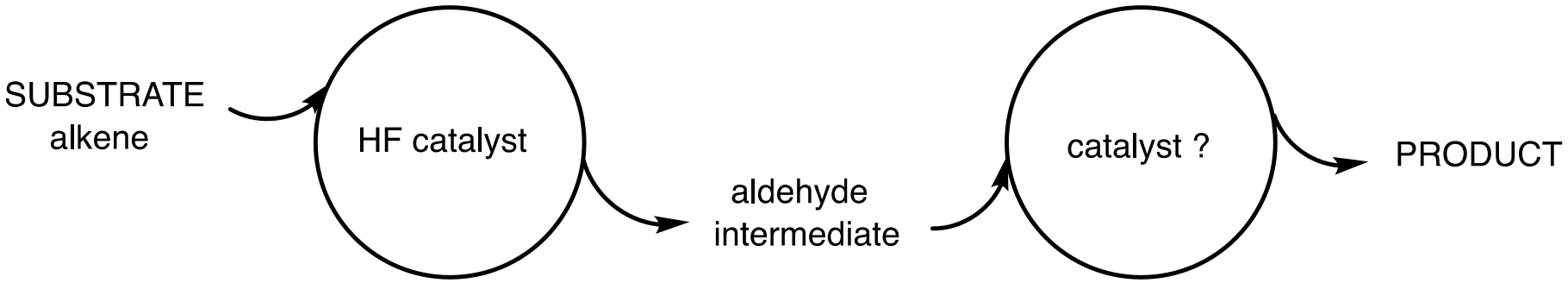
- Conclusions

Tandem reactions
(or domino reaction or cascade reaction)

chemical process that comprises at least two consecutive reactions such that each subsequent reaction occurs only in virtue of the chemical functionality formed in the previous step

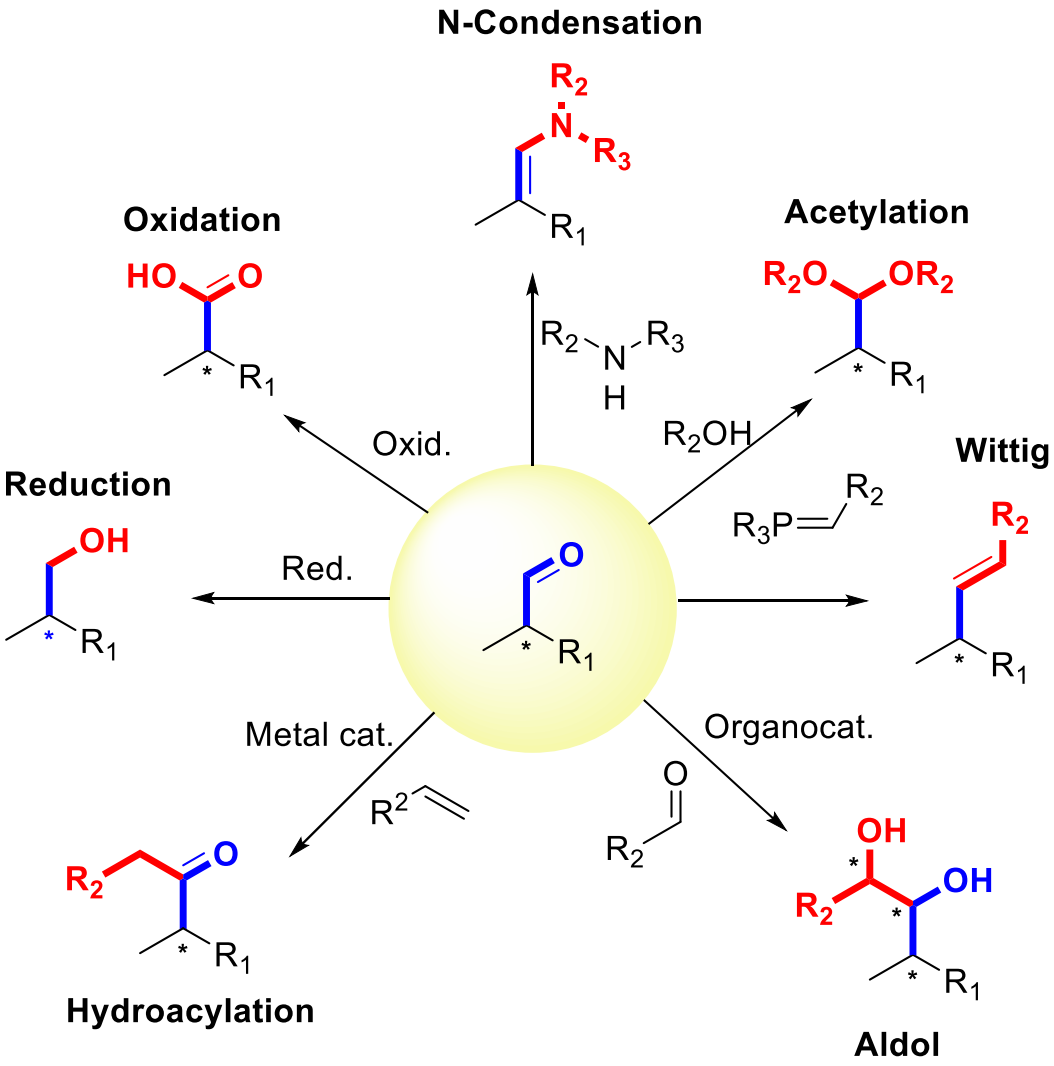
main benefits = high atom economy and reduction of waste

Tandem hydroformylation - other reaction(s)



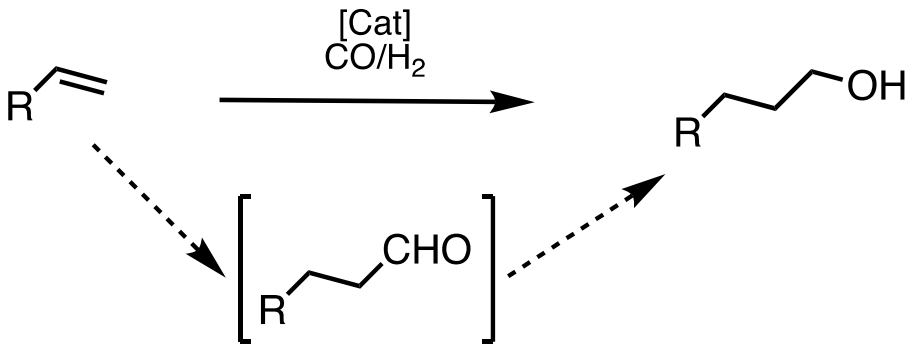
Regioselectivity
enantioselective

Catalysed?



a) *C-1 Building Blocks in Organic Synthesis 1. Additions to Alkenes, Alkynes, and Carbonyl Compounds*, *Vol.1*, van Leeuwen, P. W. N. M. Thieme, Stuttgart, Germany, **2013**. b)Breit, B. *Aldehydes: synthesis by hydroformylation of alkenes* in *Science of Synthesis*, *Vol. 25*, Thieme, Stuttgart, Germany, **2007**.

Tandem hydroformylation–hydrogenation

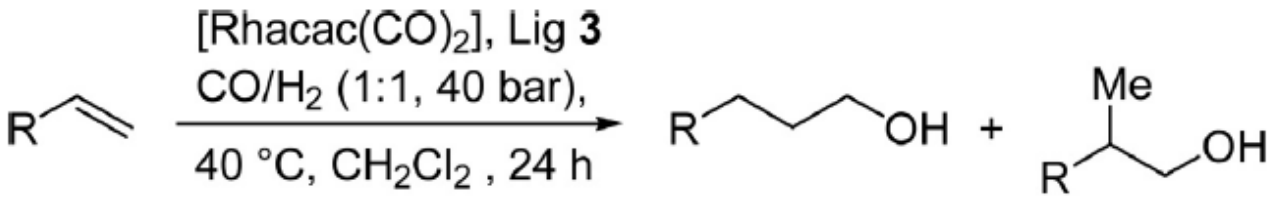


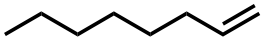
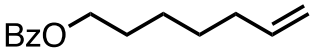
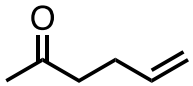
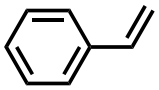
Linear 1-alkanols (n-alcohols) are widely used in industry as solvents and precursors of detergents and plasticizers

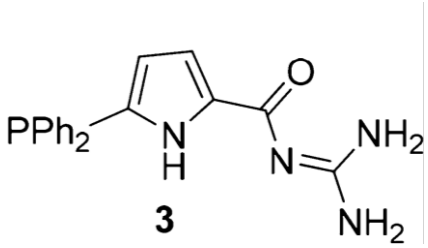
Investigated for a long time using Co-, Rh-, Ru-, and Pd-based systems

Usually low chemo- and regioselectivity

Tandem hydroformylation–hydrogenation Supramolecular catalyst system



	yield (%)	linear / branched
	87	92/8
	93	83/17
	98	91/9
	98	7/93

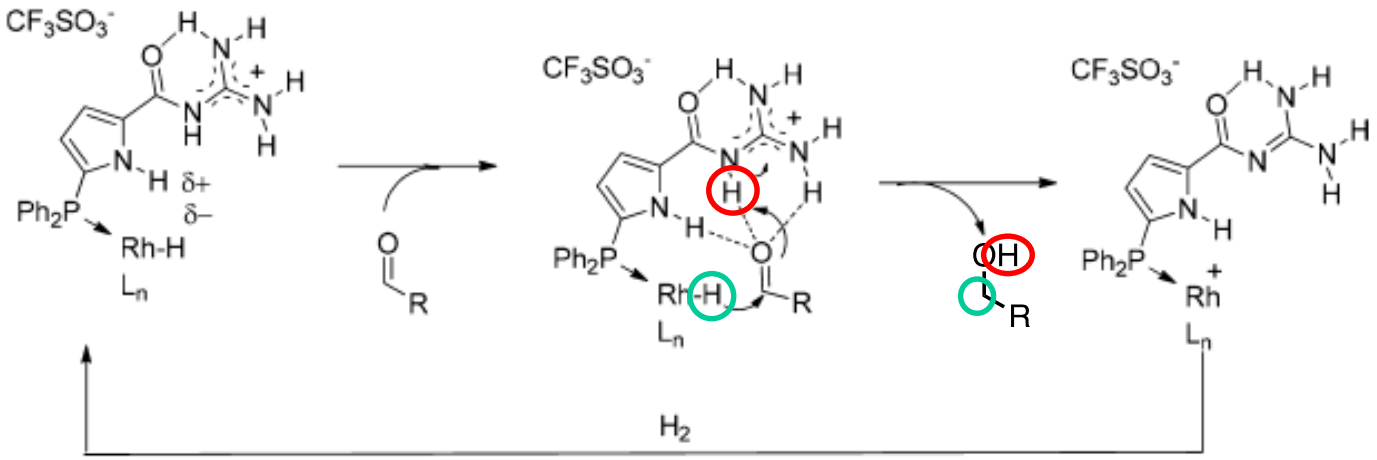


3

Good regioselectivities but not great

L. Diab, T. Smejkal, J. Geier, B. Breit, Angew. Chem. Int. Ed. 48 (2009) 8022–8026

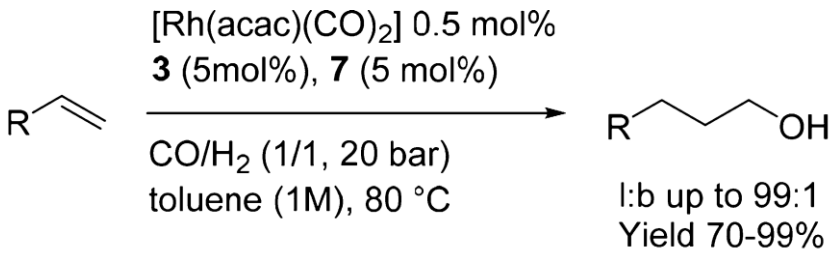
Tandem hydroformylation–hydrogenation Supramolecular catalyst system



Guanidinium unit operates by hydrogen bonding, decreasing the energy level of the lowest unoccupied molecular orbital (LUMO) of the substrate, and activating the substrate for a transition-metal-catalyzed reaction.

L. Diab, T. Smejkal, J. Geier, B. Breit, Angew. Chem. Int. Ed. 48 (2009) 8022–8026

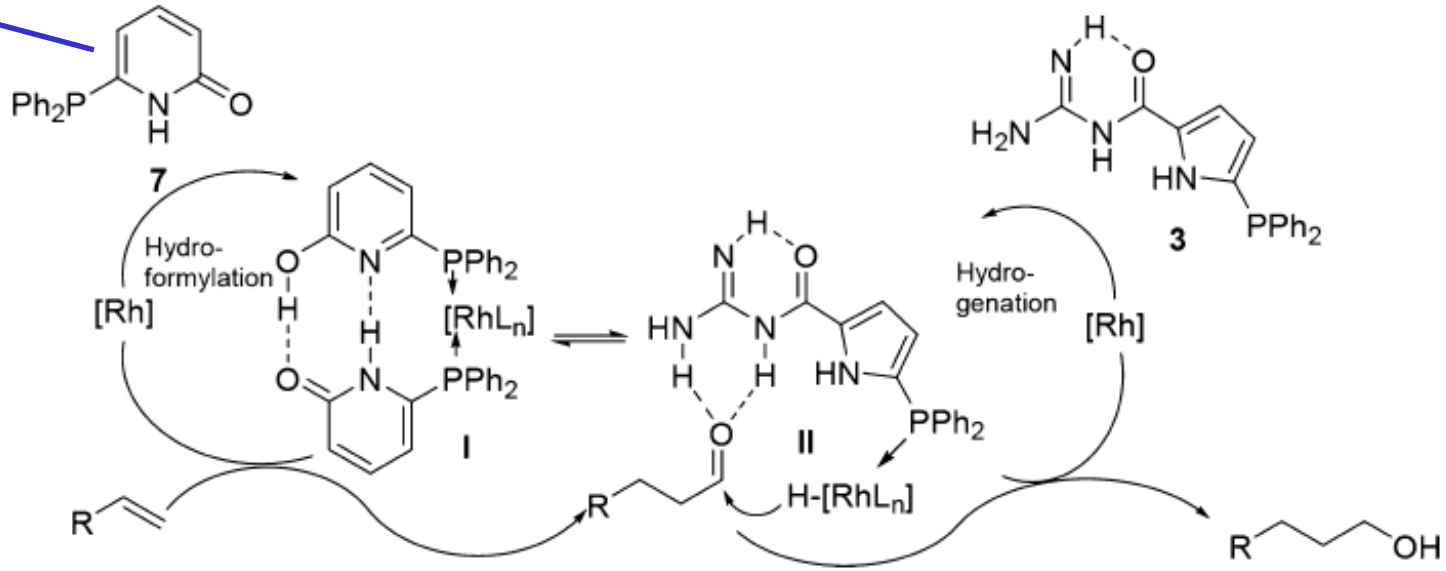
Tandem hydroformylation–hydrogenation Cooperative ligand system



Improved l/b ratio

R = Cy, $CH_3(CH_2)_5$, $(CH_2)_4OH$, $(CH_2)_4OTHP$, $(CH_2)_4OBn$, $(CH_2)_4OAc$, $(CH_2)_9OTBS$, $PhNHCO_2(CH_2)_4$

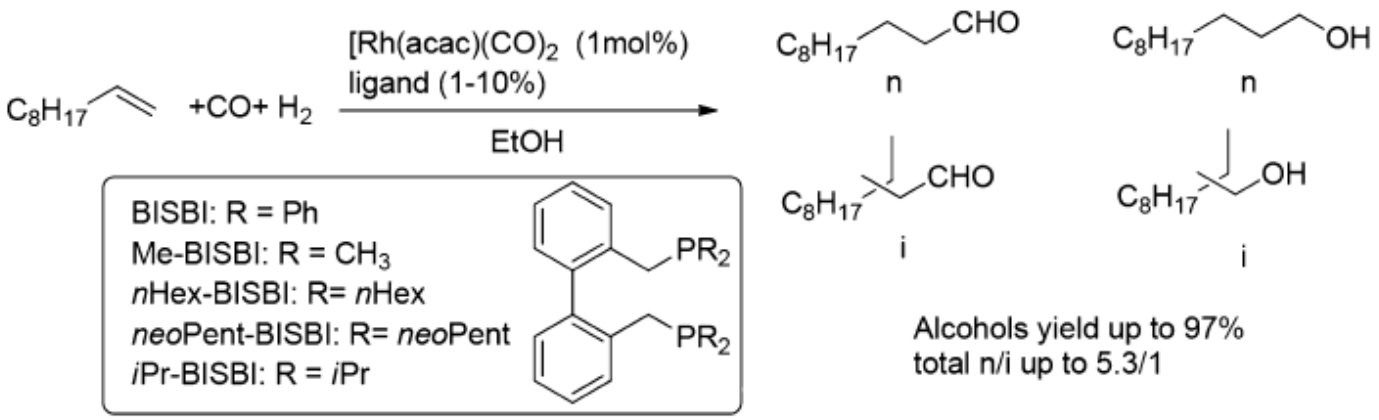
designed to self-assemble in the presence of a Rh(I) center to form a chelating catalyst system that acts as a highly active and regioselective hydroformylation catalyst



D. Fuchs, G. Rousseau, L. Diab, U. Gellrich, B. Breit Angew. Chem. Int. Ed. 51 (2012) 2178–2182,

Tandem hydroformylation–hydrogenation Bifunctional ligand: BISBI

Idea: to combine the high n/i ratio achieved by BISBI in HF and the high hydrogenation activity of trialkylphosphines for the selective formation of alcohols



Me-BISBI was the best performing ligand

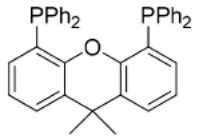
protic solvents were essential for the reaction

in aprotic solvents, the main product was the aldehyde

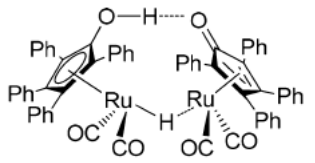
T. Ichihara, K. Nakano, M. Katayama, K. Nozaki, Chem. Asian J. 3 (2008) 1722–1728

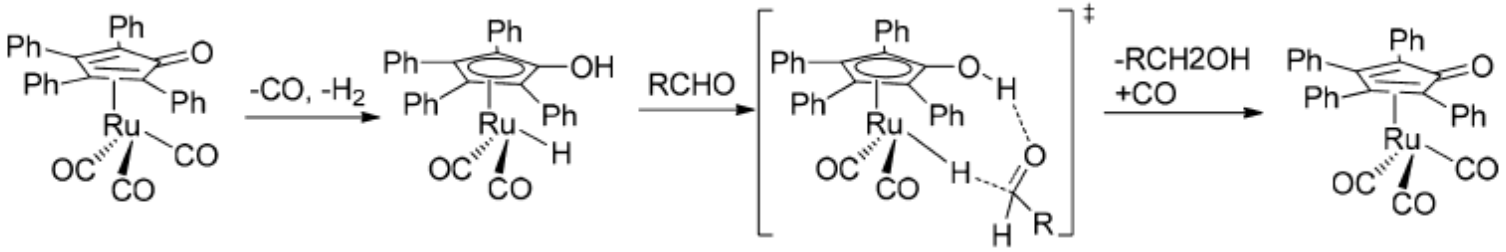
Tandem hydroformylation–hydrogenation Rh/Ru dual catalyst system

Mixture of two catalysts was used



- linear-selective hydroformylation step: Rh/XANTPHOS
- aldehyde-selective hydrogenation: Shvo's catalyst





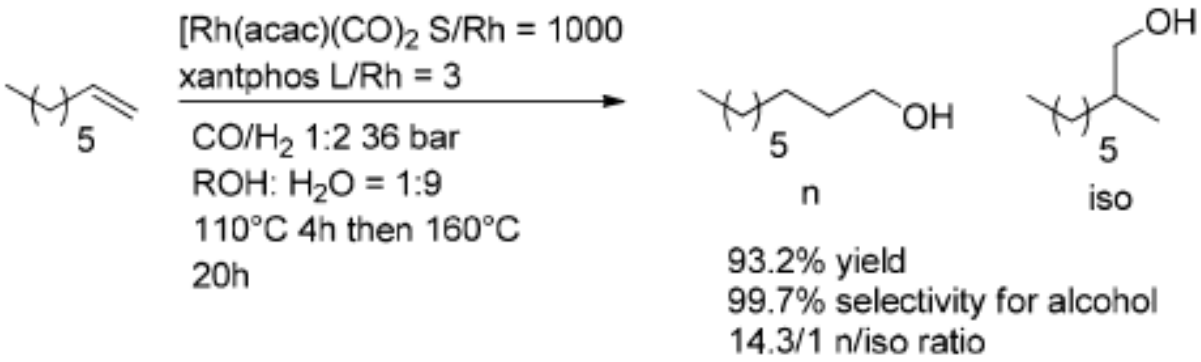
both hydroformylation and hydrogenation steps were very slow
Hydrogenation slowed down by the presence of CO

At 120 ◦C and with prolonged reaction time n-alcohol was obtained in 90% yield

K. Takahashi, M., Yamashita, T., Ichihara, K., Nakano, K. Nozaki Angew Chem. Int. Ed. 49 (2010) 4488–4490

Tandem hydroformylation–hydrogenation On water reaction with Rh/XANTPHOS catalyst

Rh/XANTPHOS was originally reported as n-selective hydroformylation catalyst and does not catalyze hydrogenation in apolar solvents



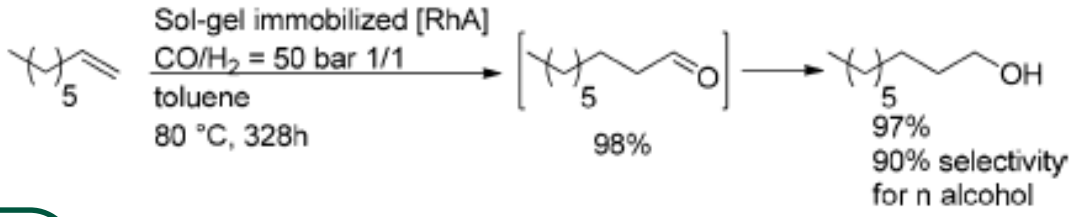
In this very polar reaction medium, the long hydrophobic aliphatic chains were pushed together, increasing the local substrate concentration= "on water" effect

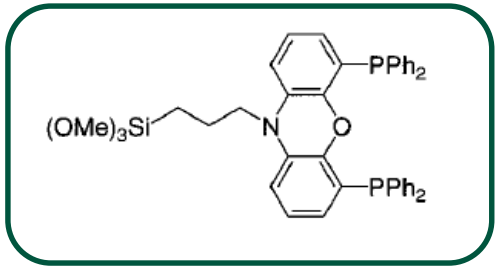
The formation of cationic Rh species would also be favored and could explain the results

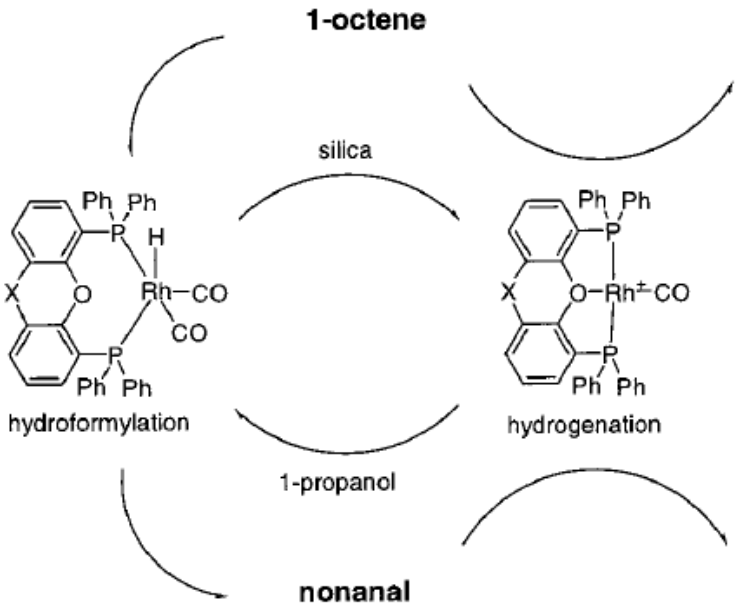
O. Diebolt, C. Mueller, D. Vogt, Catal. Sci. Technol. 2 (2012) 773–777

Tandem hydroformylation–hydrogenation Solid support reactions

rhodium-diphosphine complex immobilized on silica using the sol-gel technique and by a direct anchoring to commercially available silica.



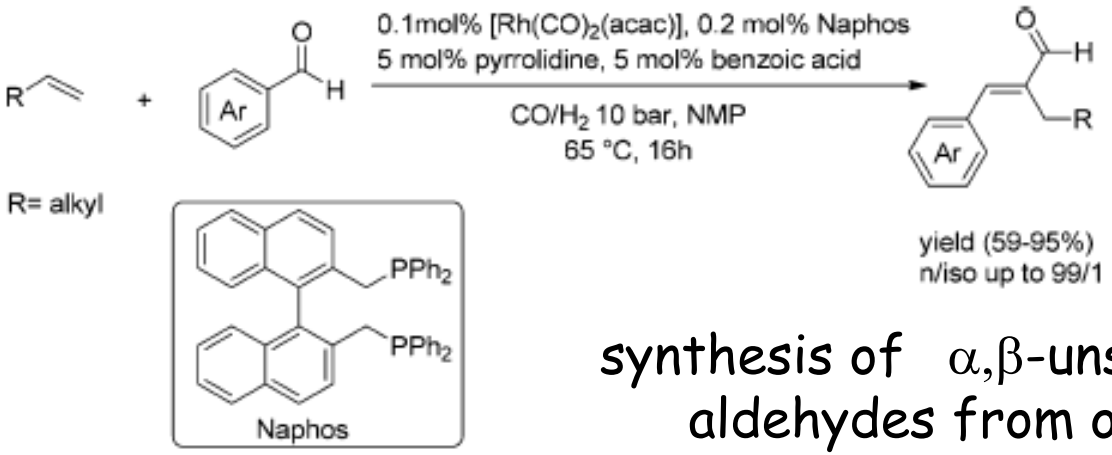




Switching between HF and hydrogenation catalysts

A.J. Sandee, J.N.H. Reek, P.C.J. Kamer, P.W.N.M. van Leeuwen, J. Am. Chem. Soc. 123 (2001) 8468–8476

Tandem hydroformylations with CC bond formations HF/aldol condensation



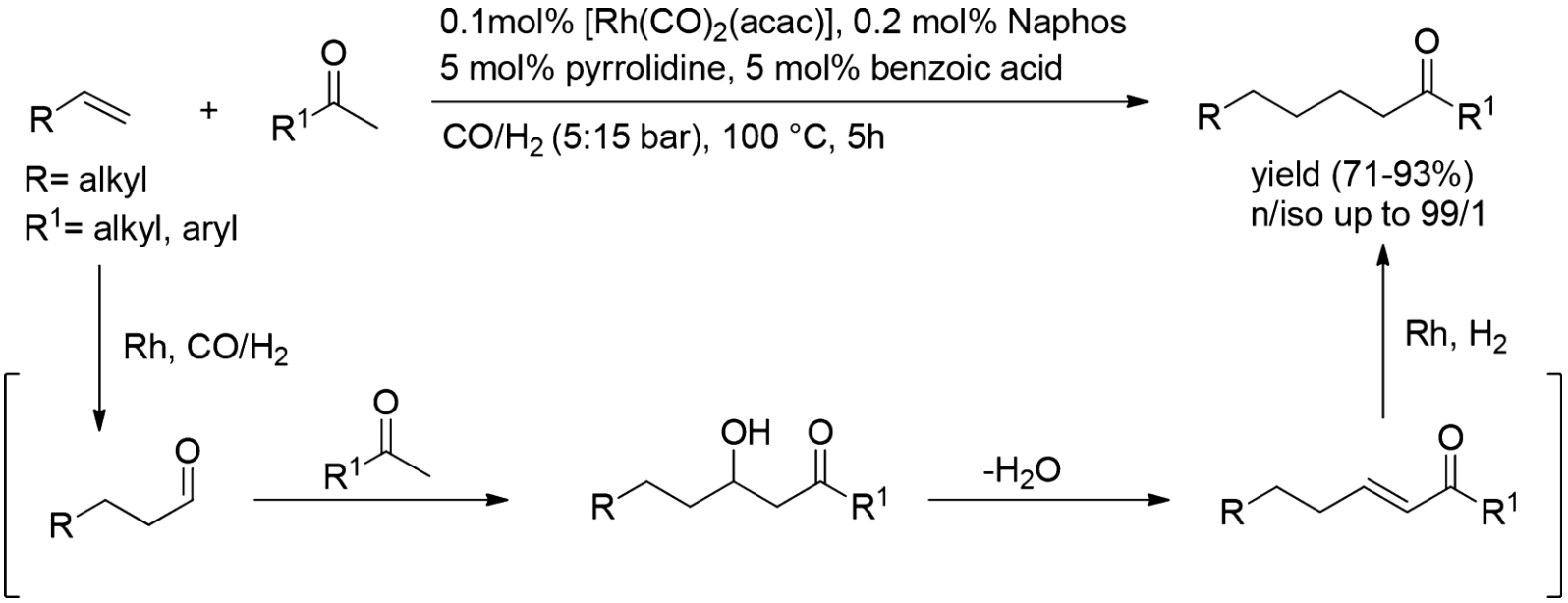
synthesis of α,β-unsaturated aldehydes from olefins

cooperative rhodium/phosphine and organocatalyst system

to avoid hydrogenation of products, low temperature was used along with low partial pressure of H2 (5 bar, 1/1 ratio to CO)

X. Fang, R. Jackstell, R. Franke, M. Beller, Chem. Eur. J. 20 (2014) 13210–13216

Tandem hydroformylations with CC bond formations HF/aldol condensation/ hydrogenation



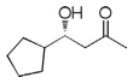
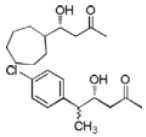
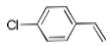
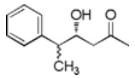
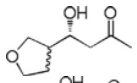
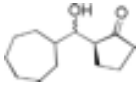
efficient synthesis of ketones starting from olefins

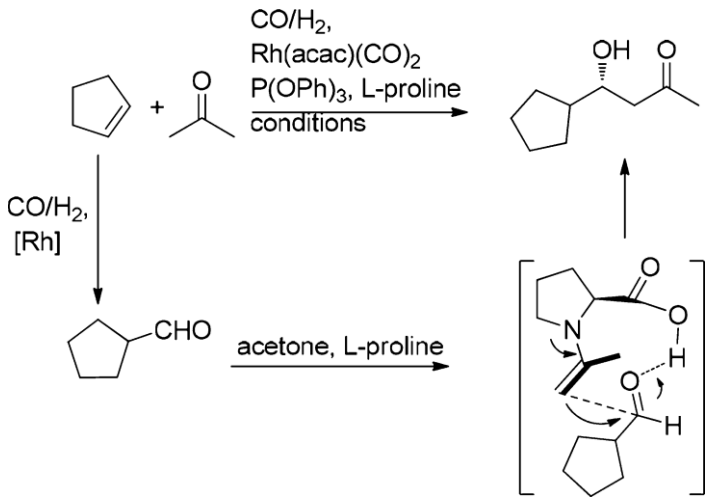
higher temperature higher and partial pressure of H_2 necessary for the hydrogenation step

X. Fang, R. Jackstell, A. Bcrner, M. Beller, Chem. Eur. J. 20 (2014) 15692–15696

Tandem hydroformylations with CC bond formations HF/enantioselective cross aldol reactions

L-proline as the organocatalyst

Entry	Substrate	Ketone = solvent	Product	Yield [%][c]	Syn:anti [d]
1				76	/
2				47	/
3				8 9	1.5:1
4				83	1.5:1
5				71	1: 1
6				59	1:2.7
7	 83/85			76	1:1.9

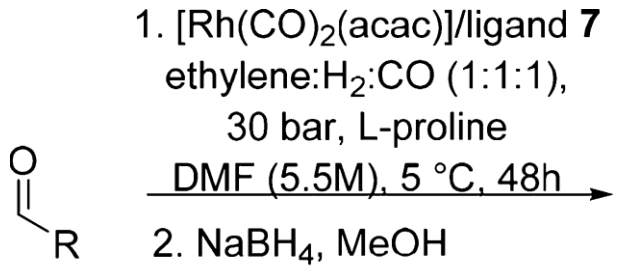


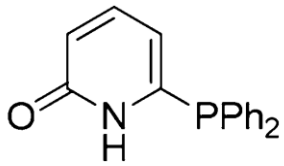
0.5 mol% Rh(acac) $(CO)_2$, 20/20 bar CO/H_2 , 2 mol% $P(OPh)_3$, 30 mol% l-proLine, 40 °C, 72 h.

S. Chercheja, P. Eilbracht, Adv. Synth. Catal. 349 (2007) 1897–1905.

Tandem hydroformylations with CC bond formations HF/enantioselective cross aldol reactions

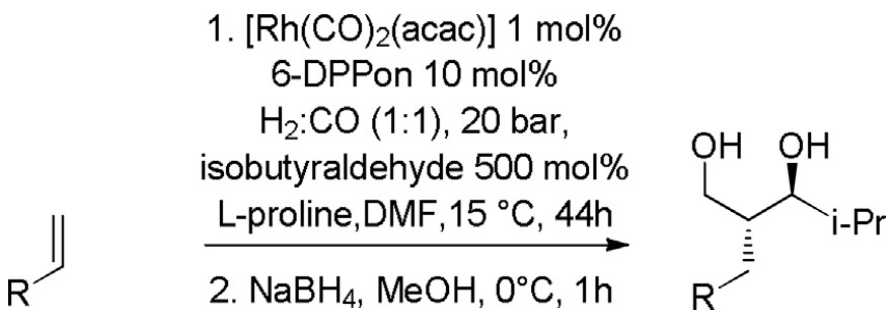
L-proline as the organocatalyst

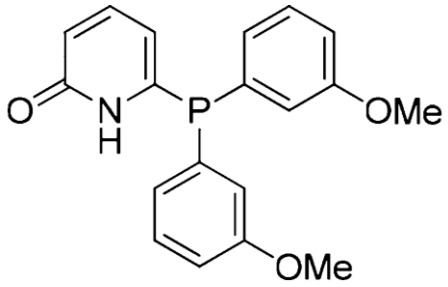




yield: 66-99%
d.r.: 3:1 to 19:1
ee: 44-99%

R = iPr, Cy, Ph, *p*-FPh, 3-Pyr



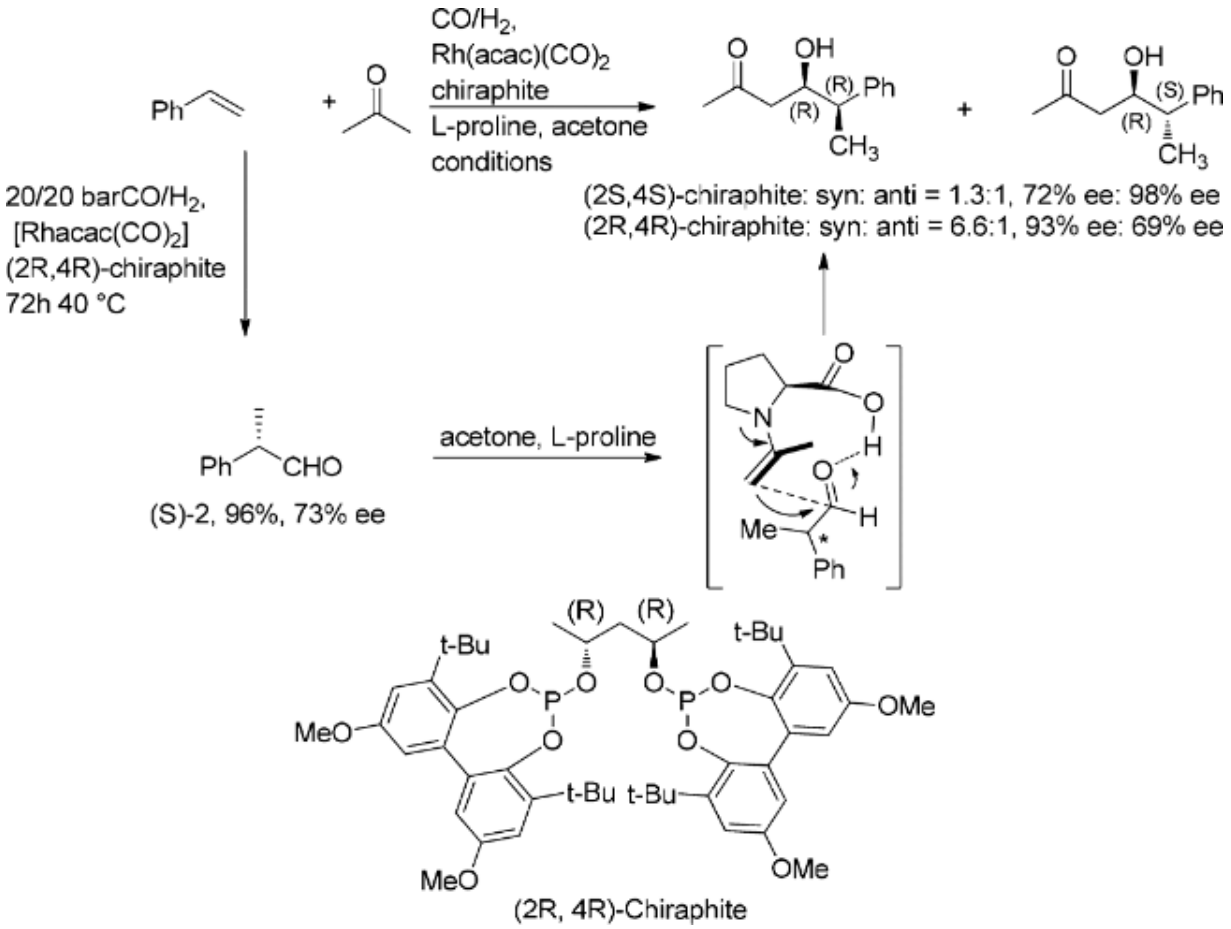


R= n-C_6H_{11} 86% yield, dr 19:1, ee 97%
R= Ph 50% yield, dr 50%, ee 99%

B. Breit et al. Adv. Synth. Catal. 349 (2007) 1891–1895; J. Am. Chem. Soc. 125 (2003) 6608–6609; Adv. Synth. Catal. 347 (2005) 1488–1494.

Tandem hydroformylations with CC bond formations AHF/enantioselective cross aldol reactions

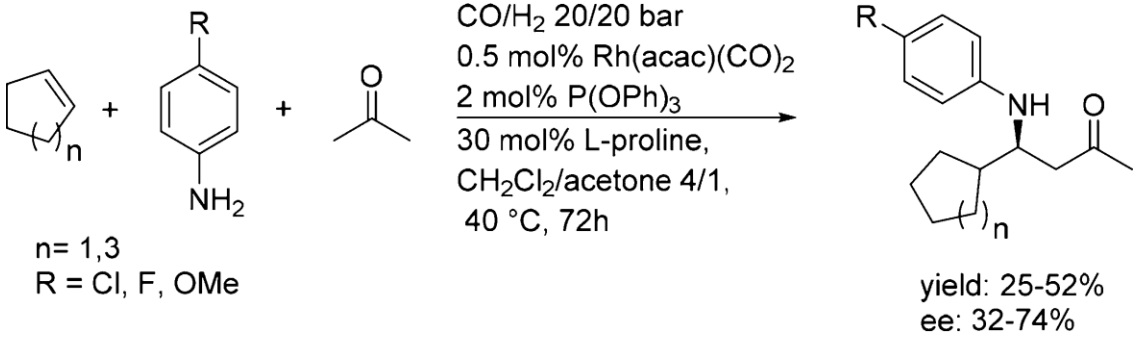
L-proline as the organocatalyst

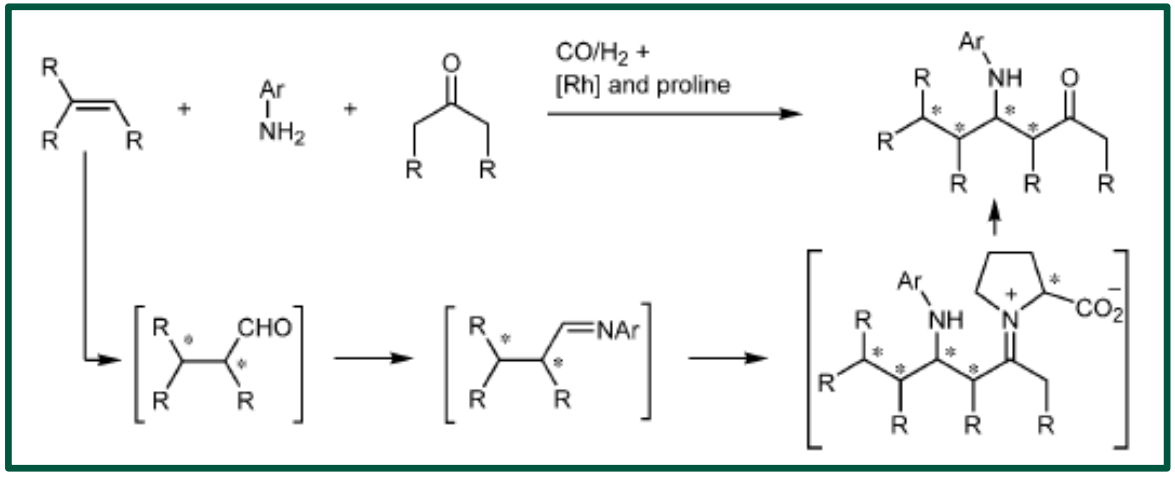


S. Chercheja, S.K. Nadakudity, P. Eilbracht, Adv. Synth. Catal. 352 (2010) 637–643

Tandem hydroformylations with CC bond formations HF/enantioselective Mannich reaction

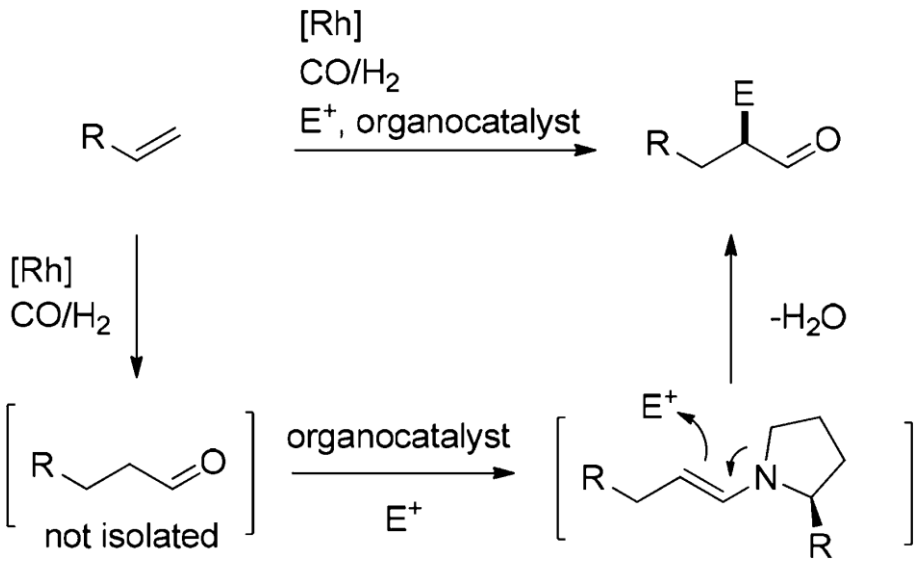
L-proline as the organocatalyst





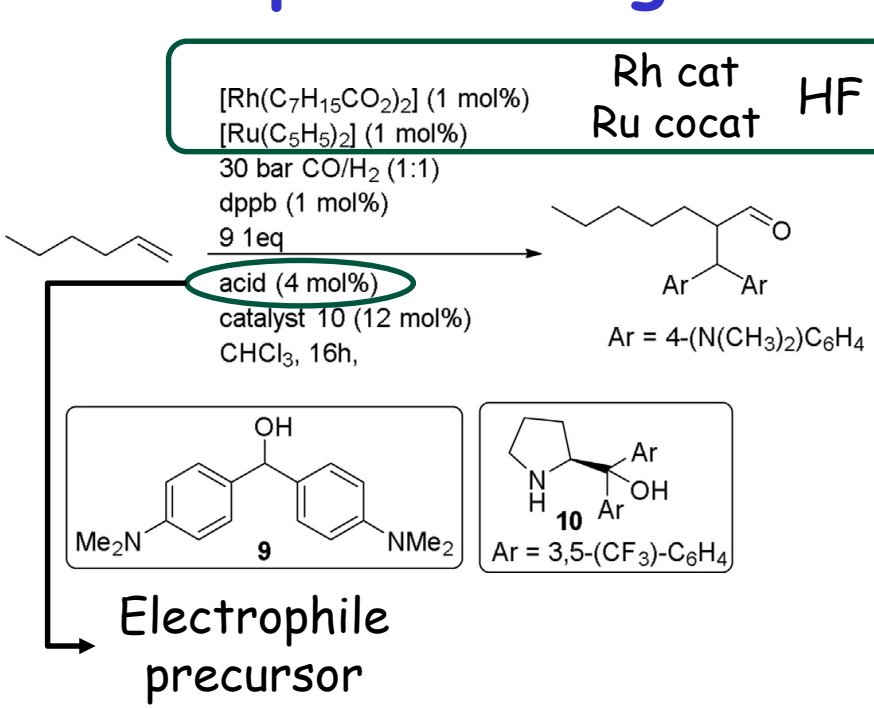
S. Chercheja, T. Rothenbuecher, P. Eilbracht, Adv. Synth. Catal. 351 (2009) 339–344.

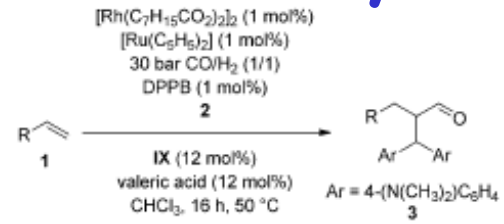
Tandem hydroformylations with CC bond formations
One-pot HF/organocatalyzed SN1 alkylation



J. Stiller, A.J. Vorholt, K.A. Ostrowski, A. Behr, M. Christmann, Chem. Eur. J. 18 (2012) 9496–9499

Tandem hydroformylations with CC bond formations
One-pot HF/organocatalyzed SN1 alkylation





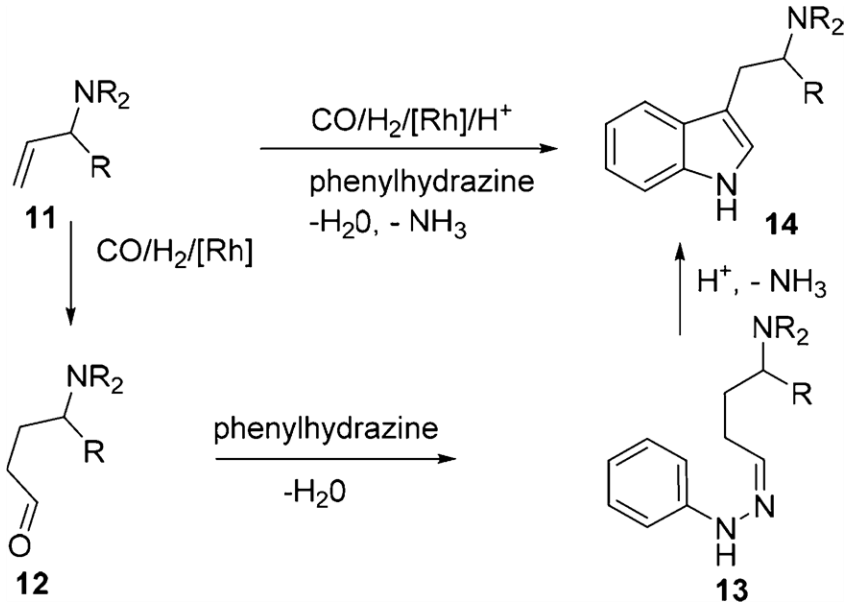
No.[a]	Substrate	t [h]	Yield [%][b]	ee [%][c]
1	1a	16	64	90
2	1b	16	58	91
3	1c	16	62	92
4	1d	16	43	93
5	1e	16	85	93 (93) (d.r. 1:1)
6	1f	16	83	83
7	1g	16	76	98 (80) (d.r. 3:1)
8	1h	16	n.r.	–
9	1i	16	n.r.	–

The Ru co-catalyst not only enhanced the HF step, but also improved the conversion in the organocatalytic reaction.

J. Stiller, A.J. Vorholt, K.A. Ostrowski, A. Behr, M. Christmann, Chem. Eur. J. 18 (2012) 9496–9499

Tandem hydroformylations with CC bond formations hydroformylation/Fischer indole synthesis

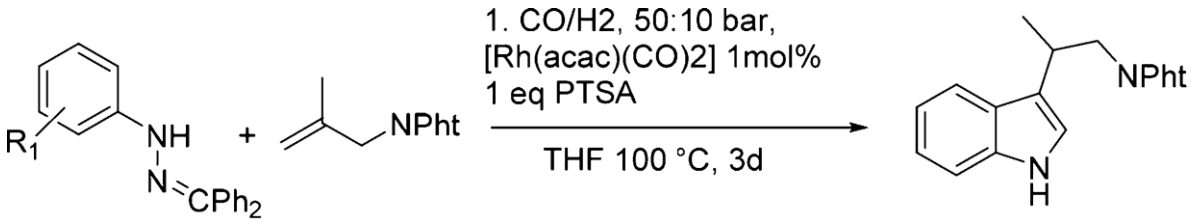
Substituted indoles = "privileged structures" owing to their binding ability to many different types of receptors



three steps:

- the in situ generation of oxo aldehyde 12
- its conversion to aryl hydrazones 13
- [3,3]-sigmatropic rearrangement to the final product 14

Tandem hydroformylations with CC bond formations hydroformylation/Fischer indole synthesis

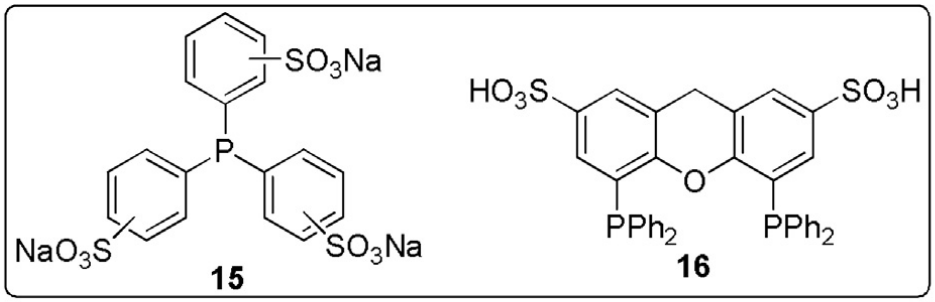


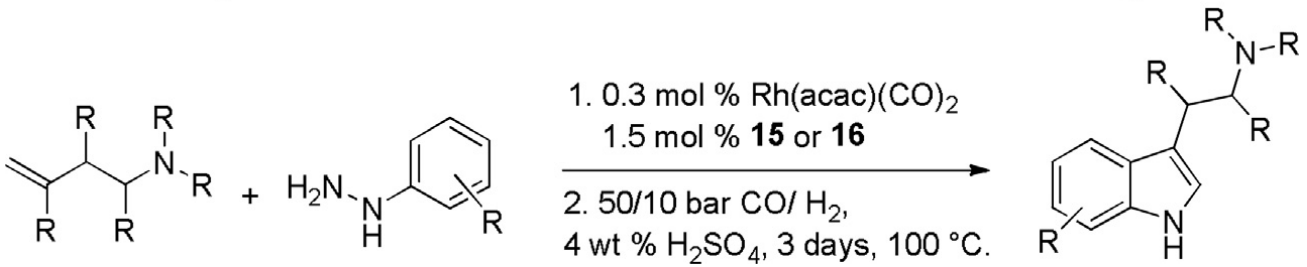
Indole derivatives with a tryptamine scaffold (3-aminoethyl indole) are important compounds and many of these are known as synthetic medicines and physiologically active substances (serotonin, melatonin, psilocin, etc.).

P. Koehling, A.M. Schmidt, P. Eilbracht, Org. Lett. 5 (2003) 3213–3216

Tandem hydroformylations with CC bond formations hydroformylation/Fischer indole synthesis

Synthesis of branched tryptamines and homo tryptamines in water



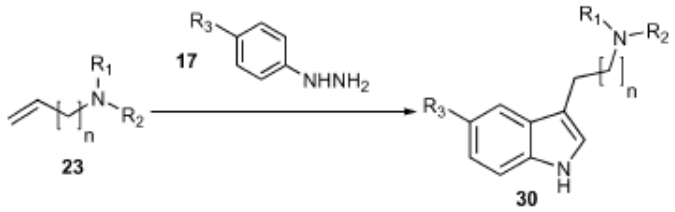


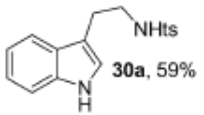
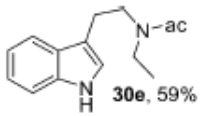
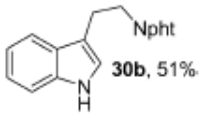
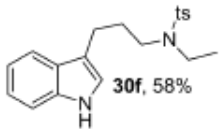
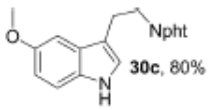
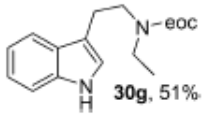
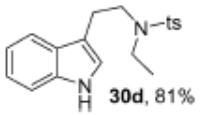
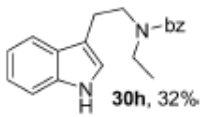
Up to 99% yield

A.M. Schmidt, P. Eilbracht, J. Org. Chem. 70 (2005) 5528–5535; A.M. Schmidt, P. Eilbracht, Org. Biomol. Chem. 3 (2005) 2333–2343

Tandem hydroformylations with CC bond formations
hydroformylation/Fischer indole synthesis

synthesis towards non-branched tryptamides



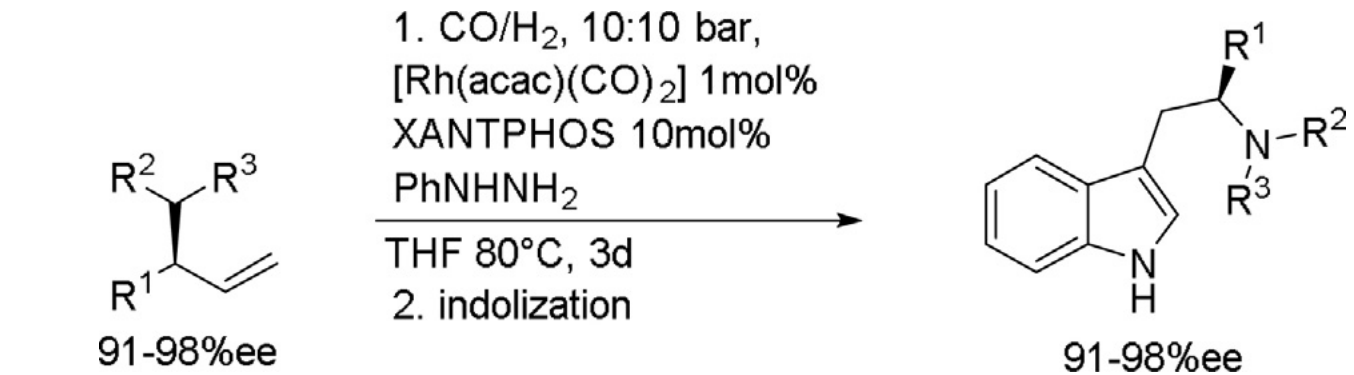
Entry	Olefin **23**	Hydrazine **17**	Yield **30**	Entry	Olefin **23**	Hydrazine **17**	Yield **30**
1	**23c** ($n = 1$, $R_1 = H$, $R_2 = ts$)	**17a**	 **30a**, 59%	5	**23f** ($n = 1$, $R_1 = Et$, $R_2 = ac$)	**17a**	 **30e**, 59%
2	**23a** ($n = 1$, $R_1 = R_2 = pht$)	**17a**	 **30b**, 51%	6	**23h** ($n = 2$, $R_1 = Et$, $R_2 = ts$)	**17a**	 **30f**, 58%
3	**23a** ($n = 1$, $R_1 = R_2 = pht$)	**17j**	 **30c**, 80%	7	**23g** ($n = 1$, $R_1 = Et$, $R_2 = eoc$)	**17a**	 **30g**, 51%
4	**23e** ($n = 1$, $R_1 = Et$, $R_2 = ts$)	**17a**	 **30d**, 81%	8	**23i** ($n = 1$, $R_1 = Et$, $R_2 = bz$)	**17a**	 **30h**, 32%

Cond.: (a) 1 eq **17**, 1 eq **23**, 0.3 mol% $Rh(acac)(CO)_2$, 3 mol% XANTPHOS, 10 bar CO, 10 bar H_2, 68 h, 70 °C. (b) 4 wt% H_2SO_4–THF, 2 h, 80 °C.

A.M. Schmidt, P. Eilbracht, Org. Biomol. Chem. 3 (2005) 2333–2343

Tandem hydroformylations with CC bond formations
hydroformylation/Fischer indole synthesis

Synthesis of chiral tryptamines and homologues



91-98%ee

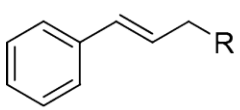
Obtained by enantioselective Ir catalyzed allylation

91-98%ee

Yields up to 76% complete retention of chirality

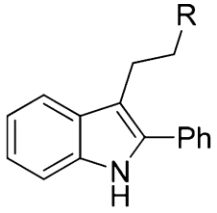
B.P. Bondzic, A. Farwick, J. Liebich, P. Eilbracht, Org. Biomol. Chem. 20 (2008) 3723–3731

Tandem hydroformylations with CC bond formations hydroformylation/Fischer indole synthesis



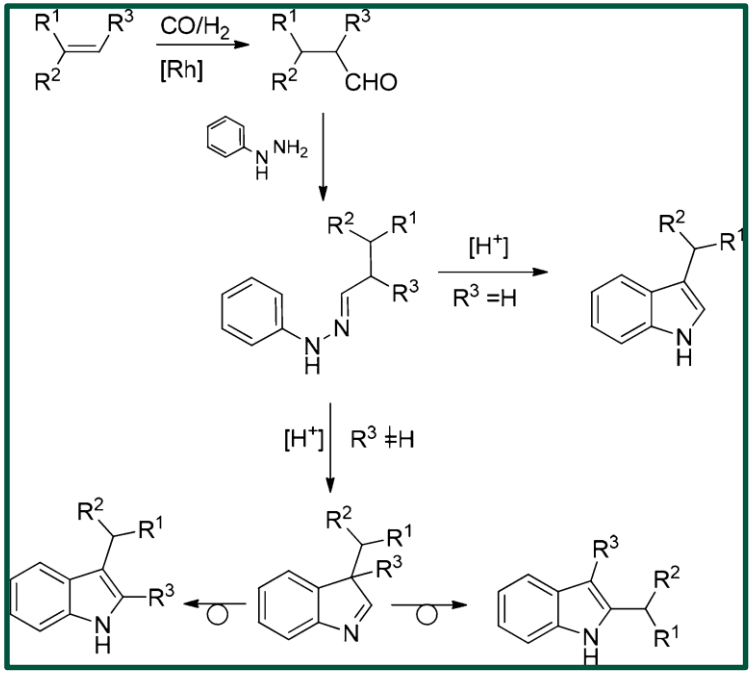
17

a) 1 eq. phenylhydrazine,
0.5 mol% $Rh(acac)(CO)_2$,
10 mol% BIPHEPHOS,
10 bar CO, 10 bar H2,
100 °C, 3 d;
b) 4 wt% H_2SO_4
THF, reflux, 3 h.



18

(R= OBz; 54%)
(R= NC_6H_5; 60%)

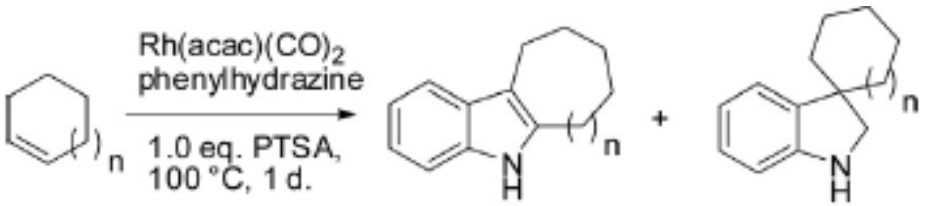


When internal or cyclic olefins are used, 2,3 disubstited indoles or carbazoles (in the case of cyclic olefins) can also be obtained

P. Linnepe, A.M. Schmidt, P. Eilbracht, Org. Biomol. Chem. 4 (2006) 302–313

Tandem hydroformylations with CC bond formations hydroformylation/Fischer indole synthesis

Cyclic olefins: ring size effect



19 **20**

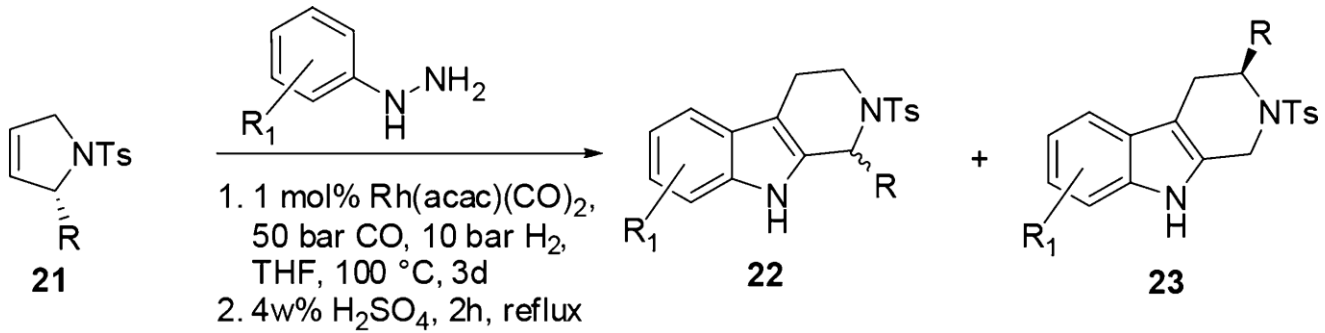
Entry	*n*	CO (bar)	H_2 (bar)	19 (%)	20 (%)
1	0	50	20	98	–
2	0	20	50	95	–
3	2	50	20	60	11
4	2	20	50	0	59

- In the case of pentene, the carbazole product 19 is obtainedregardless of ratio of syngas
- For six membered or higher cyclic olefins, hydrogenation of the spiro imino intermediate was possible and 20 was isolated in good yield

P. Linnepe, A.M. Schmidt, P. Eilbracht, Org. Biomol. Chem. 4 (2006) 302–313

Tandem hydroformylations with CC bond formations hydroformylation/Fischer indole synthesis

Hydroformylation/tetrahydro-β-carboline synthesis



R= Ph, Et, Pr, *p*-MeO-Ph, *o*-MeO-Ph, *p*-Cl-Ph, *p*-CF-Ph

22/23= 1/1.4 to 1/5.5
yield= 41-85%
ee= 93-98%

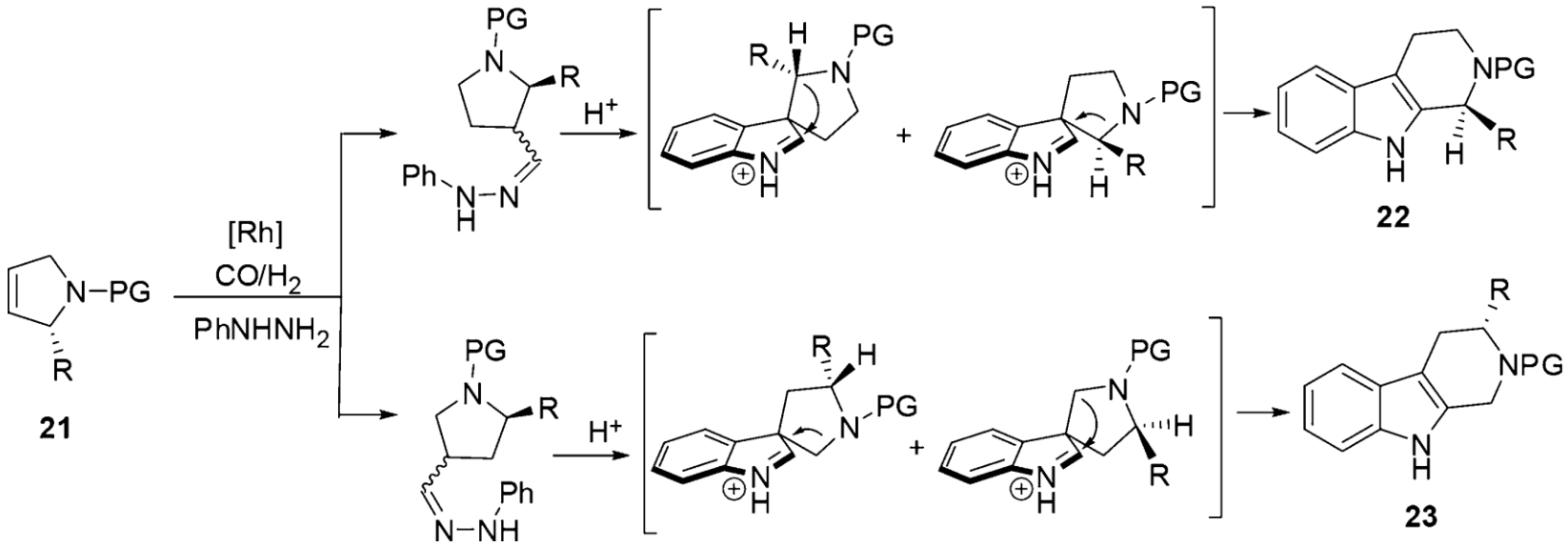
good overall yields with clear preference for the formation of 5-subsituted THBCs 23.
3-substituted carbolines 22 were isolated as racemates while 5-substituted retained enantiopurity of starting material

B.P. Bondzic, P. Eilbracht, Org. Lett. 10 (2008) 3433–3436.

Tandem hydroformylations with CC bond formations
hydroformylation/Fischer indole synthesis

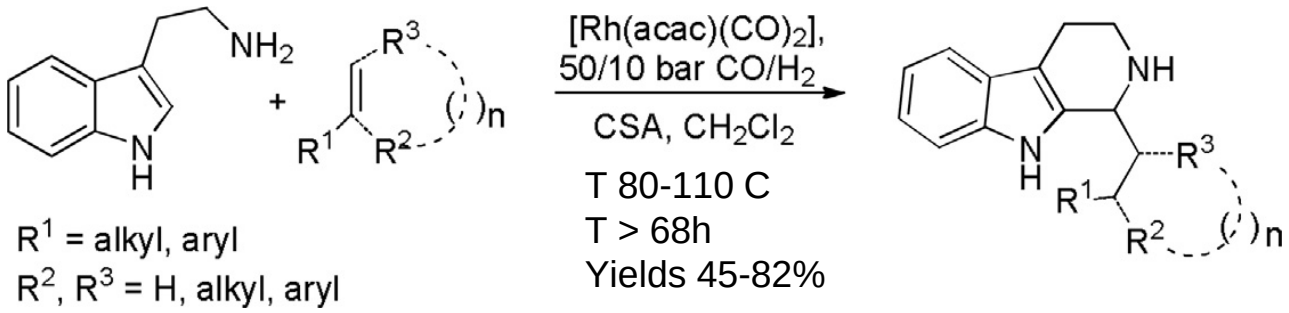
Hydroformylation/tetrahydro-β-carboline synthesis

MECHANISM

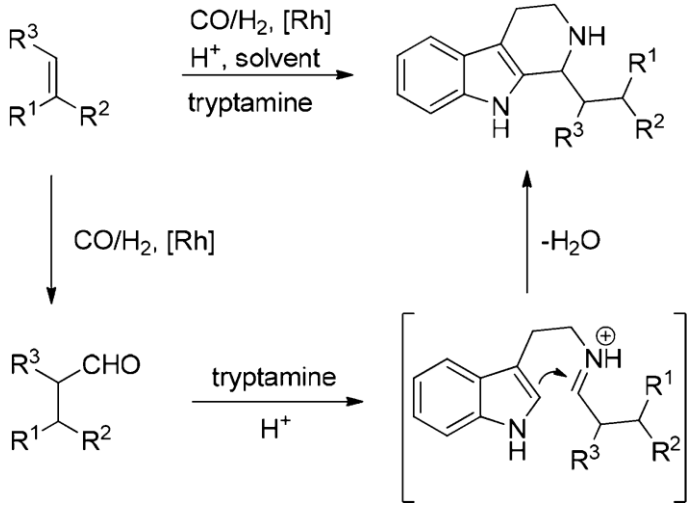


B.P. Bondzic, P. Eilbracht, Org. Lett. 10 (2008) 3433–3436.

Tandem hydroformylations with CC bond formations hydroformylation/Pictet–Spengler reaction



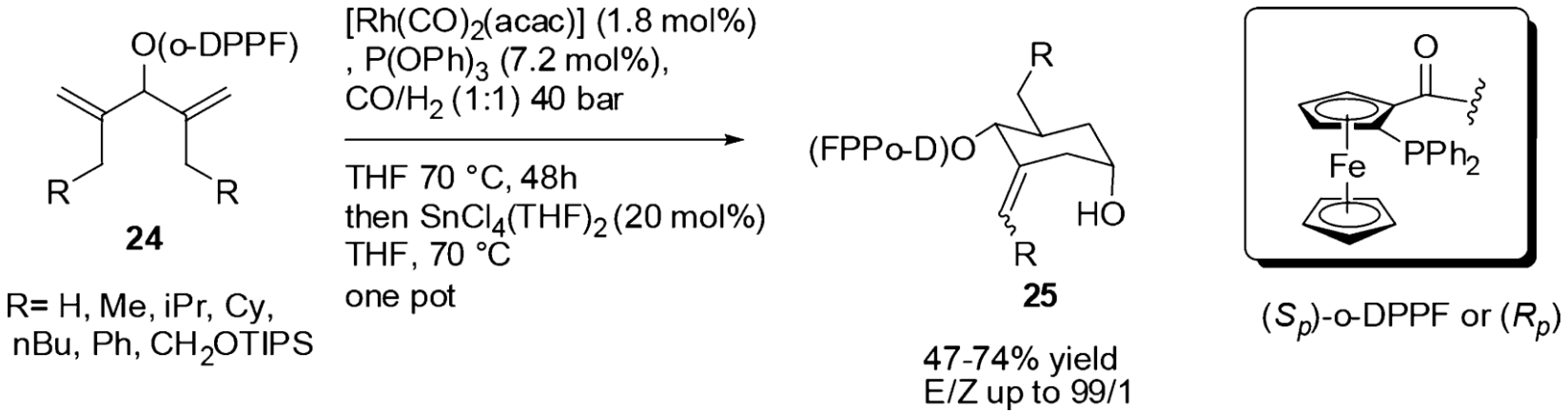
cyclic or 1,1 disubstituted olefins as substrates



B.P. Bondzic, P. Eilbracht, Org. Biomol. Chem. 6 (2008) 4059–4063

Tandem hydroformylations with CC bond formations

HF/carbonyl ene cyclization reaction

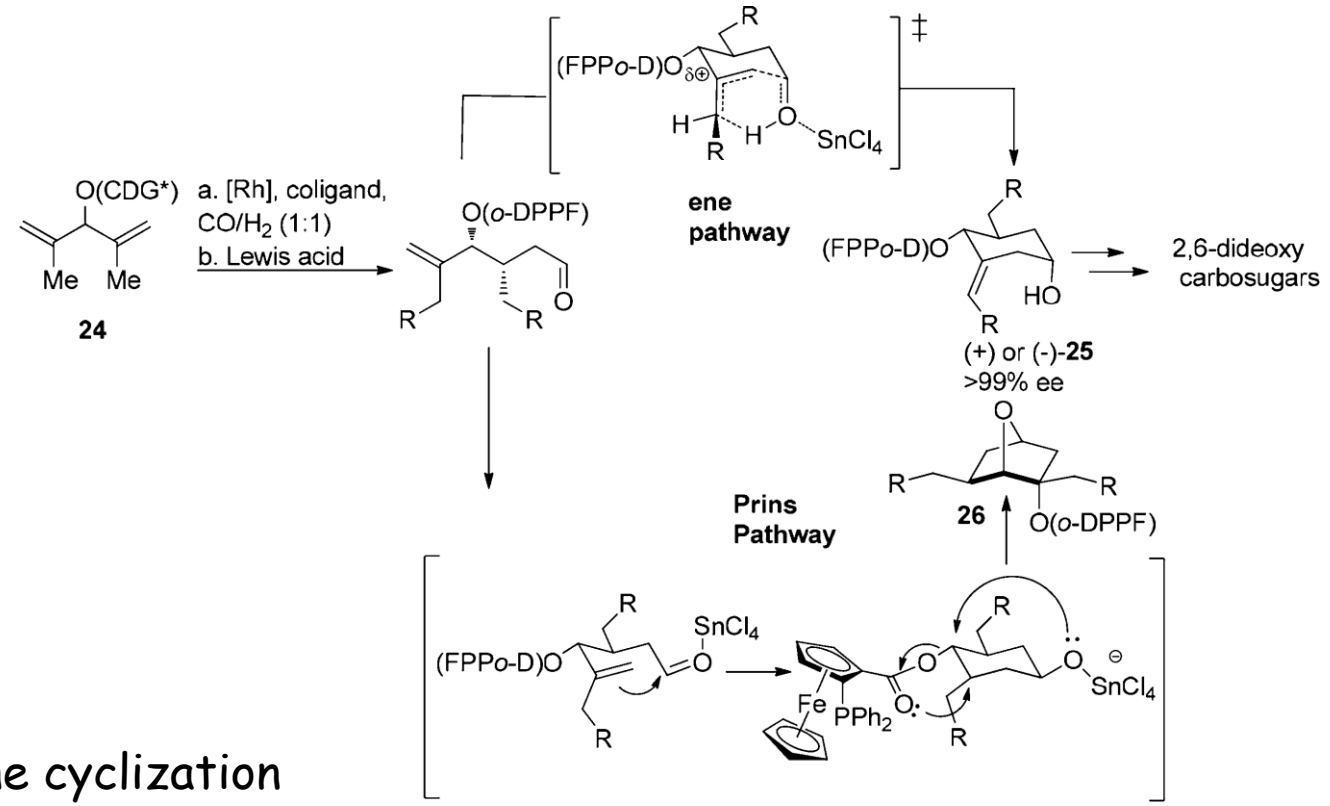


planar-chiral catalyst-directing group (o-DPPF) moiety attached to the symmetrical bis-2-propenyl-methanol for diastereotopic alkene group and face discrimination in the HF of 24 to selectively form the syn-aldehyde

A. Bigot, D. Breuninger, B. Breit, Org. Lett. 10 (2008) 5321–5324.B. Breit, A. Bigot, Chem. Commun. (2008) 6498–6500.

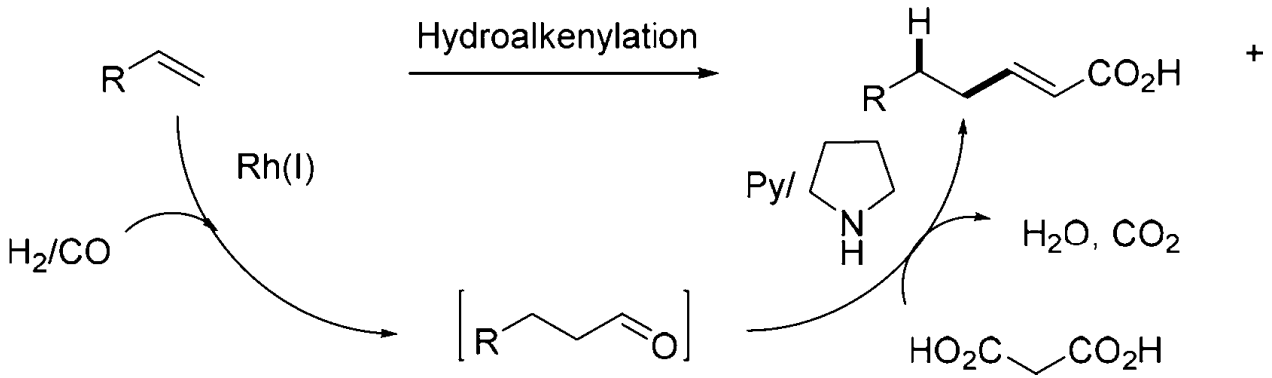
Tandem hydroformylations with CC bond formations

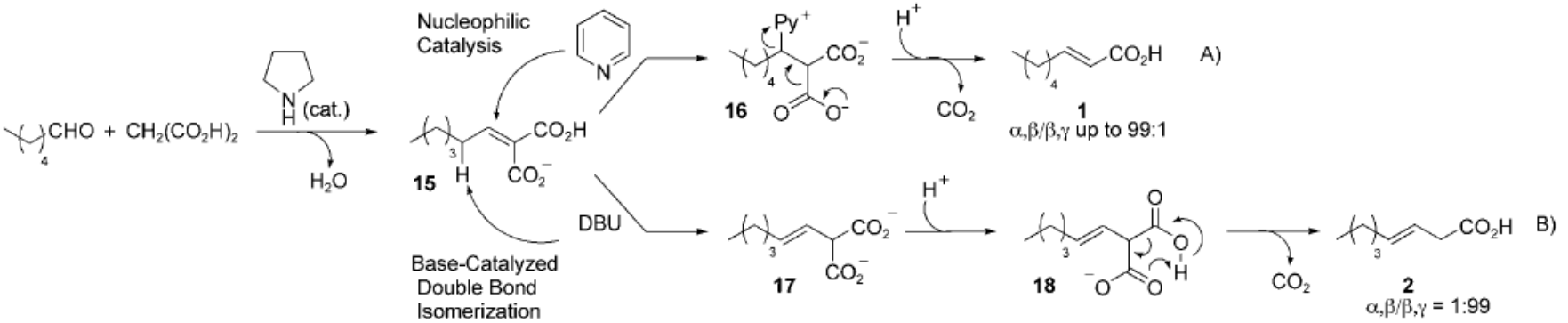
HF/carbonyl ene cyclization reaction



- HF
- carbonyl ene cyclization
- cleavage of the directing group in the same pot gave both optical antipodes of 25, either starting from (Sp)-o-DPPF ester or its (Rp) enantiomer

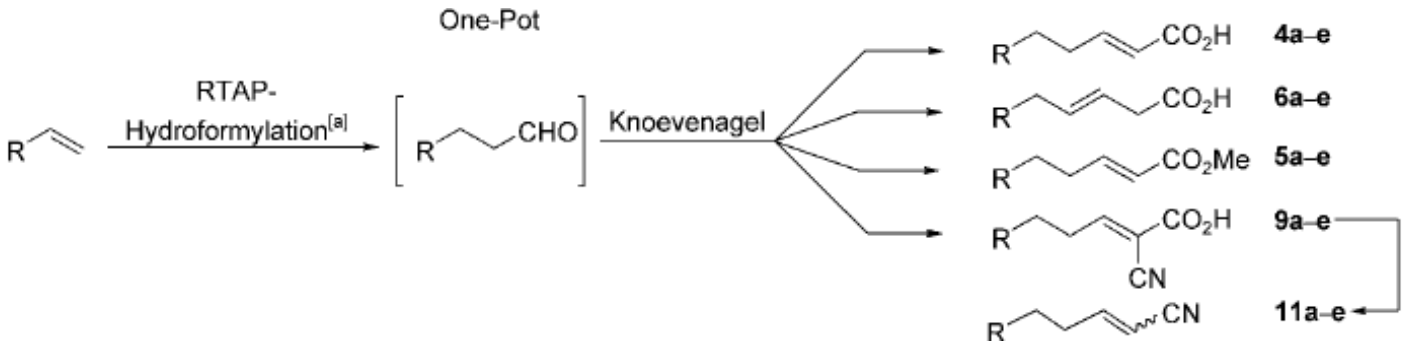
Tandem hydroformylations with CC bond formations HF/decarboxylative Knoevenagel reaction

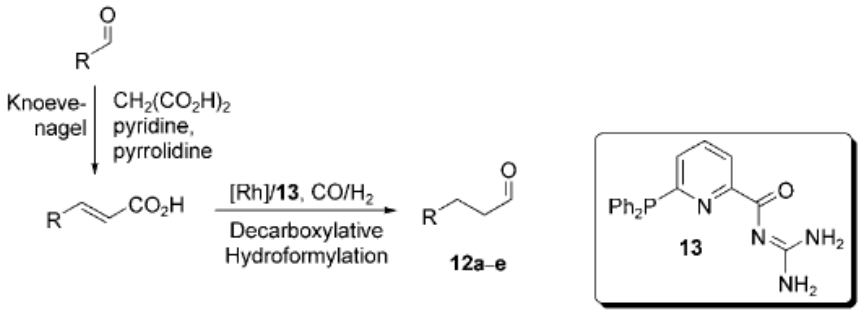


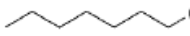
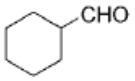
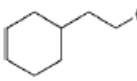
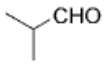
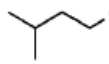
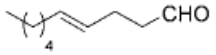
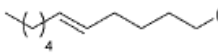


S.T. Kemme, T. Smejkal, B. Breit, Adv. Synth. Catal. 350 (2008) 989–994; S.T. Kemme, T. Smejkal, B. Breit, Chem. Eur. J. 16 (2010) 3423–3433

Tandem hydroformylations with CC bond formations HF/decarboxylative Knoevenagel reaction





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

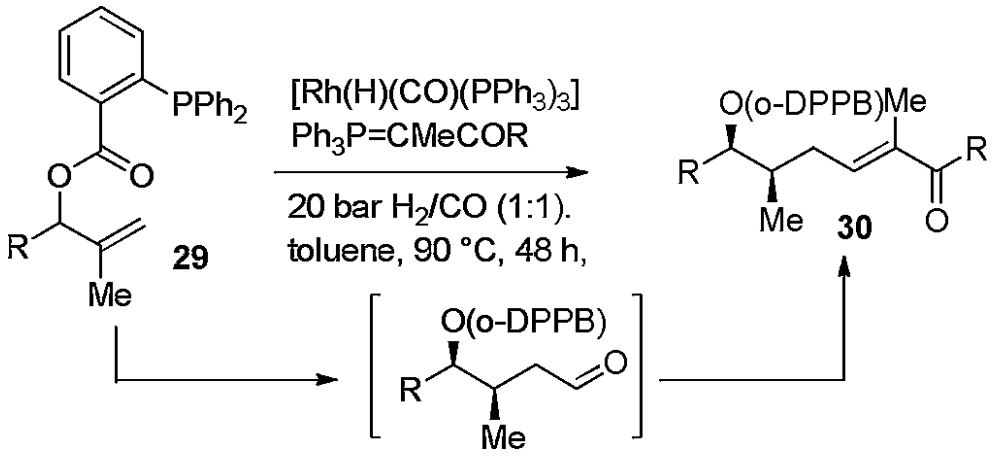
decarboxylative Knoevenagel reaction/ decarboxylative HF

=

2 carbon-chain elongation

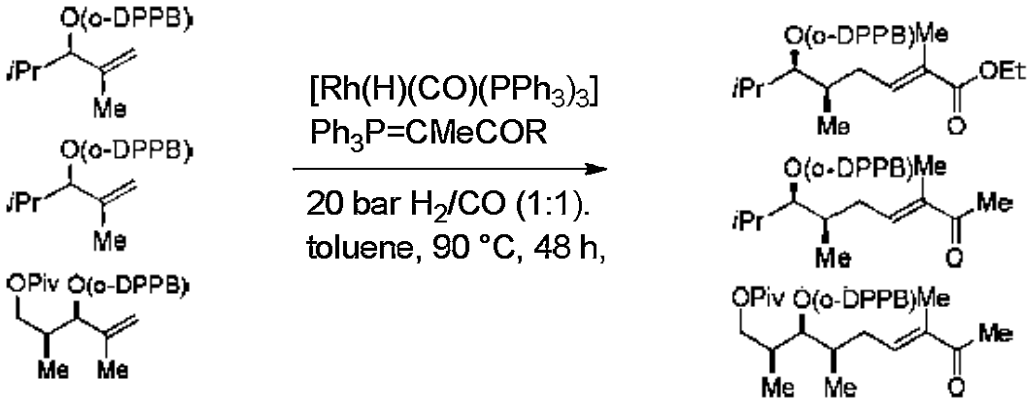
B. Breit et al. , Adv. Synth. Catal. 350 (2008) 989–994; Chem. Eur. J. 16 (2010) 3423–3433

Tandem hydroformylations with CC bond formations hydroformylation/Wittig reaction



The E-selectivity of the olefination step stems from the intrinsically high E-preference of stabilized phosphorus ylides.

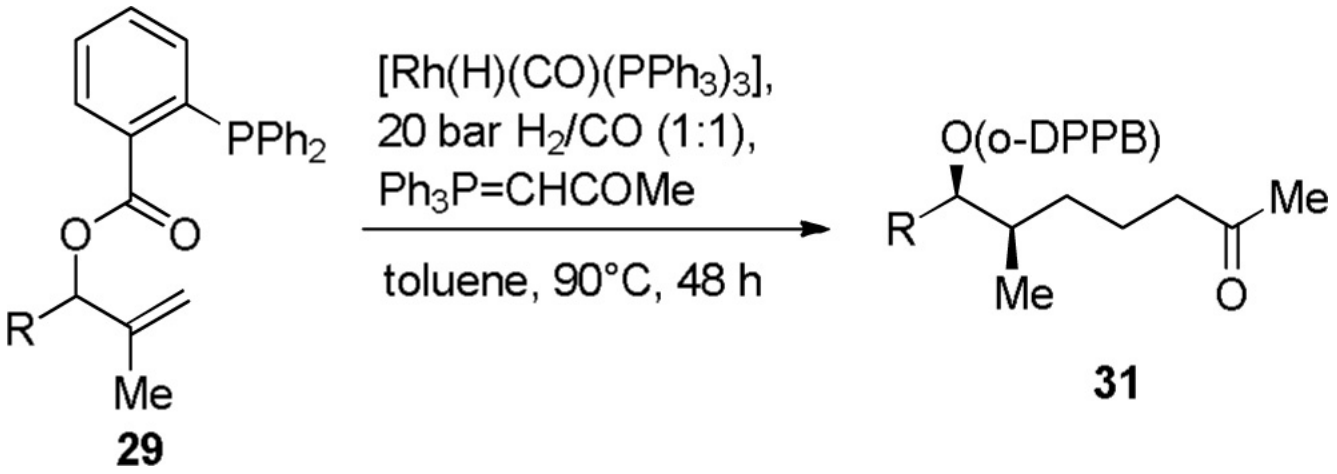
The syn-diastereocontrol= directed hydroformylation step using the o-DPPB group.



	Syn/anti	Yield
	96/4	75
	93/7	78
	92/8	60

B. Breit, S.K. Zahn, Tetrahedron 61 (2005) 6171–6179.

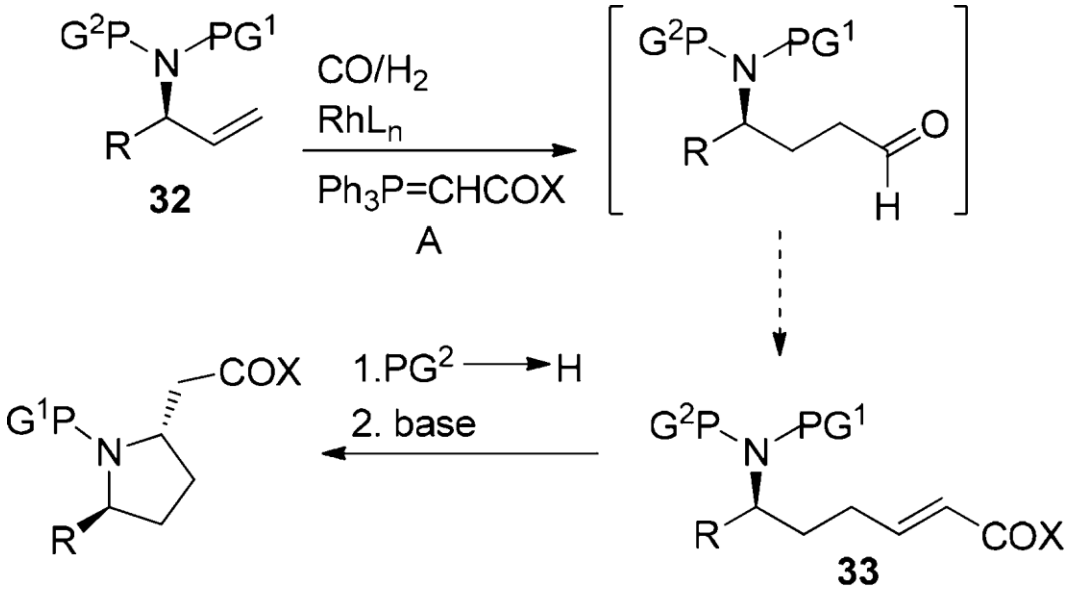
Tandem hydroformylations with CC bond formations hydroformylation/Wittig reaction



Using mono-substituted ylides, the saturated ketone was obtained

B. Breit, S.K. Zahn, Tetrahedron 61 (2005) 6171–6179.

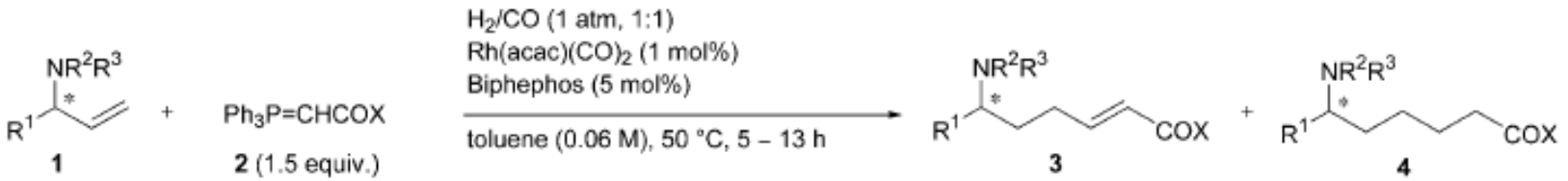
Tandem hydroformylations with CC bond formations HF/Wittig reaction/Aza-Michael addition



preparation of α, β-unsaturated carbonyl compounds from unsubstituted stabilized ylides and chiral allylic amines

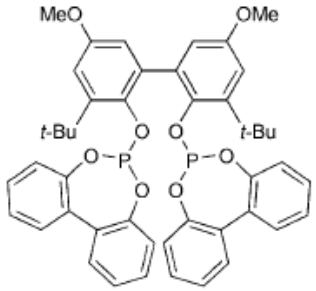
A. Farwick, G. Helmchen, Adv. Synth. Catal. 352 (2010) 1023–1032.

Tandem hydroformylations with CC bond formations HF/Wittig reaction



R^1 = *n*-Pr, Ph, *n*-Hept, CH_2OCPh_3, $CH_2OSi(t\text{-}Bu)Ph_2$
R^2, R^3 = CHO, Boc, Phth, Cbz
X = OMe, Me, N(OMe)Me

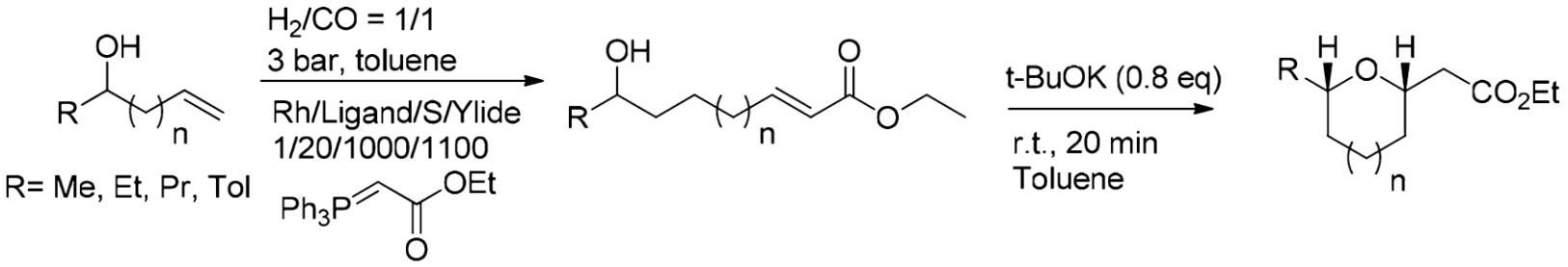
Ratio 3/4 > 80/20
E/Z > 90/10
Yields > 75%

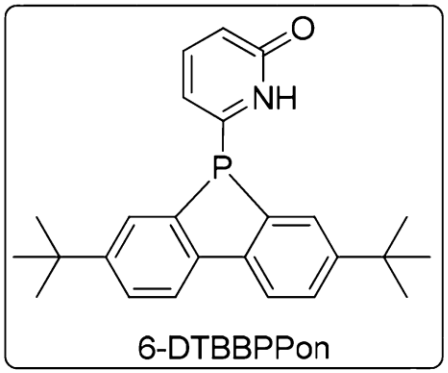


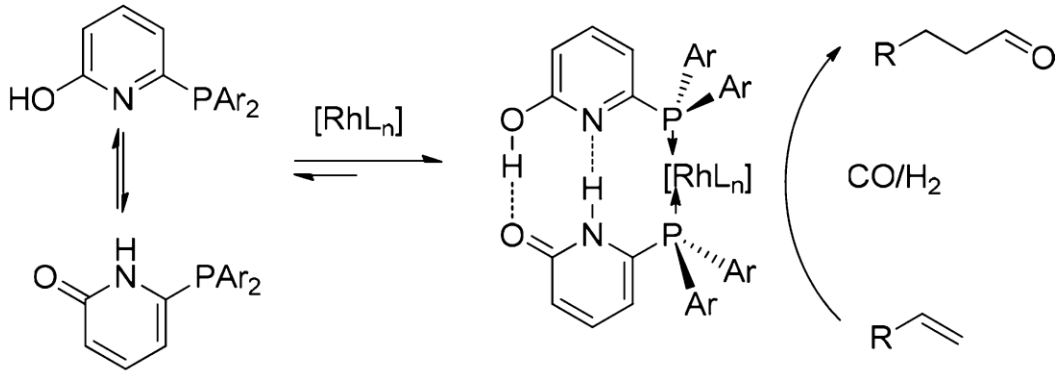
Biphephos (BP)

A. Farwick, G. Helmchen, Adv. Synth. Catal. 352 (2010) 1023–1032.

Tandem hydroformylations with CC bond formations
HF-Wittig olefination-Pyran synthesis



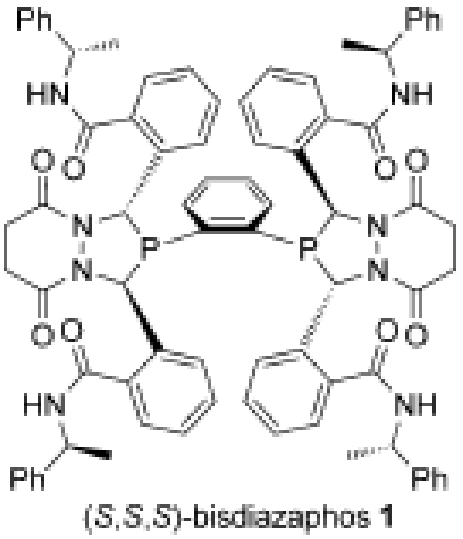




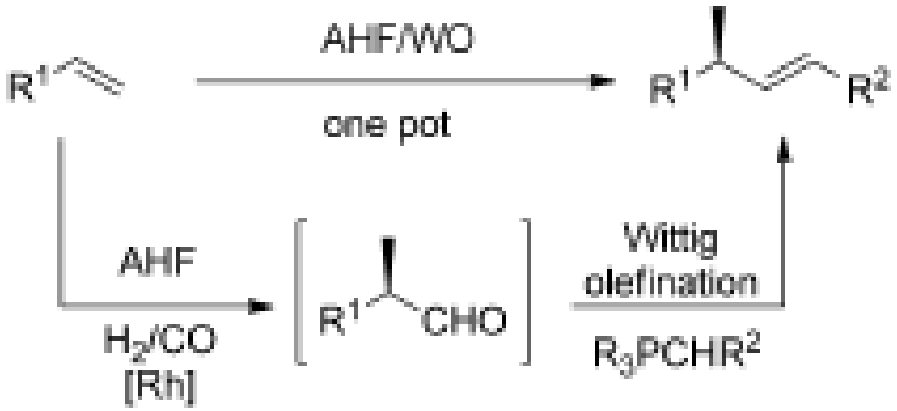
cis-pyrans obtained in excellent yields (87-93%) and diastereo selectivities

Q. Ruan, L. Zhou, B. Breit, Catal. Commun. 53 (2014) 87–90

Tandem hydroformylations with CC bond formations
Asymmetric HF-Wittig reaction

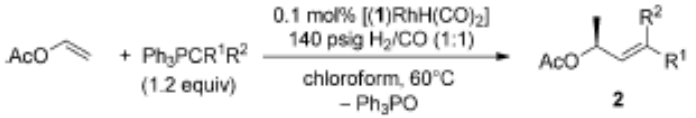


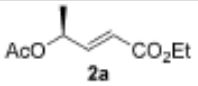
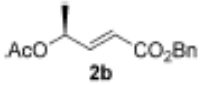
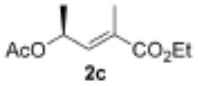
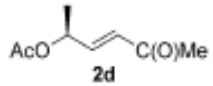
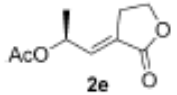
(*S*,*S*,*S*)-bisdiazaphos **1**

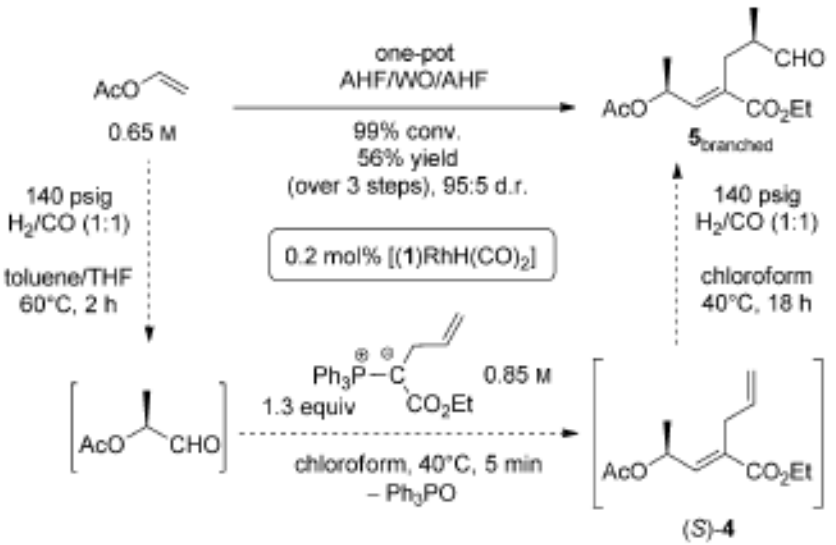


G. W. Wong, C. R. Landis Angew. Chem. Int. Ed. 2013, 52, 1564-1567

Tandem hydroformylations with CC bond formations Asymmetric HF-Wittig reaction

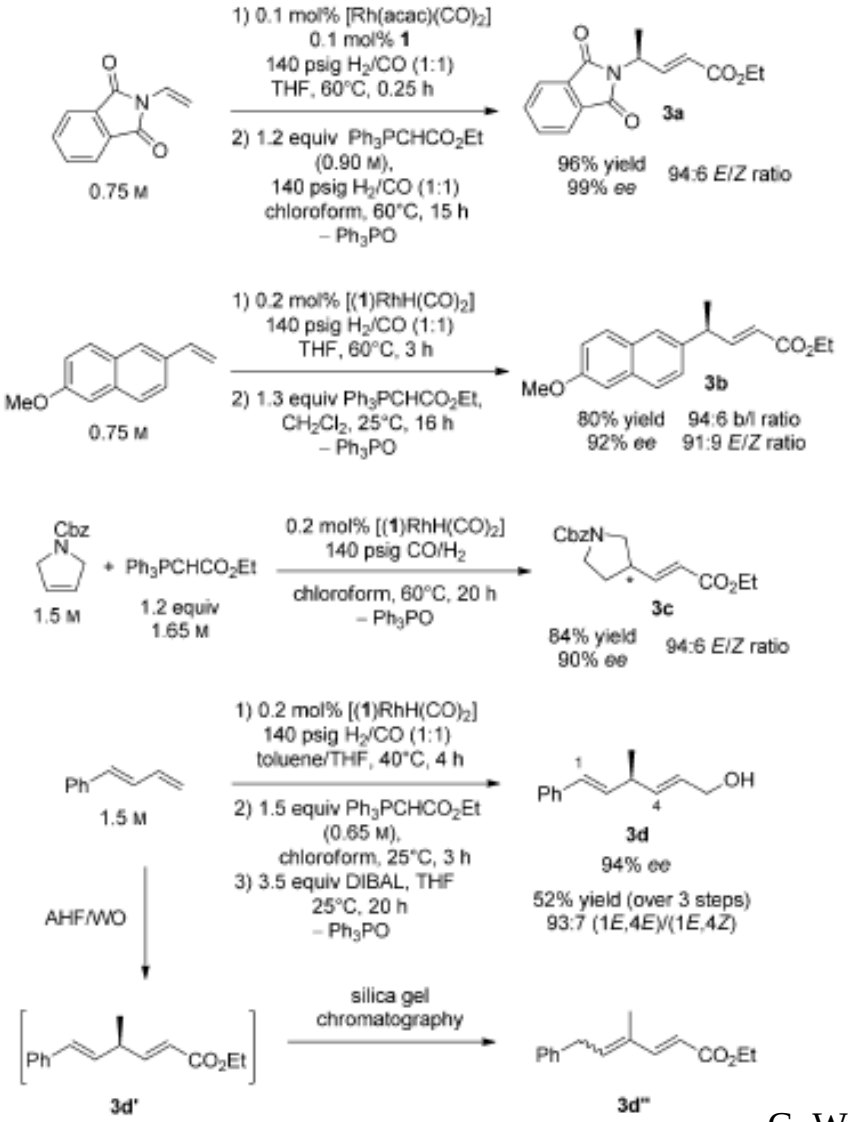


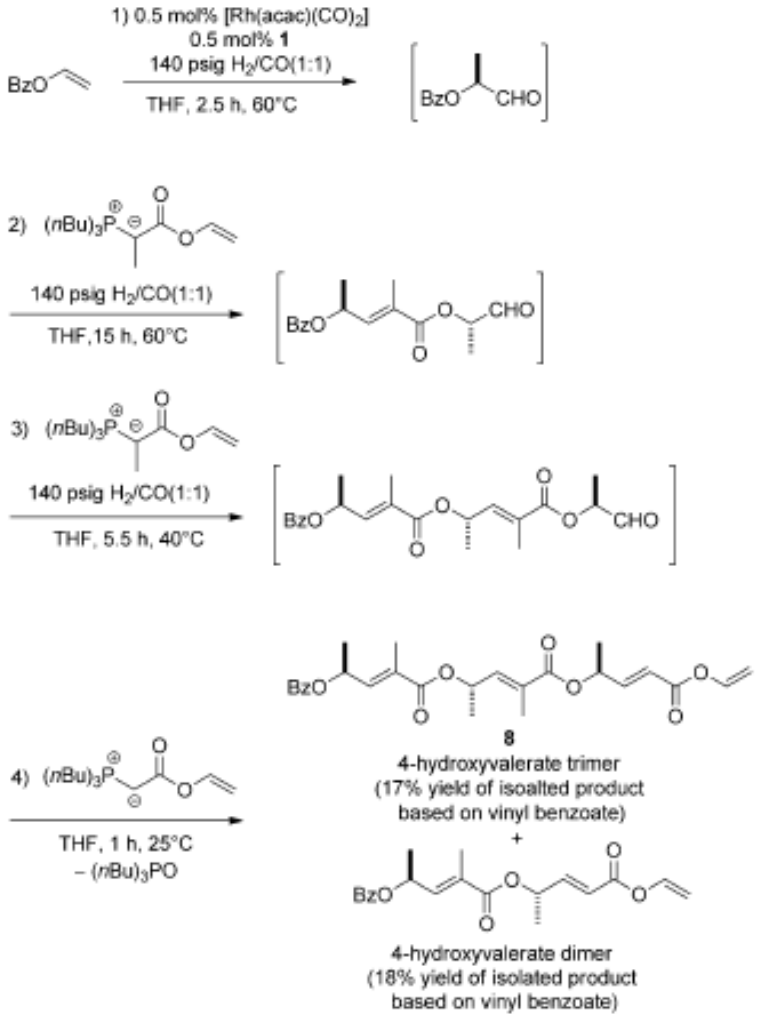
Entry	Product	t [h]	E/Z[b]	Yield [%]	ee [%][c]
1	 2a	18	>95:5	79	99
2	 2b	15	>95:5	46	99
3	 2c	18	>95:5	68	90
4	 2d	21	>95:5	71	97
5	 2e	18	>95:5	67	98



G. W. Wong, C. R. Landis Angew. Chem. Int. Ed. 2013, 52, 1564-1567

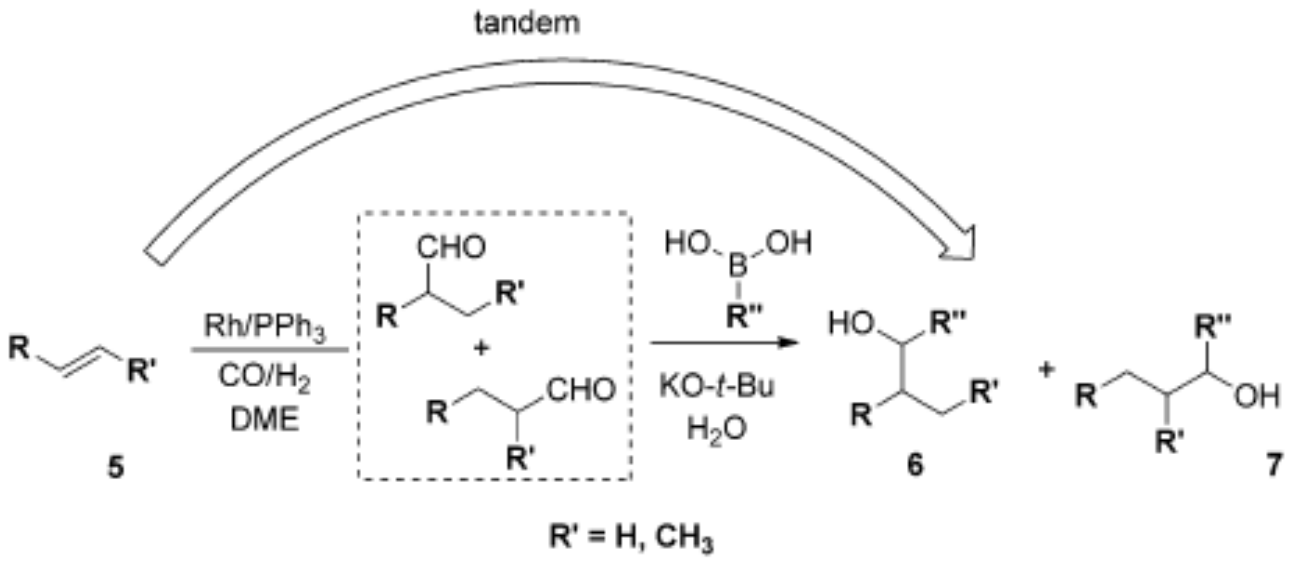
Asymmetric HF-Wittig reaction





G. W. Wong, C. R. Landis Angew. Chem. Int. Ed. 2013, 52, 1564-1567

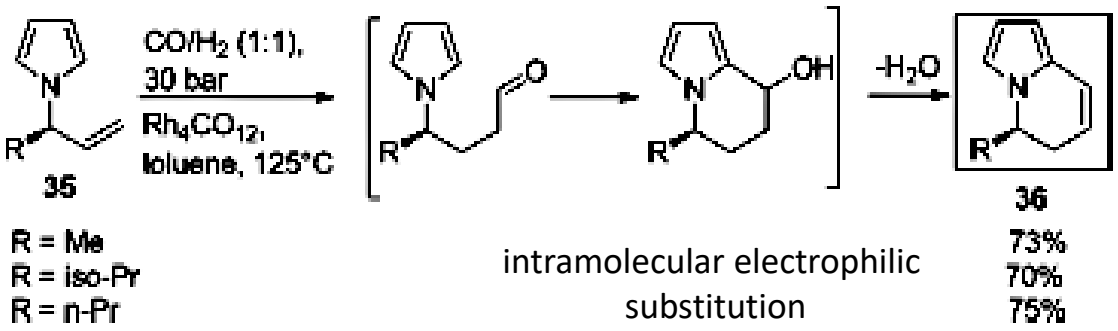
Tandem hydroformylations with CC bond formations
HF/Arylation reaction with boronic acids



Transformation of olefins into secondary alcohols
Highest yields using styrene derivatives as substrates and Ph-B(OH)2 as alkylating agents

A.R. Almeida, R.D. Dias, C.J.P. Monteiro, A.R. Abreu, P.M.P. Gois, J.C. Bayon, M.M. Pereiraa, Adv. Synth. Catal. 356 (2014) 1223–1228

Tandem hydroformylations with CC bond formations HF/cyclization reaction of enantioenriched N-allylpyrroles

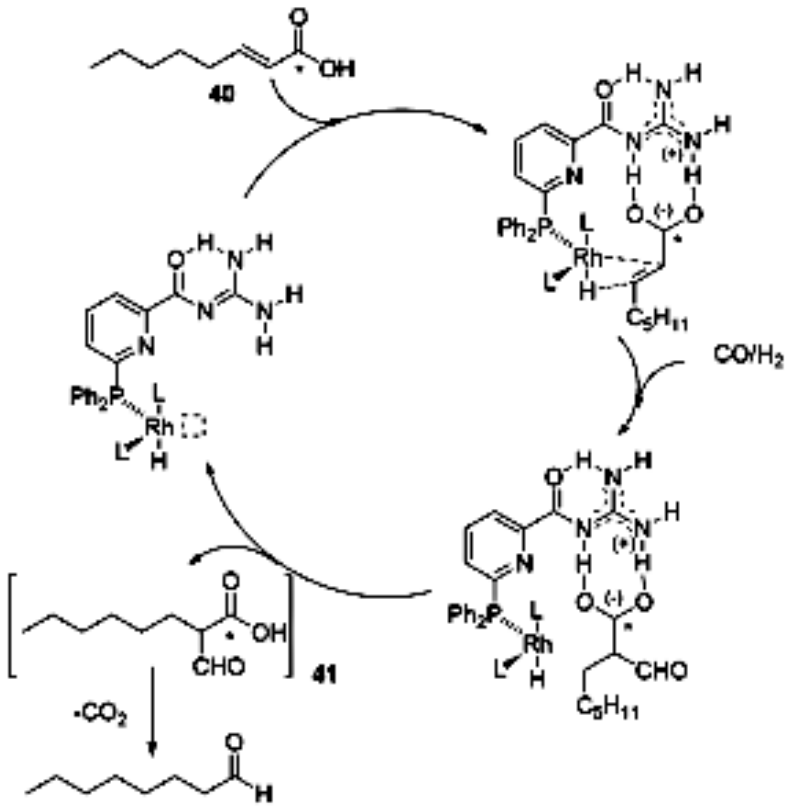


Experimental conditions were key to avoid racemization and enhance regioselectivity

R. Settambolo, G. Guazzelli, A. Mandoli, R. Lazzaroni, Tetrahedron: Asymmetry 15 (2004) 1821–1823.
G. Guazzelli, R. Lazzaroni, R. Settambolo, Beilstein J. Org. Chem. 4 (2008) 2.

Tandem hydroformylation/elimination reactions

HF/decarboxylation of α,β-unsaturated carboxylic acids



3 steps:

- Binding and deprotonation of substrate to the ligand
  - α-selective HF
- Decarboxylation of a-formyl intermediate

=

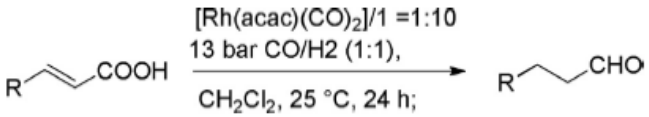
Decarboxylative HF

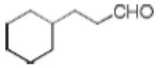
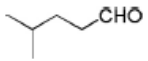
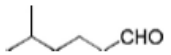
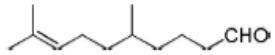
Formal reduction of α,β-unsaturated acids to aldehydes

T. Smejkal, B. Breit, Angew. Chem. Int. Ed. 47 (2008) 3946–3949

Tandem hydroformylation/elimination reactions

HF/decarboxylation of α,β-unsaturated carboxylic acids



Entry	Product	Yield (%)
1		91
2		74
3		47
4		92
5		94
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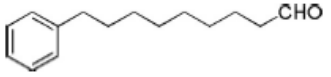
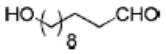
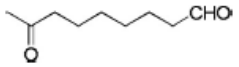
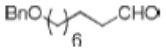
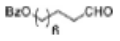
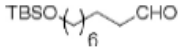
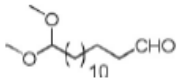
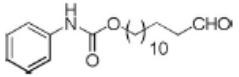
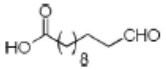
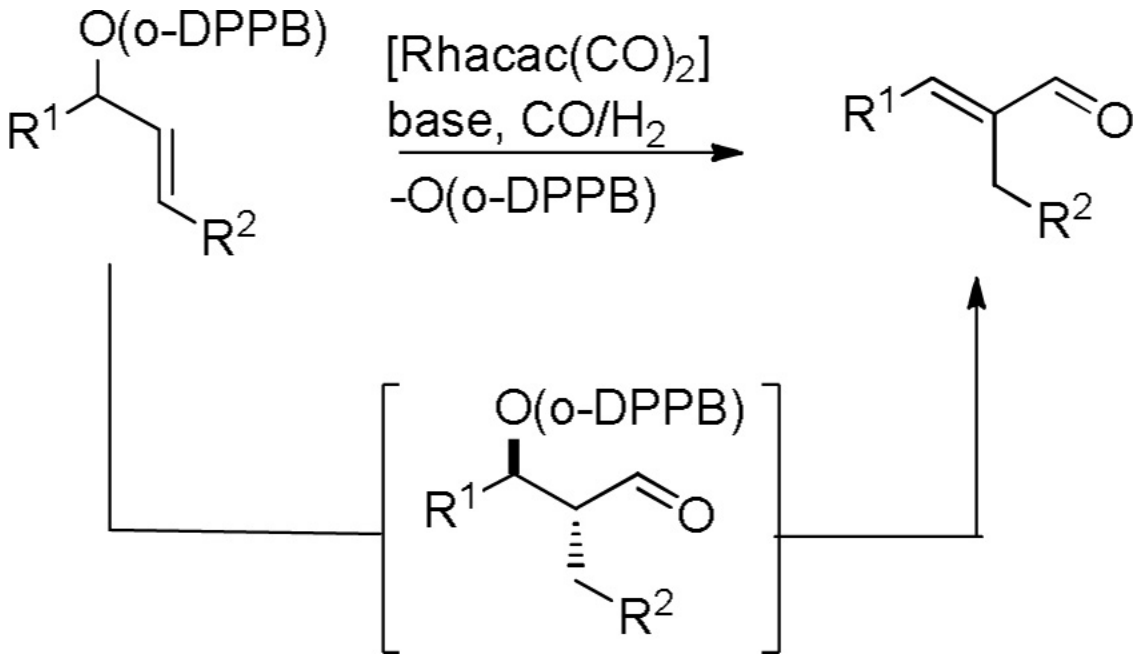
7		94
8		87
9		91
10		74
11		75
12		96
13		95
14		68
15		77
16		50

good yields obtained with substrates possesing olefins, alcohols, amides,acetals or carboxilic acids in side chain

T. Smejkal, B. Breit, Angew. Chem. Int. Ed. 47 (2008) 3946–3949

Tandem hydroformylation/elimination reactions

hydroformylation/β-elimination of o-DPPB esters

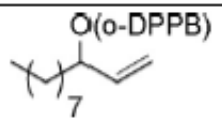
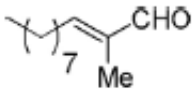
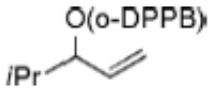
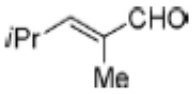
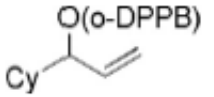
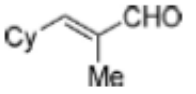
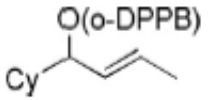
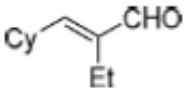
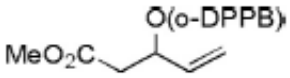
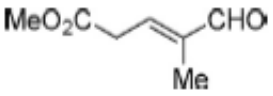
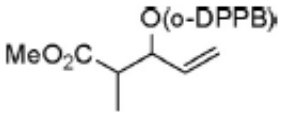
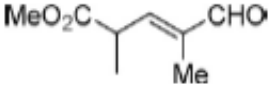
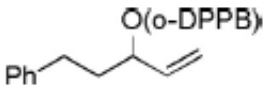
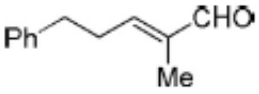
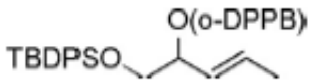
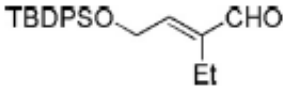


The o-DPPB group = controller for regioselectivity of the hydroformylation subsequently eliminated in situ by mild standard bases.

A.E. Bruch, A. Gebert, B. Breit, Synthesis 14 (2008) 2169–2176.

Tandem hydroformylation/elimination reactions

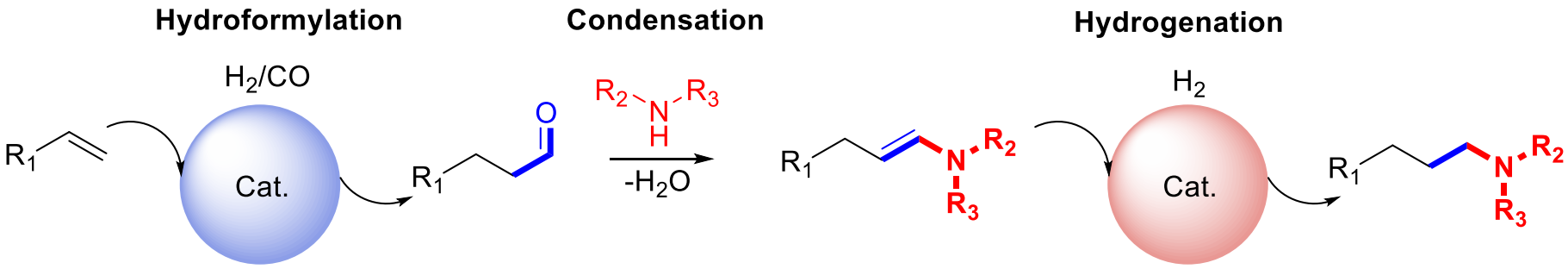
hydroformylation/β-elimination of o-DPPB esters

Substrate	Time (h)	Base (equiv)	Product	Yield(%)
	31	Et_3N (1.1)		96
	24	K_2CO_3 (0.1)		67
	24	K_2CO_3 (0.1)		92
	42	$HNEt_2$ (2.0)		86
	24	K_2CO_3 (0.1)		78
	24	Et_3N (1.1)		84
	24	Et_3N (1.1)		92
	48	Et_3N (5.0)		80

[$Rh(CO)_2acac$] (1.8 mol%), CO/H_2 (40 bar), THF (c = 0.1 M), tandem process, base present during hydroformylation.

A.E. Bruch, A. Gebert, B. Breit, Synthesis 14 (2008) 2169–2176.

Tandem hydroformylation in the presence of N-nucleophiles Hydroaminomethylation

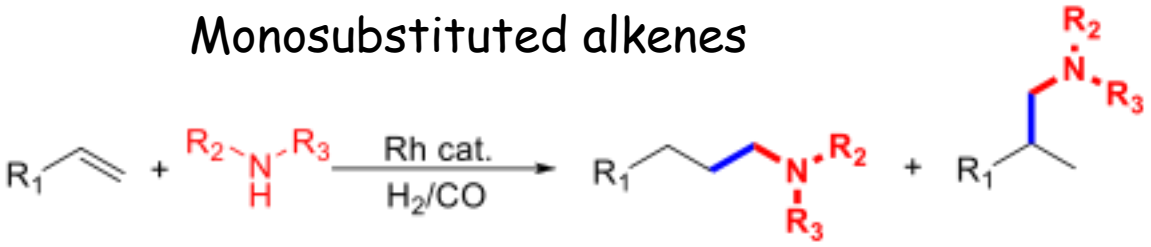


- First discovered by Reppe *et al.* at BASF in 1950
- Direct synthesis of amines via autotandem reaction
- Readily available reagents
- High atom economy process

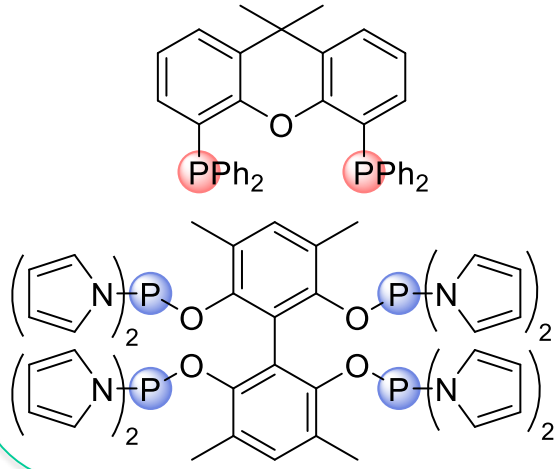
a) Kalck, P.; Urrutigoïty, M. *Chem. Rev.* **2018**, *118*, 3833-3861. b) Chen, C.; Dong, X-Q.; Zhang, X. *Org. Chem. Front.* **2016**, *3*, 1359-1370.

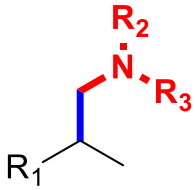
Hydroaminomethylation

Monosubstituted alkenes

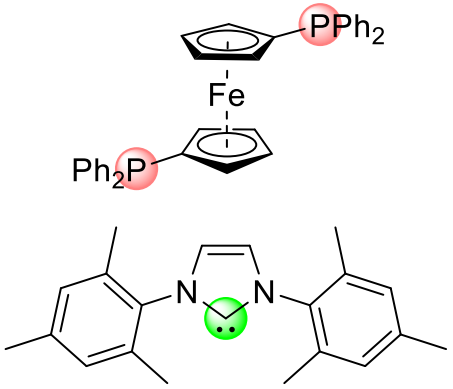


n:iso up to >99:1
>99% amine selectivity





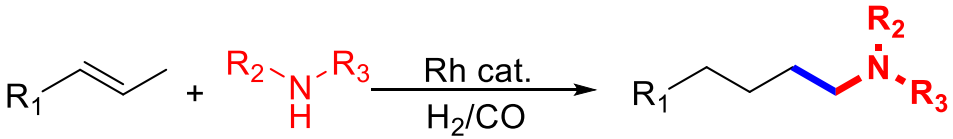
n:iso up to 12:88
up to 98% amine selectivity

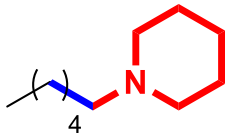


a) Ahmed, M.; Seayad, A. M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* **2003**, *125*, 10311-10318. b) Li, S.; Huang, K.; Zhang, J.; Wu, W.; Zhang, X. *Org. Lett.* **2013**, *15*, 3078-3081. c) Routaboul, L.; Buch, C.; Klein, H.; Jackstell, R.; Beller, M. *Tetrahedron Lett.* **2005**, *46*, 7401-7405. d) Moballigh, A.; Cathleen, B.; Lucie, R.; Ralf, J.; Holger, K.; Anke, S.; Matthias, B. *Chem. Eur. J.* **2007**, *13*, 1594-1601.

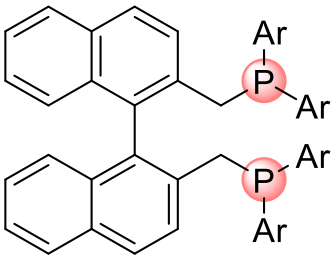
Hydroaminomethylation

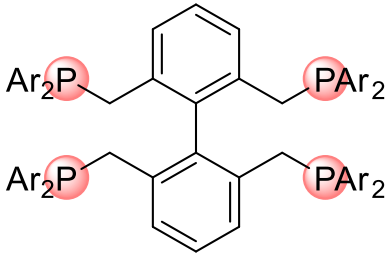
1,2-disubstituted alkenes

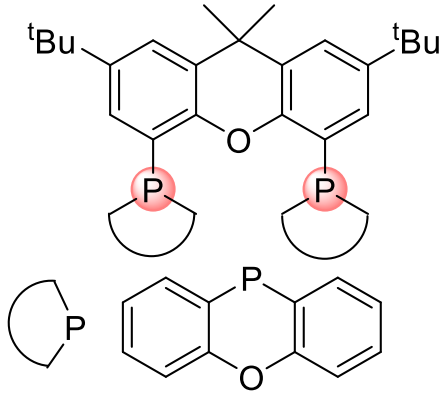




n:iso up to 39:1
83% amine selectivity



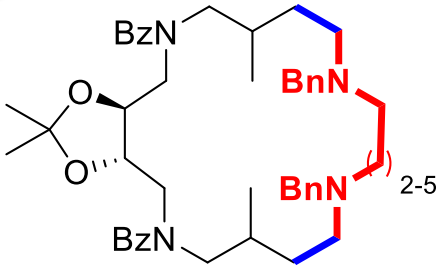




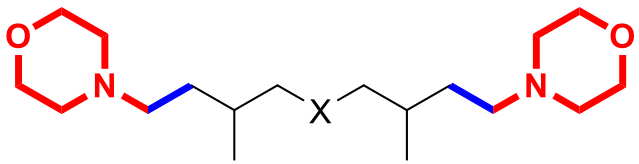
a) Holger, K.; Ralf, J.; Klaus-Diether, W.; Cornelia, B.; Matthias, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 3408-3411. b) Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676-1678. c) Liu, G.; Huang, K.; Cao, B.; Chang, M.; Li, S.; Yu, S.; Zhou, L.; Wu, W.; Zhang, X. *Org. Lett.* **2012**, *14*, 102-105.

Hydroaminomethylation

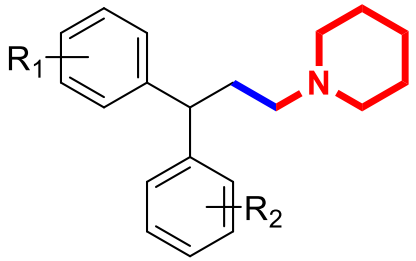
1,1-disubstituted alkenes



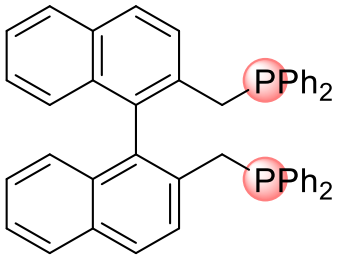
up to 57% yield
$[Rh(acac)(CO)_2]$

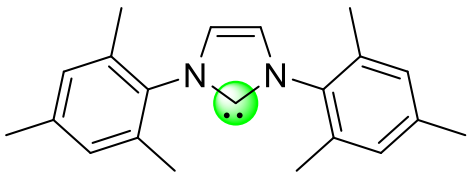


up to 93% yield
$[Rh(\mu\text{-}Cl)(COD)]_2$



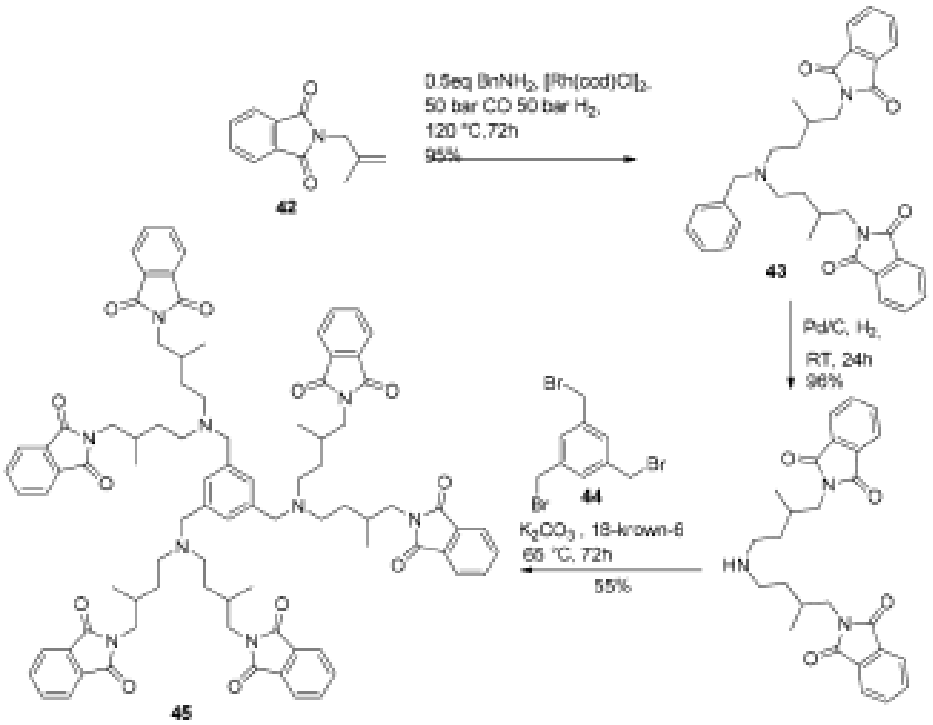
n:iso up to >99:1
up to 90% amine selectivity





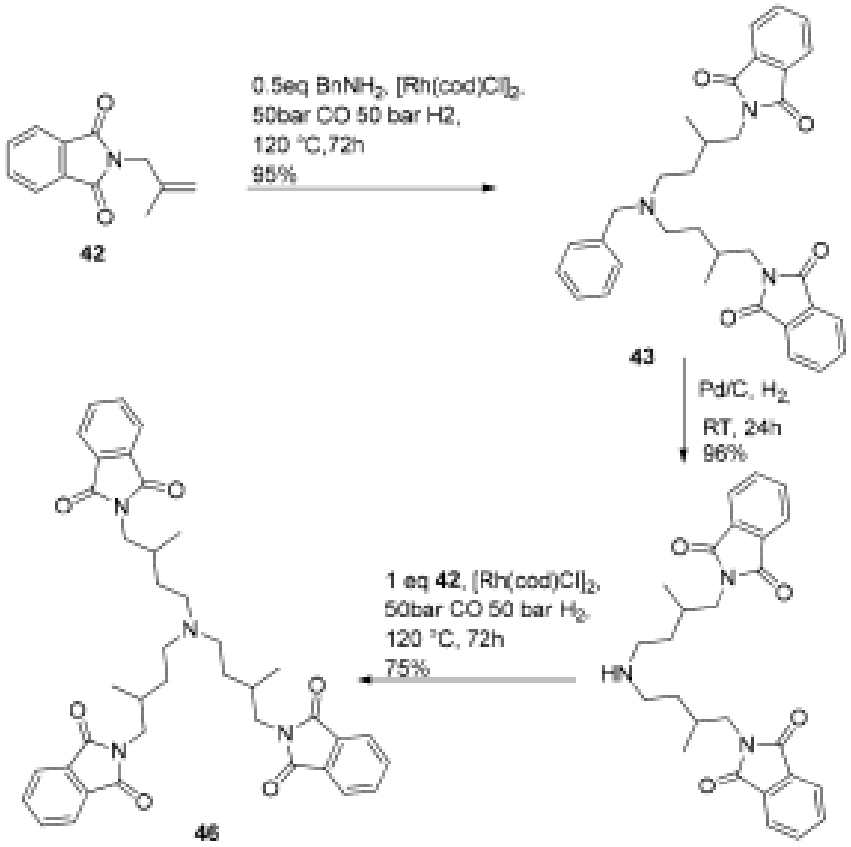
a) Rische, T.; Eilbracht, P. *Tetrahedron* **1999**, *55*, 1915-1920. b) Li, S.; Huang, K.; Zhang, J.; Wu, W.; Zhang, X. *Org. Lett.* **2013**, *15*, 1036-1039.

Hydroaminomethylation in the synthesis of dendrimers



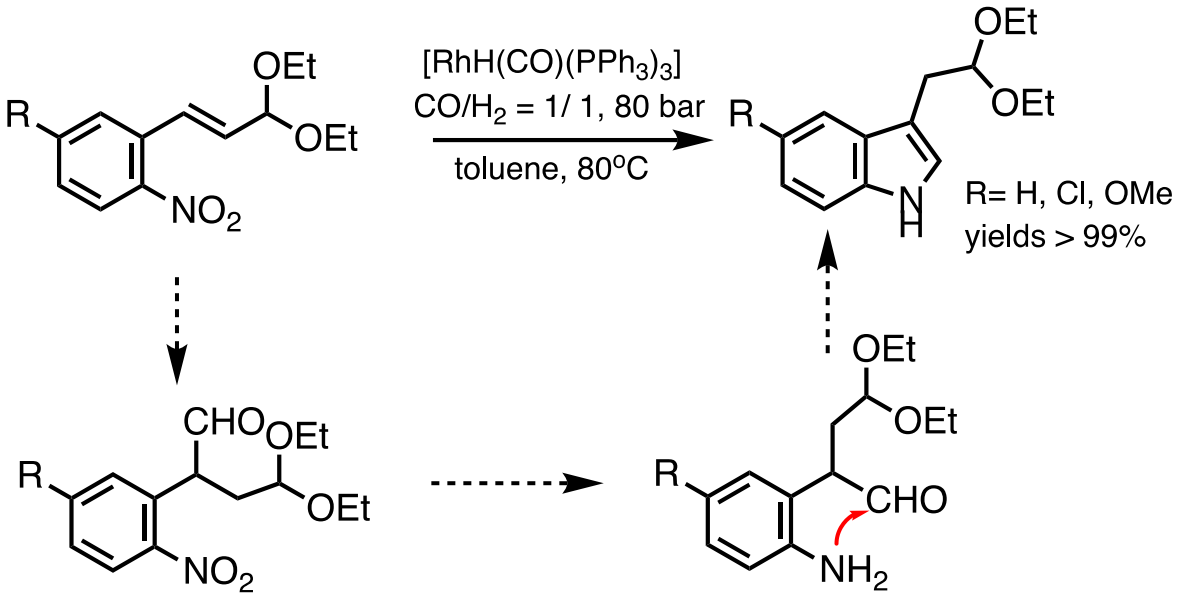
F. Koç, P. Eilbracht, Tetrahedron 60 (2004) 8465–8476.

Hydroaminomethylation in the synthesis of dendrimers



F. Koç, P. Eilbracht, Tetrahedron 60 (2004) 8465–8476.

Tandem hydroformylation/indolization of 2-nitrocinnamaldehydes



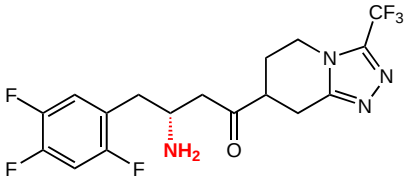
This reaction sequence required efficient hydroformylation, reduction of the nitro group and intramolecular amino reduction followed by dehydration

best yield obtained when [RhH(CO)(PPh3)$_3$] was the catalyst

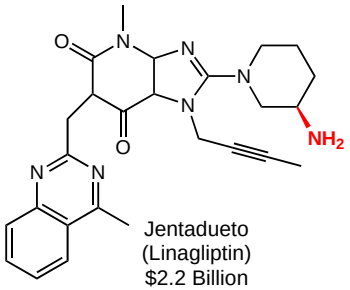
M. Marchetti, S. Paganelli, D. Carbonia, F. Ulgheria, G. Del Pontec, J. Mol. Catal. A 288 (2008) 103–108.

Chiral amines

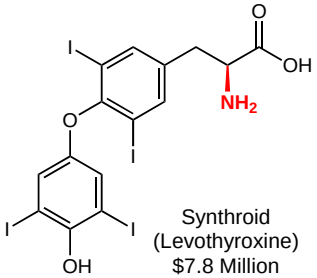
- Significant roles as building blocks in the synthesis of pharmaceuticals and agrochemicals
- At least one chiral amine subunit in ca. 35% of the top 200 small molecule drugs sold in 2018
- High interest in their synthesis from readily available sources



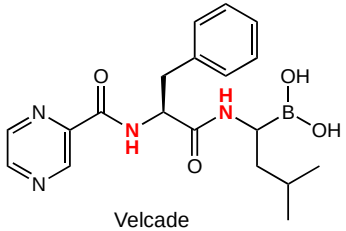
Januvia
(Sitagliptin)
$3.7 Billion



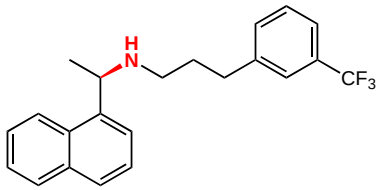
Jentadueto
(Linagliptin)
$2.2 Billion



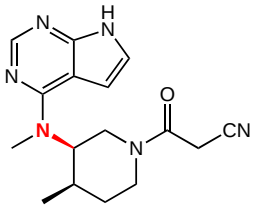
Synthroid
(Levothyroxine)
$7.8 Million



Velcade
(Bortezomib)
$2.3 Billion



Sensipar
(Cinacalcet)
$1.8 Billion

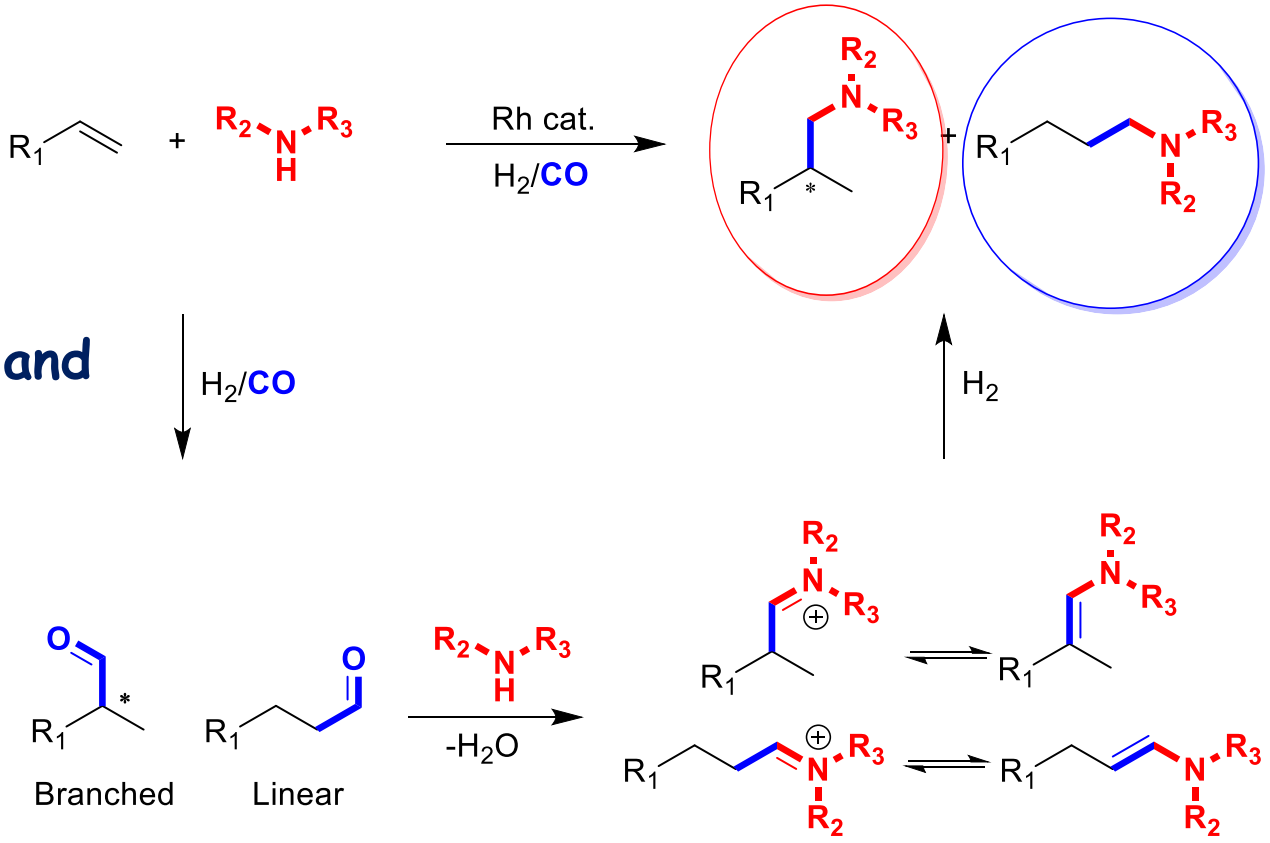


Xeljanz
(Tofacitinib)
$1.8 Billion

Yin, O.; Shi, Y.; Wang, J.; Zhang, X. *Chem. Soc. Rev.*, 2020, *49*, 6141

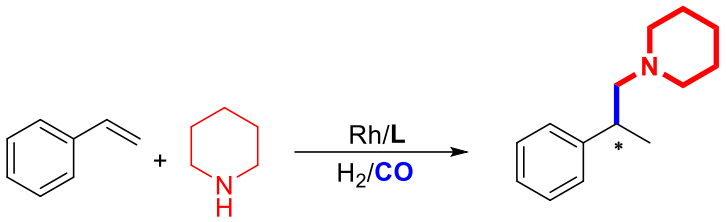
Asymmetric hydroaminomethylation

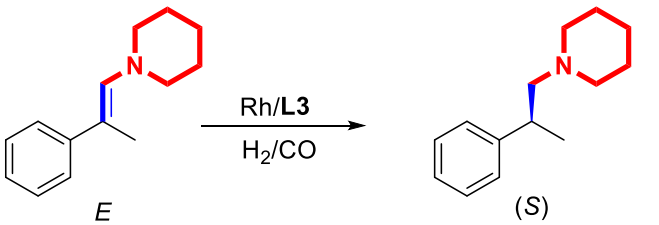
- Extensively studied
- Phosphorus ligands and carbenes applied
- Rh and Ru used as metals

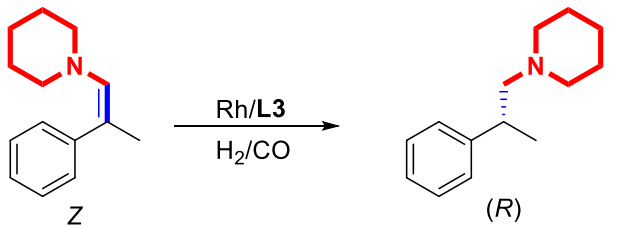


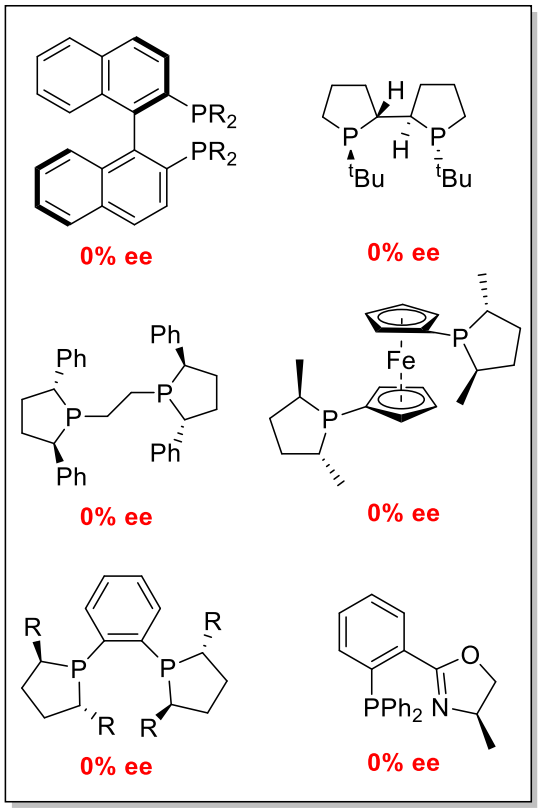
a) Kalck, P.; Urrutigoïty, M. *Chem. Rev.* **2018**, *118*, 3833-3861. b) Chen, C.; Dong, X-Q.; Zhang, X. *Org. Chem. Front.* **2016**, *3*, 1359-1370. c) Eilbracht, P.; Schmidt, A. M. In Transition Metals for Organic Synthesis, 2nd ed.; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, Germany, **2004**; *Vol. 1*, pp 57−85. d) Crozet, D.; Urrutigoïty, M.; Kalck, P. *ChemCatChem* **2011**, *3*, 1102-1118.

Asymmetric hydroaminomethylation





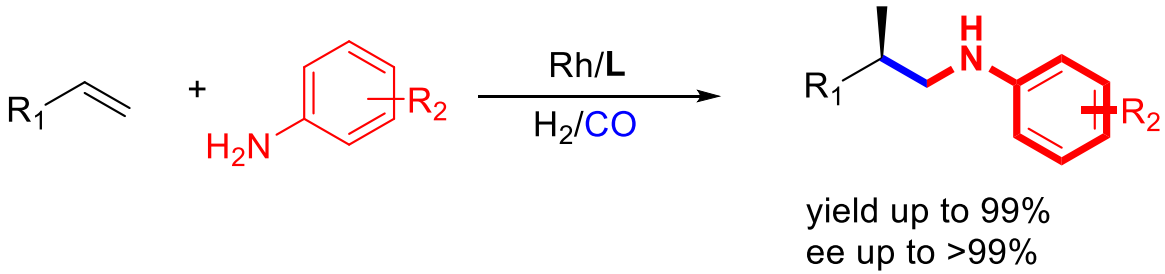




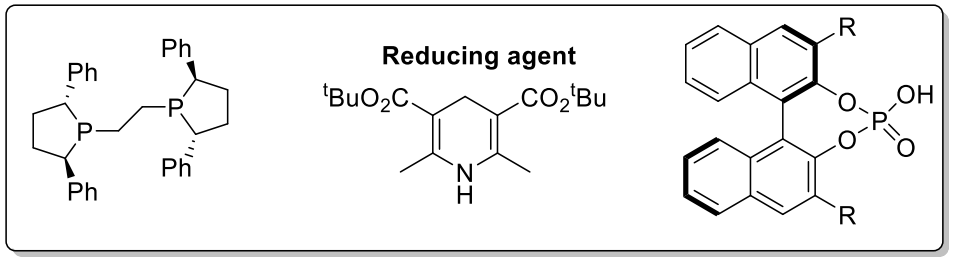
Crozet, D.; Kefalidis, C. E,; Urritigoïty, M.; Maron, L.; Kalck, P. *ACS Catal.* **2014**, *4*, 435-447.

Indirect Rh-catalyzed asymmetric HAM

Metal and organocatalyzed asymmetric HAM



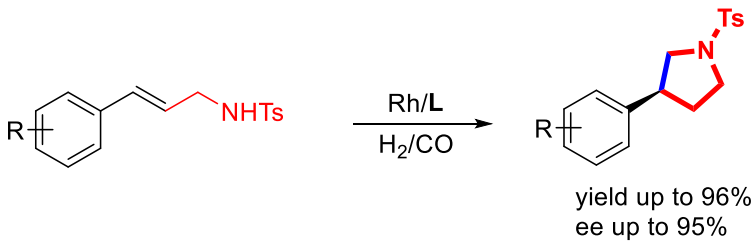
yield up to 99%
ee up to >99%

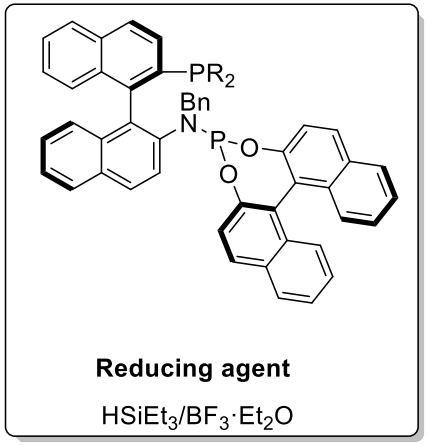


Han and coworkers *Org. Lett.* **2017**, *19*, 1076-1079

Indirect Rh-catalyzed asymmetric HAM

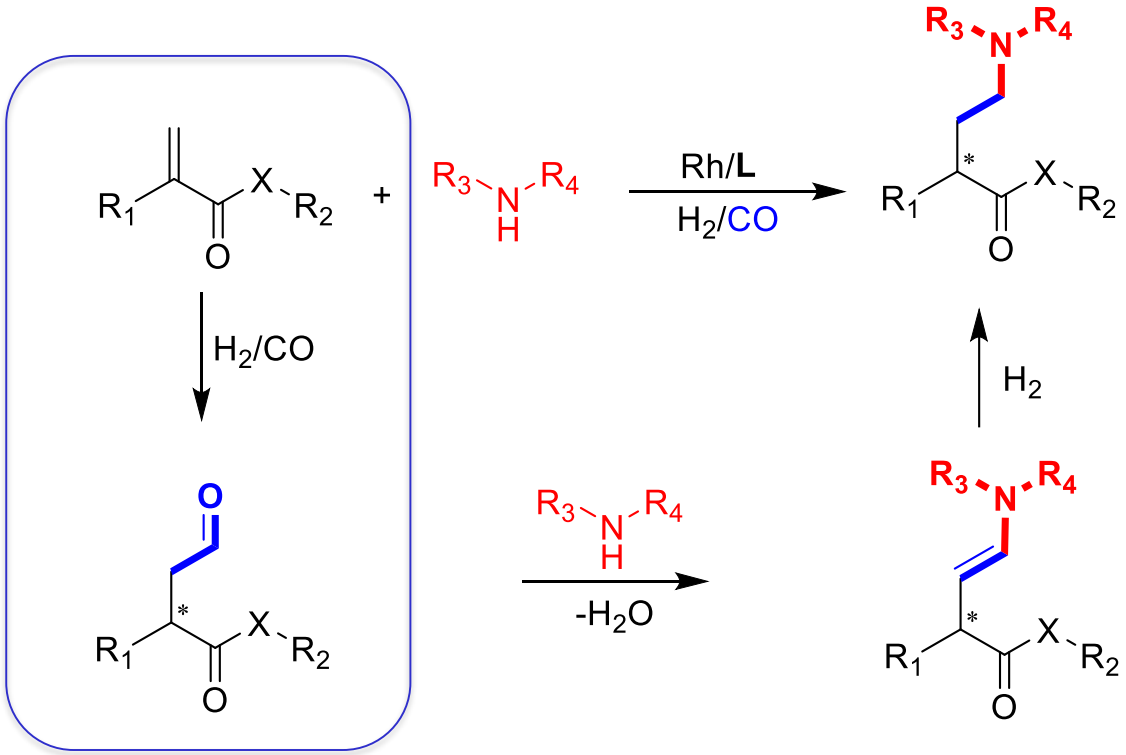
Rh-catalyzed interrupted asymmetric HAM





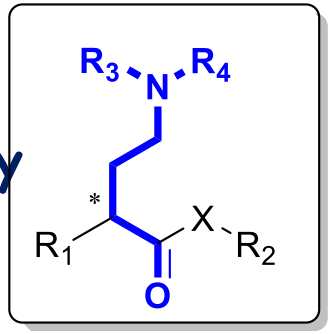
Zhang and coworkers *J. Am. Chem. Soc.* **2016**, *138*, 9017-9020.

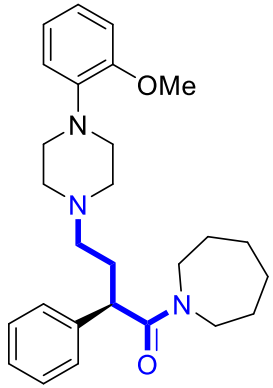
Rh-catalyzed asymmetric hydroaminomethylation of α-substituted acrylates and acrylamides



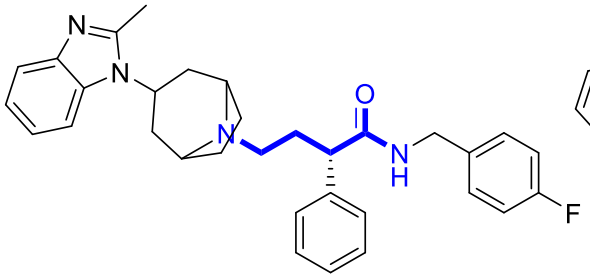
γ-aminobutyric acids and derivatives

- Play an important role in the neurological system
- Great importance in bioorganic and medicinal chemistry
- Scaffold present in large number of natural products

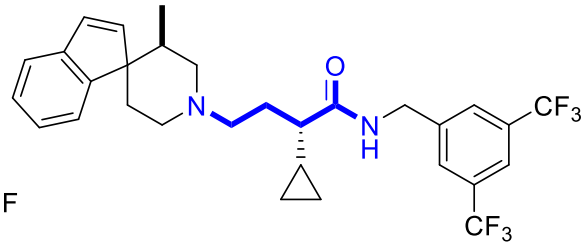




RWAY (brain imaging)



CCR5 antagonist (HIV drug)

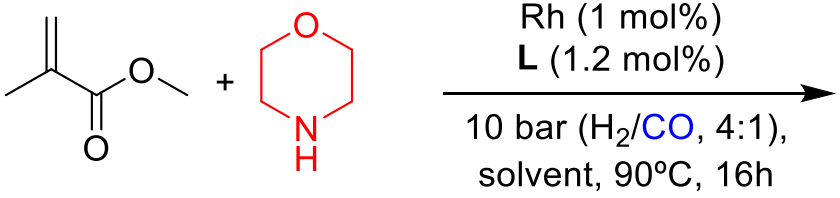


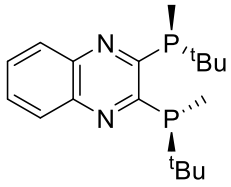
CCR2 antagonist
(inflammatory processes)

a) Maslivetc, V. A.; Rubina, M.; Rubin, M. *Org. Biomol. Chem.* **2015**, *13*, 8993-8996 b) Butora, G. *et al. Bioorg. Med. Chem. Lett.* **2006**, *16*, 4715-4722. c) Pike, V. *et al. Eur. J. Nucl. Med. Mol. Imaging*, **2007**, *34*, 1670-1682. d) Long, Y. *et al. Bioorg. Med. Chem. Lett.* **2010**, *20*, 2219-2223.

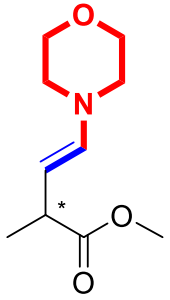
HAM of α-alkyl acrylates

Reaction conditions



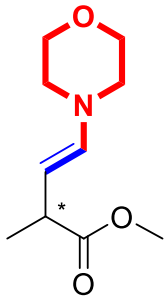


[Rh(acac)(CO)$_2$] toluene

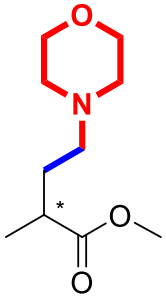


45% yield

[Rh(acac)(CO)$_2$] toluene/DCE

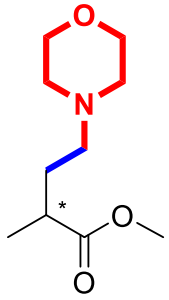


4% yield



38% yield
72% ee

[Rh(COD)$_2$]BF$_4$ toluene/DCE



63% yield
73% ee

Stops at the enamine

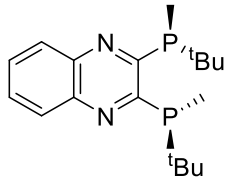
Uncomplete reaction

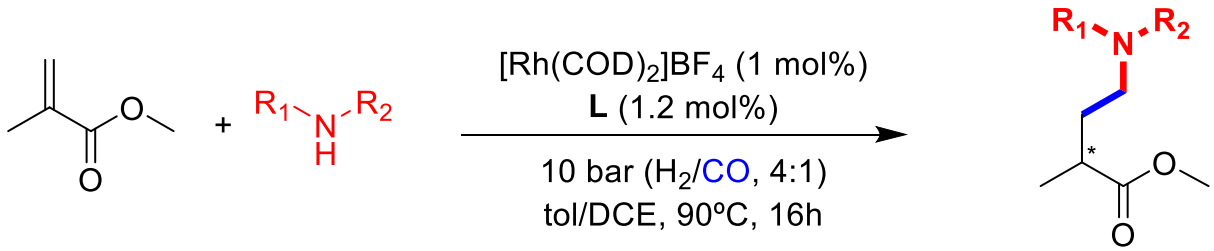
Full conversion High yield

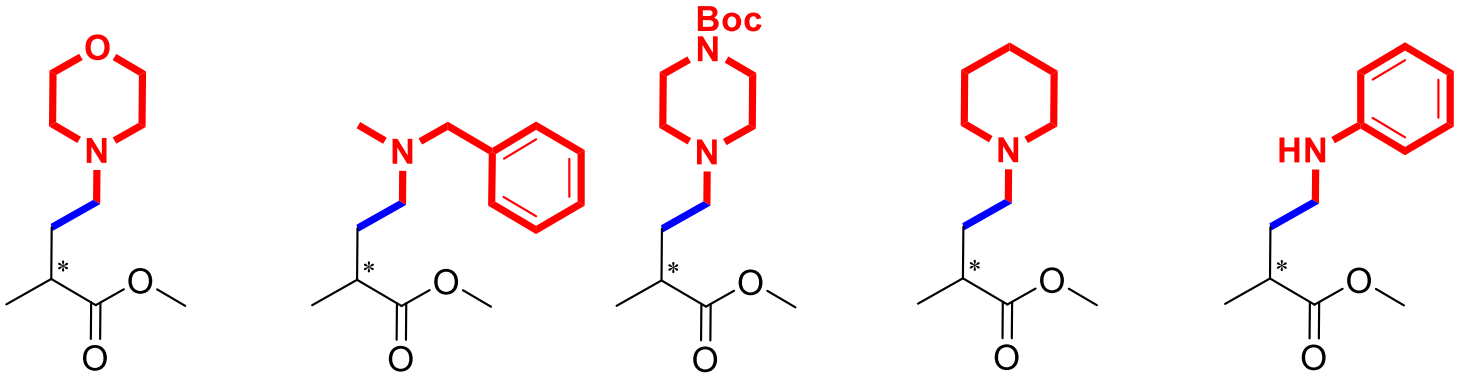
Catal. Sci. Technol., **2020**, *10*, 630–634

HAM of α-alkyl acrylates

Scope of amines





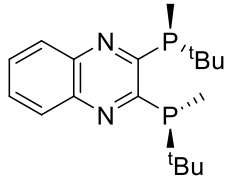


60%, 73% ee | 50%, 72% ee | 50%, 68% ee | 50%, n.d.% ee | 19%, 60% ee

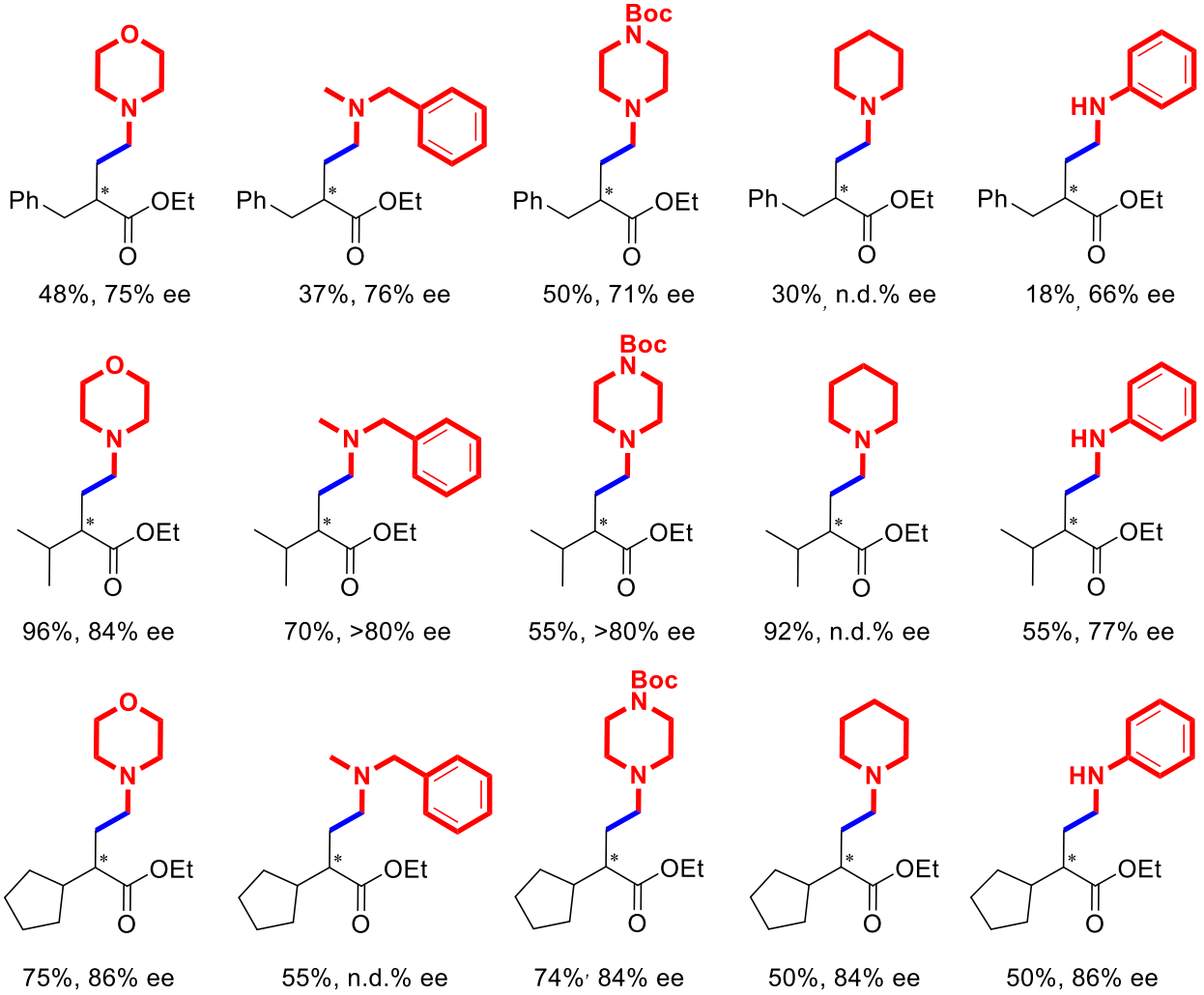
[Rh(acac)(CO)$_2$]

Catal. Sci. Technol., **2020**, *10*, 630–634

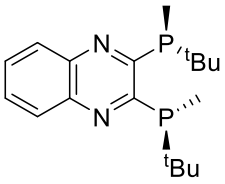
HAM of α-alkyl acrylates



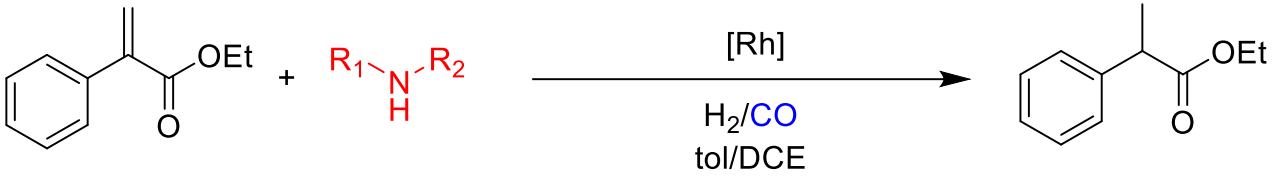
Scope of substrates



Catal. Sci. Technol., **2020**, *10*, 630–634



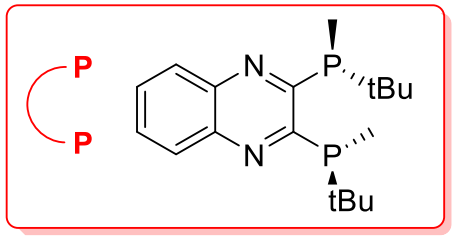
Phenyl-substituted acrylates

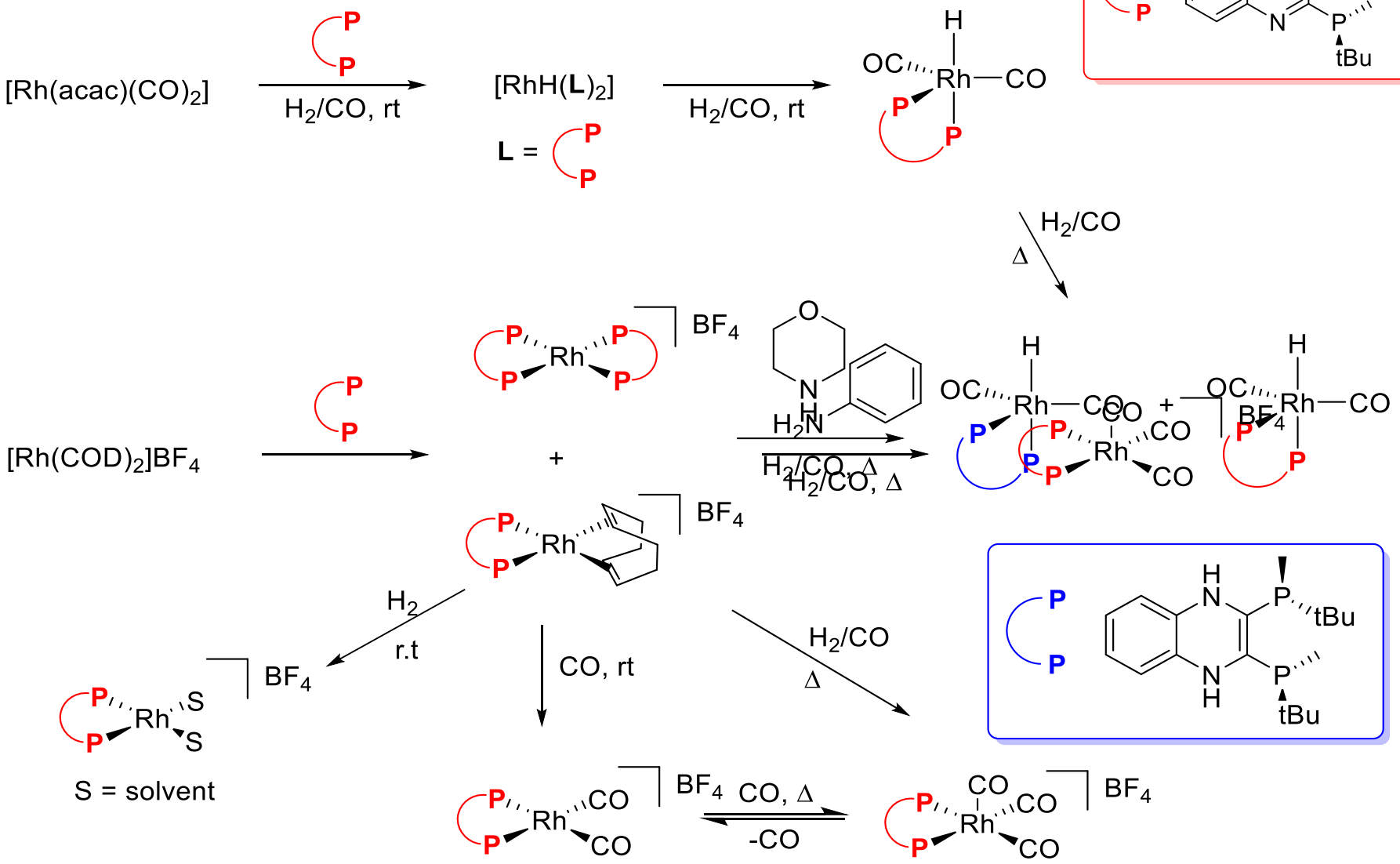


Only alkene hydrogenation products detected

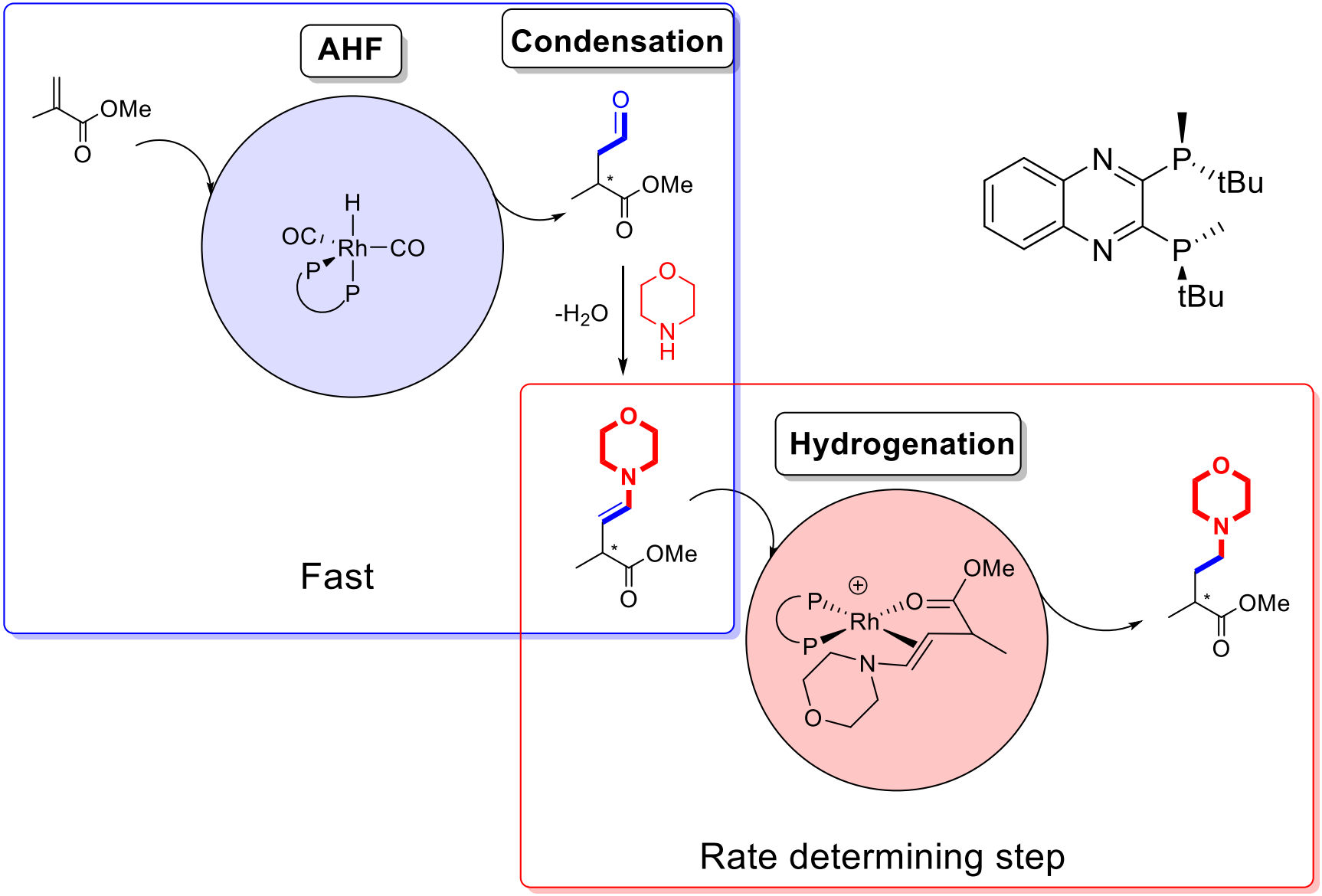
Catal. Sci. Technol., **2020**, *10*, 630–634

High-Pressure NMR studies





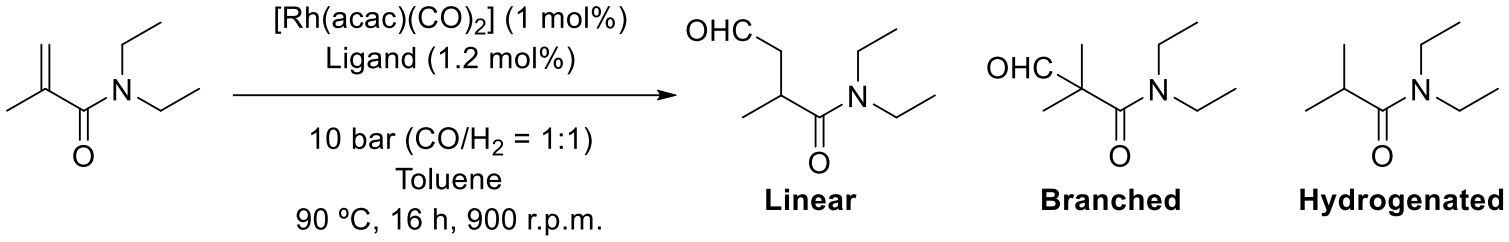
HAM of α-alkyl acrylates



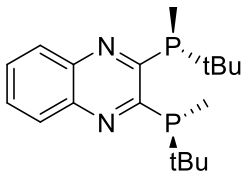
Catal. Sci. Technol., **2020**, *10*, 630–634

HAM of α-alkyl acrylamides

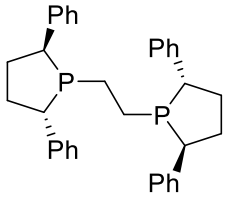
Asymmetric hydroformylation



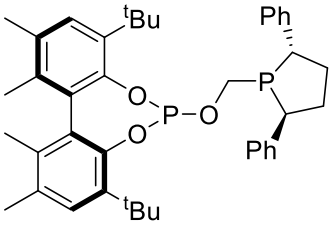
Ligand screening



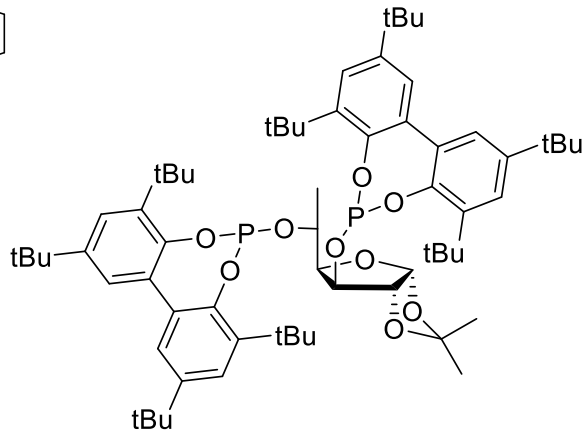
Conv. 0%



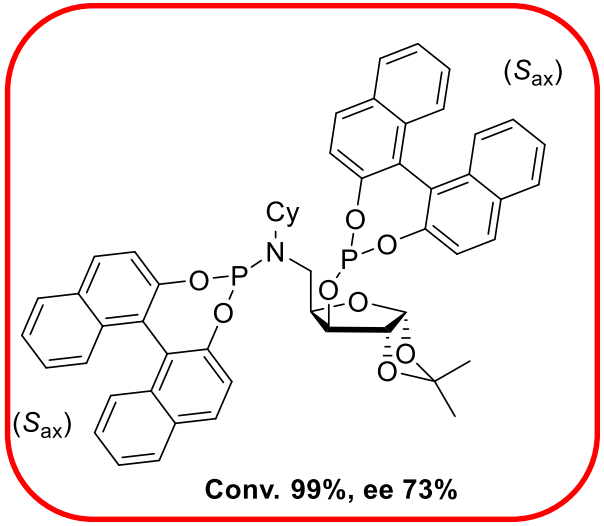
Conv. 2%



Conv. 64%, ee 8%



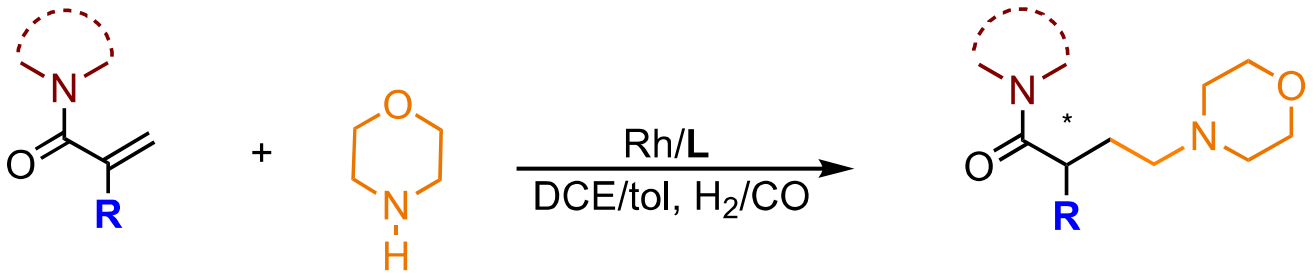
Conv. 74%, ee 4%

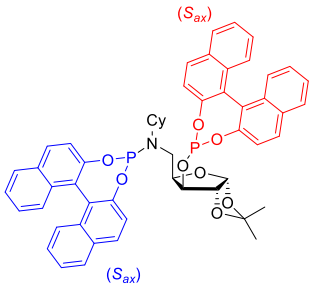


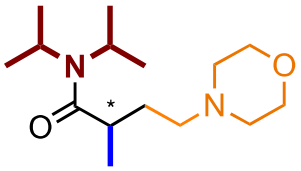
Conv. 99%, ee 73%

Org. Lett. **2020**, *22*, 9036−9040

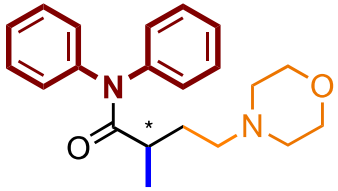
HAM of α-alkyl acrylamides



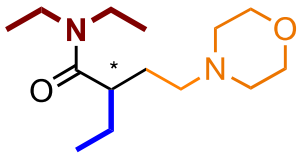




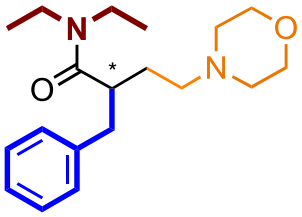
67%, 84% ee



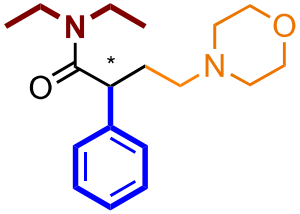
57%,70% ee



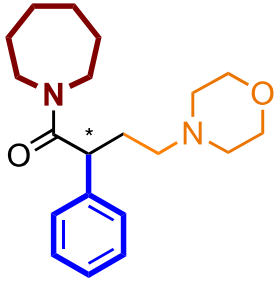
78%, 84% ee



75%, 86% ee



65%, 78% ee



59%, 84% ee

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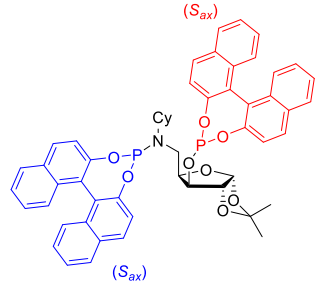
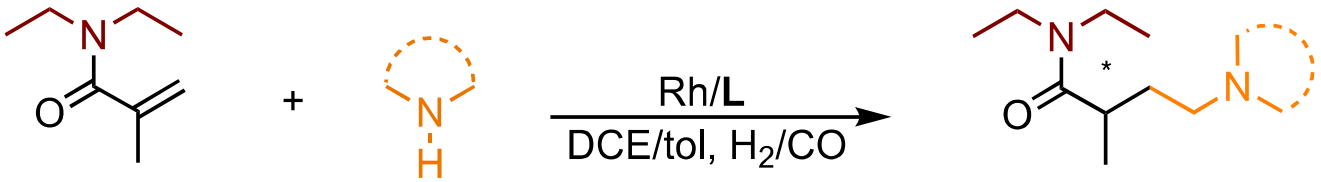
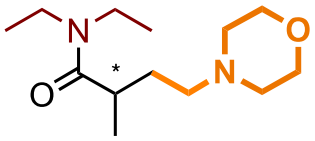
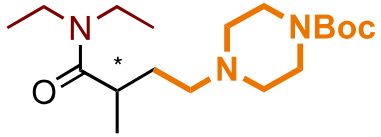
HAM of α-alkyl acrylamides



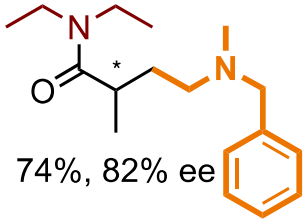




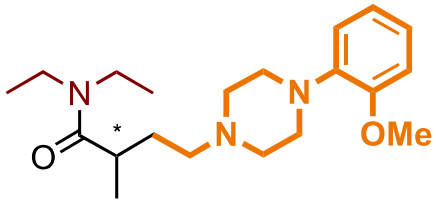
79%, 85% ee



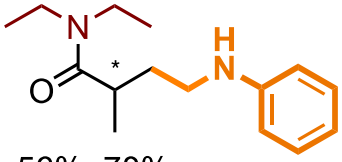
73%, 84% ee



74%, 82% ee



48%, 82% ee



56%, 78% ee

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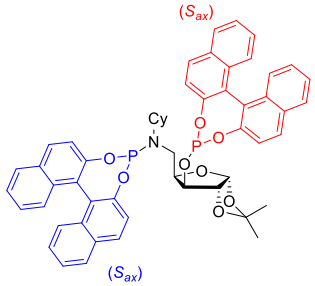
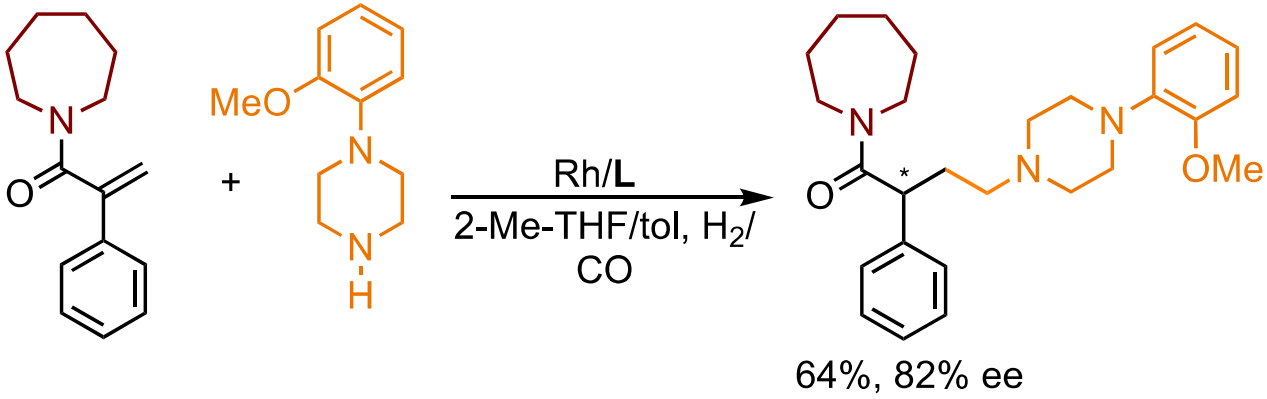
HAM of α-alkyl acrylamides



Direct synthesis of RWAY (brain imaging)



64%, 82% ee

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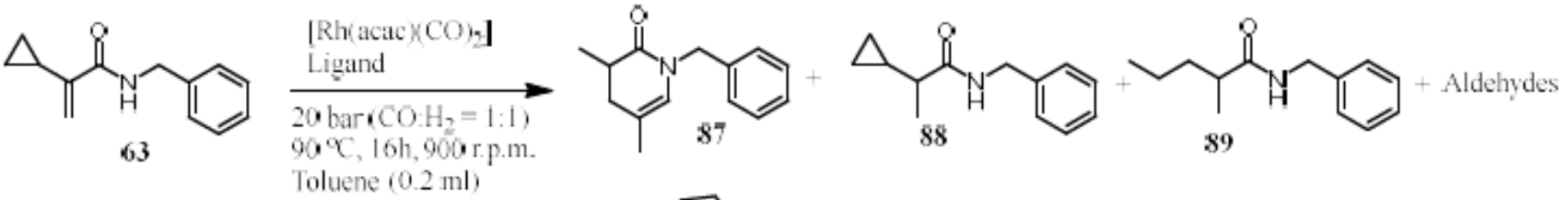
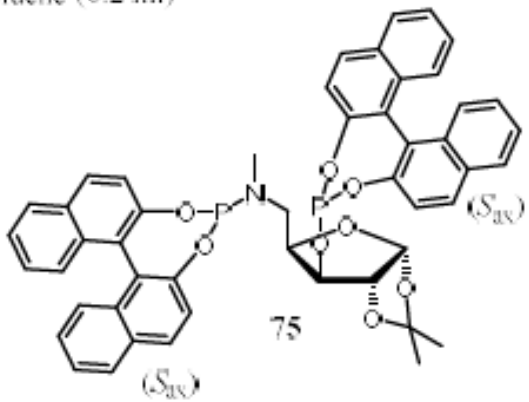
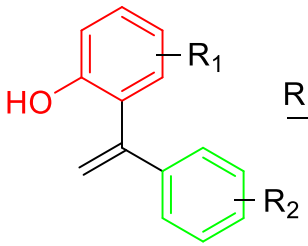
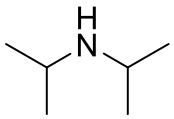

[Rh(acac)(CO)2]
Ligand
20 bar (CO:H2 = 1:1)
90 °C, 16h, 900 r.p.m.
Toluene (0.2 ml)
63
87
88
89
+ Aldehydes


(Sax)
(Sax)
75

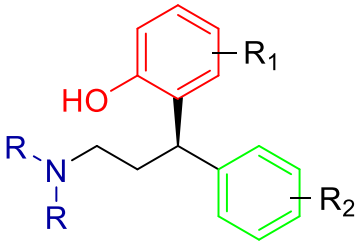
A) 1,1-diarylethenes





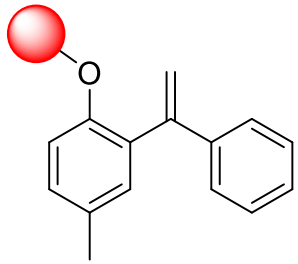
$Rh(acac)(CO)_2$ (1 mol%), L1 (1.2 mol%)

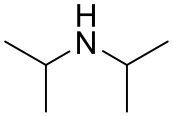
MeTHF, CO, H_2 (30 bar 2:1),
125 °C, 16 h



Tolterodine derivatives

53%, 41% ee

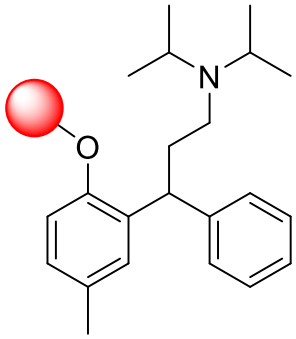




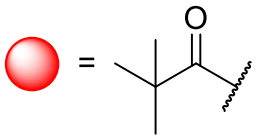
$Rh(acac)(CO)_2$ (1 mol%)
L2 (1.2 mol%)

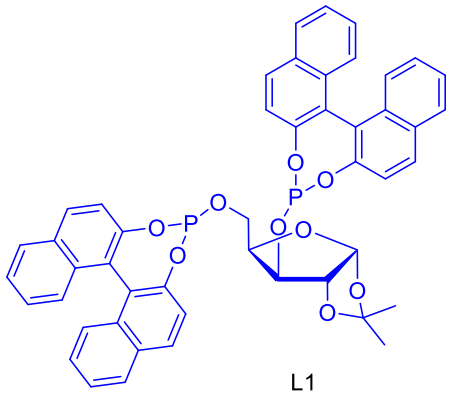
MeTHF, CO, H_2 (30 bar 2:1)
>100°C, 20 h

Conv. 52%

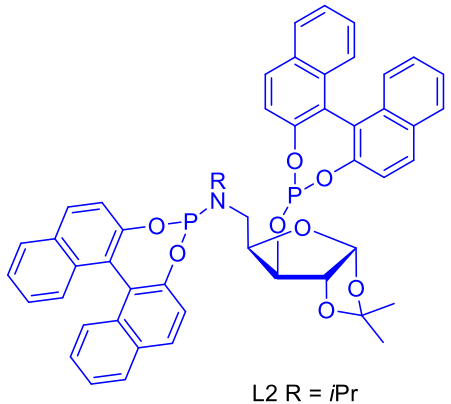


90%
ee 46%



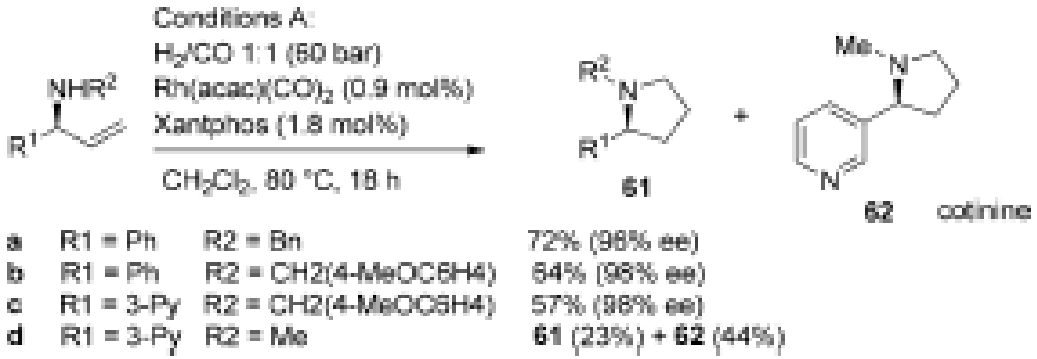


L1

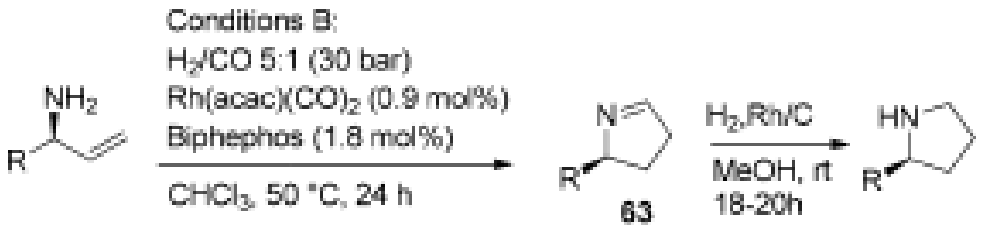


L2 R = *i*Pr
L3 R = Bn

Tandem hydroformylation/intramolecular hydroaminomethylation



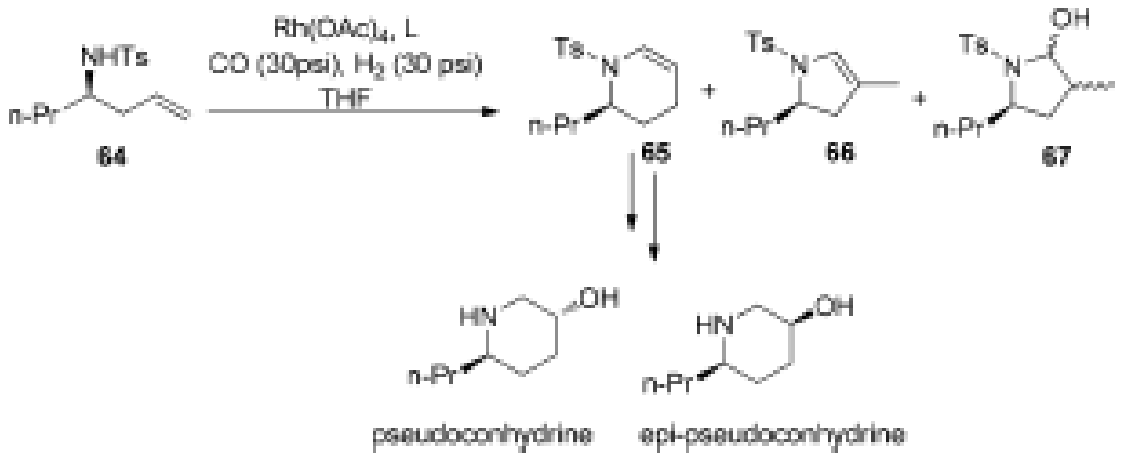
a	R1 = Ph	R2 = Bn	72% (98% ee)
b	R1 = Ph	R2 = CH2(4-MeOC6H4)	64% (98% ee)
c	R1 = 3-Py	R2 = CH2(4-MeOC6H4)	57% (86% ee)
d	R1 = 3-Py	R2 = Me	**61** (23%) + **62** (44%)



R = Ph	57% (98% ee)	73% (96%
R = n-Hept	69%	89%

P. Dübon, A. Farwick, G. Helmchen, Synlett 9 (2009) 1413–1416.

Tandem hydroformylation/cyclization sequence

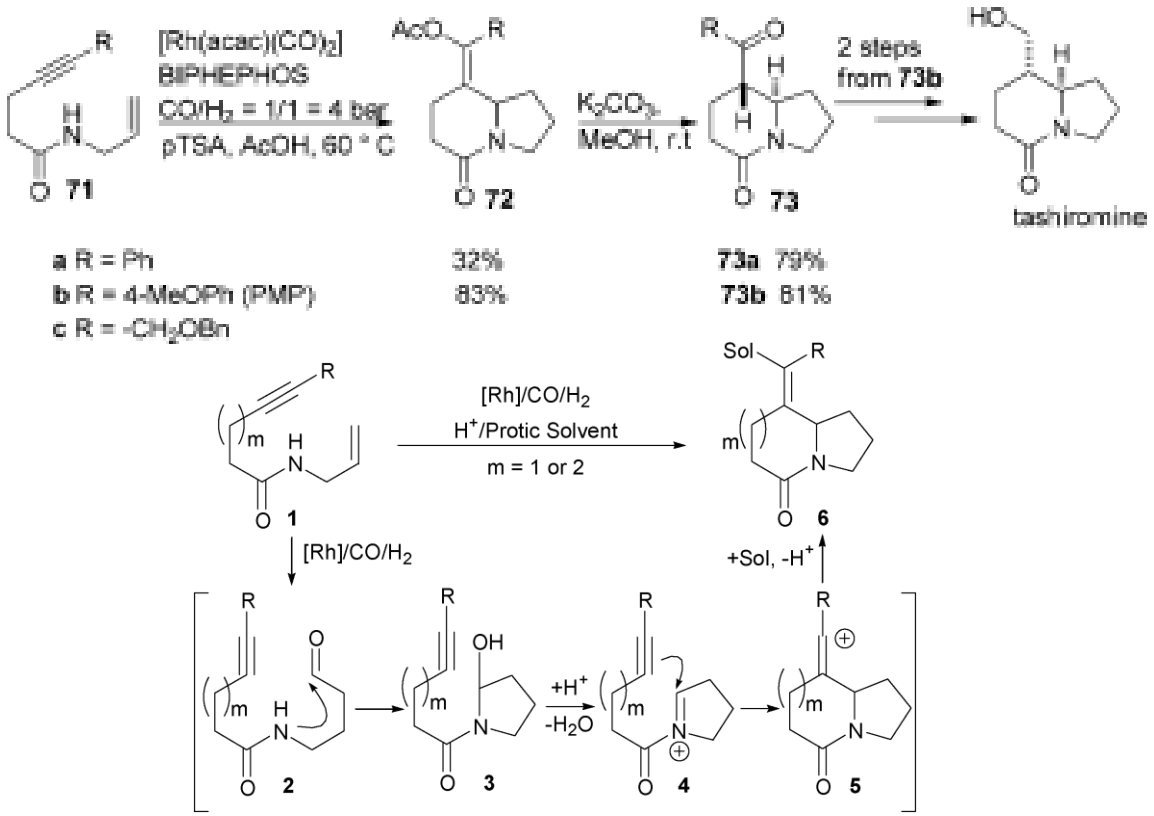


oxidation of the resulting enamine derivative provided pseudoconhydrine, one of the alkaloids from hemlock

use of the bulky bisphosphite BIPHEPHOS resulted in complete selectivity for the linear isomer 65

R.W. Bates, K. Sivarajan, B.F. Straub, J. Org. Chem. 76 (2011) 6844–6848

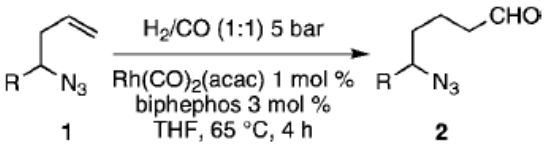
Alkyne-mediated domino hydroformylation/double cyclization

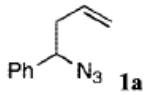
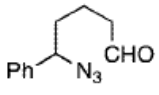
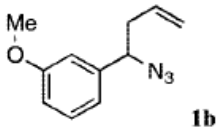
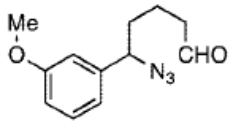
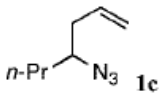
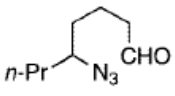
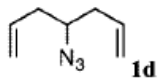
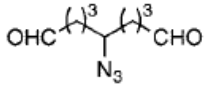
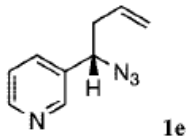
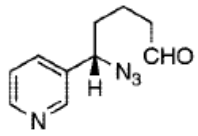
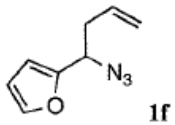
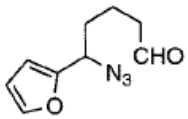
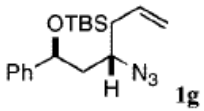
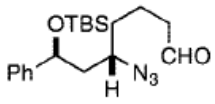
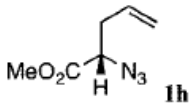
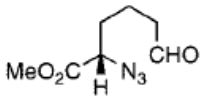


Electron donating group on the phenyl moiety enhances the nucleophilicity of the triple bond moiety

W.-H. Chiou, Y.-H. Lin, G.-T. Chen, Y.-K. Gao, Y.-C. Tseng, C.-L. Kao, J.-C. Tsai, Chem. Commun. 47 (2011) 3562–3564

Hydroformylation of homoallylic azides

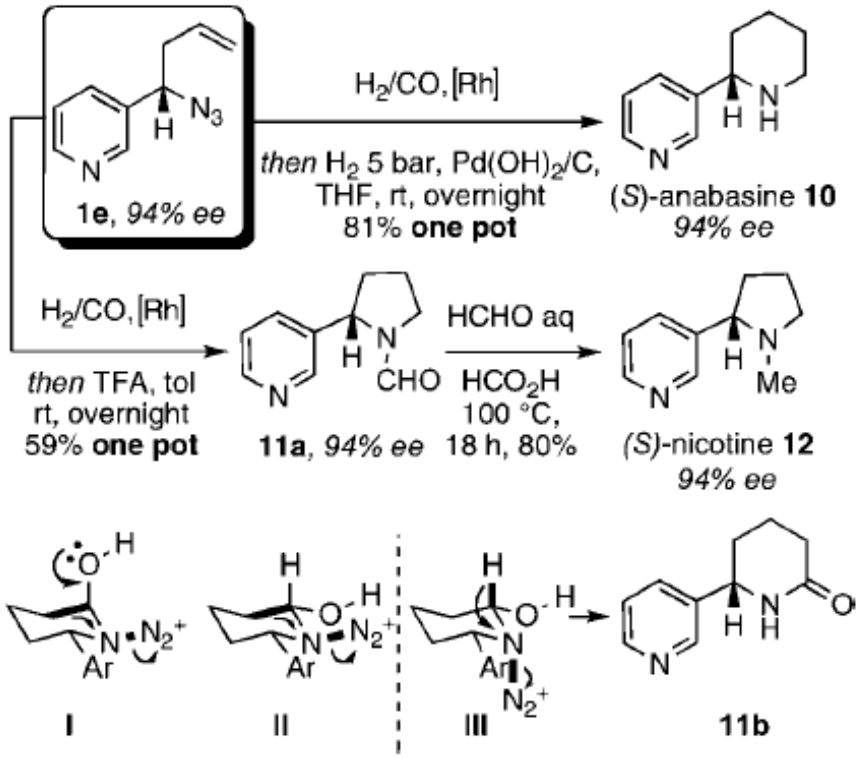


substrate	product	yield[a]
 **1a**	 **2a**	87%
 **1b**	 **2b**	92%
 **1c**	 **2c**	83%
 **1d**	 **2d**	84%
 **1e**	 **2e**	92%
 **1f**	 **2f**	89%
 **1g**	 **2g**	89%
 **1h**	 **2h**	87%

[a] Isolated yield after silica gel chromatography.
[b] $Rh(CO)_2(acac)$ 1 mol%, biphephos 3 mol %, *p*TSA·H_2O 10 mol %, H_2/CO (1:1) 5 bar, MeOH [0.04 M], 50 °C, 4 h.
[c] $Rh(CO)_2(acac)$ 2 mol %, triphenylphosphite 8 mol%, H_2/CO (1:1) 20 bar, THF [0.04 M], 65 °C, 24 h.

T. Spangenberg, B. Breit, A. Mann, Org. Lett. 11 (2009) 261–264

Hydroformylation of homoallylic azides



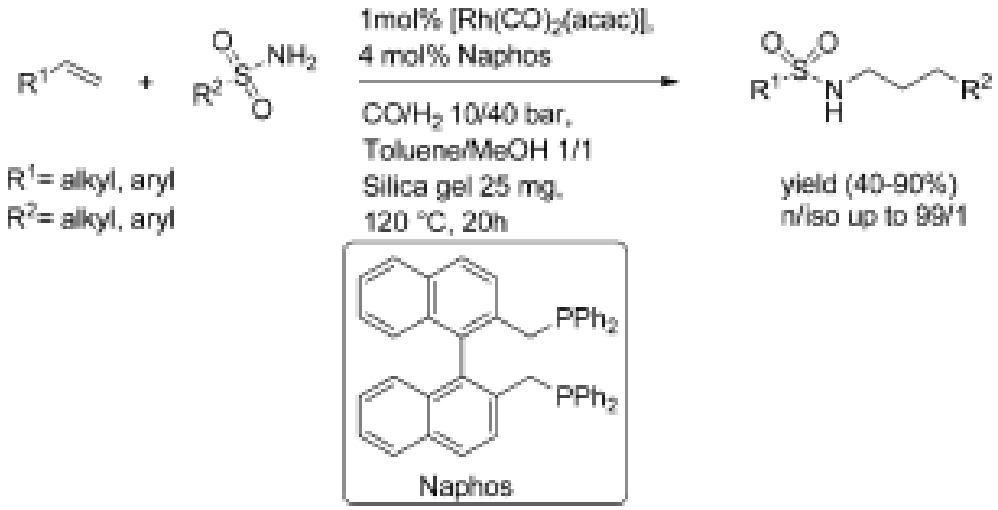
one-pot hydroformylation/ hydrogenation

hydroformylation/schmidt rearrangement

access to pyrrolidine and piperidine alkaloidses

T. Spangenberg, B. Breit, A. Mann, Org. Lett. 11 (2009) 261–264

Tandem hydroformylation/reductive sulphonamidation



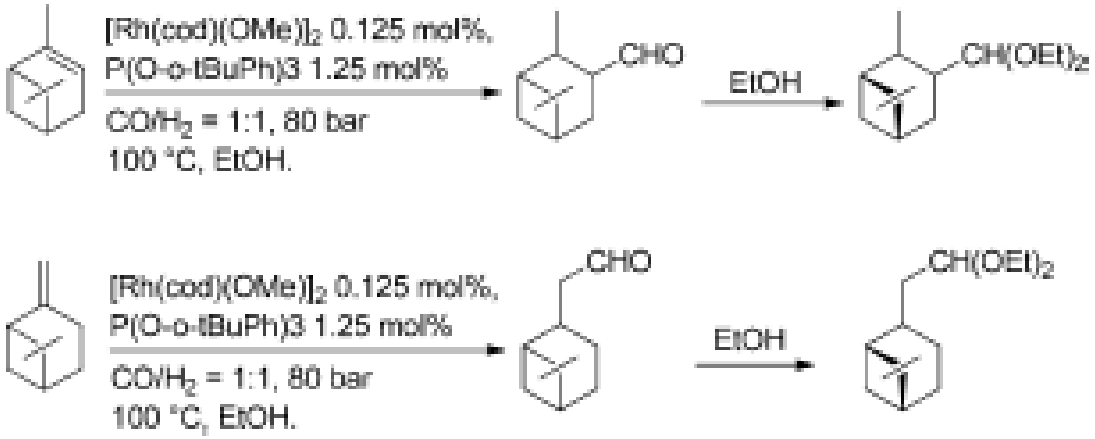
harsh conditions were required for the condensation step (120 ◦C, 20 h) due to the low nucleophilicity of the reagent

K. Dong, X. Fang, R. Jackstell, M. Beller, Chem. Commun. 51 (2015) 5059–5062

Tandem hydroformylation–acetalization

intermolecular HF/acetalization

Hydroformylation/acetalization of α- and β-pinene



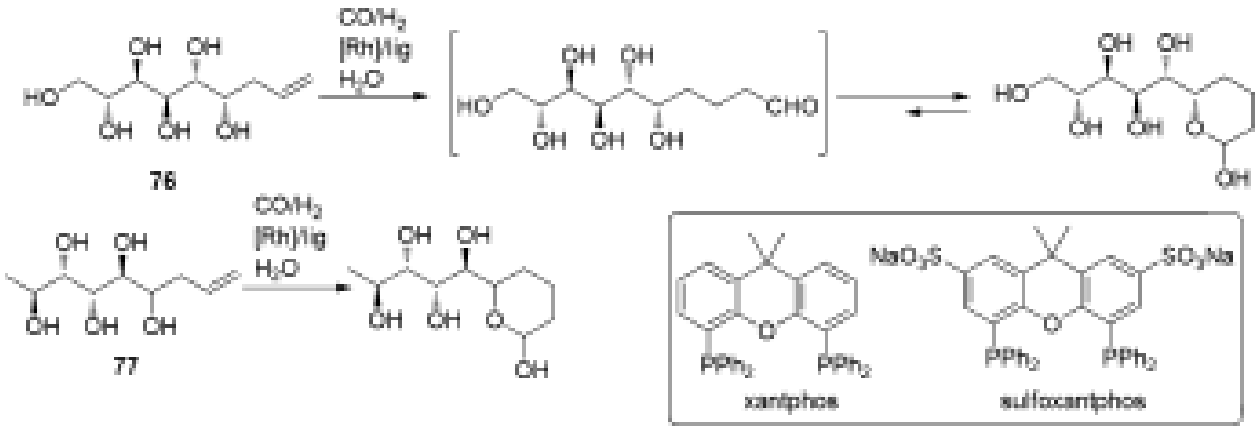
M.C. de Freitas, C.G. Vieira, E.N. dos Santos, E.V. Gusevskaya, ChemCatChem 5 (2013) 1884–1890

For intermolecular HF/acetalization, the reaction must be carried out in the presence of an alcohol

H.M. Colquhoun, D.J. Thompson, M.V. Twigg, Carbonylation-Direct Synthesis of Carbonyl Compounds, Plenum, New York, 1991; P. Kalck, Y. Peres, J. Jenck, Adv. Organomet. Chem. 32 (1991) 121–146; M. Beller, B. Cornils, C.D. Frohning, C.W. Kohlpaintner, J. Mol. Catal. 104 (1995) 17–85; X. Jin, K. Zhao, F. Kong, F. Cui, Q. Liu, Y. Zhang, Catal. Lett. 144 (2014) 192–196; A.B. El, J. Tijani, M. Fettouhi, J. Mol. Catal. A 230 (2005) 9–16.

Tandem hydroformylation–acetalization

intramolecular HF/acetalization



spontaneous formation of lactols by subsequent intramolecular cyclisation

C. Müller, D. Vogt, R. Leino, Chem. Eur. J. 14 (2008) 10539–10542.

CONCLUSIONS

- A vast number of new reaction sequences under hydroformylation conditions were developed
- Efficient synthetic methodology for the production of structurally complex molecules
- direct route towards enantioenriched fine chemicals starting from widely available and cheap olefins.