Enantioselective synthesis of a 2,3-benzodiazepine intermediate of BET inhibitor BAY 1238097 via catalytic asymmetric hydrogenation

Supporting Information

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1. General information

All laboratory scale reactions were performed in a dry nitrogen atmosphere using standard Schlenk techniques or in the glove box. Solvents used in these experiments were reagent grade or better. Dry DCM and THF were obtained from MBraun SPS system. $[Ir(COD)Cl]_2$ was purchased from Umicore and Heraeus. Ligands were purchased at Aldrich or Strem.

The libraries of catalysts were prepared using a Zinsser Lissy liquid handling robot equipped with 4 syringes and placed inside a glove box (See picture below).

The hydrogenation reaction is carried out in a Premex 96-Multi Reactor[1] that can accommodate 96 reactions vessels at the same temperature and hydrogen pressure (See picture below).

^{31}P NMR spectra were recorded on a Bruker Advance 300 (300 MHz) NMR spectrometer and reported in units of parts per million (ppm).

Figure S1. Hardware available at InnoSyn for high throughput screening: Liquid handling robot (Zinsser Lissy, left) and Premex 96-Multi Reactor (right).

2. Analytical method

Conversion and enantiomeric excess were determined by HPLC (Agilent system equipped with a UV-Vis Detector).

Column:	Chiralpak ID 250mm x 4.6 mm ID 5 µm
Mobile phase:	75 v/v n-Heptane; 0.1% v/v diethylamine
	25 v/v isopropanol; 0.1% v/v diethylamine
Flow:	1.7 mL/min
Oven :	35 °C
Injection volume :	4 µL
Detection :	UV wavelength 256 nm
Analysis time :	20 min

Substrate and racemate were dissolved in EtOH/MeOH 1/1 (v/v)

Concentrations: Substrate 1: 2.306 mg/mL; Racemate 2: 2.08 mg/mL

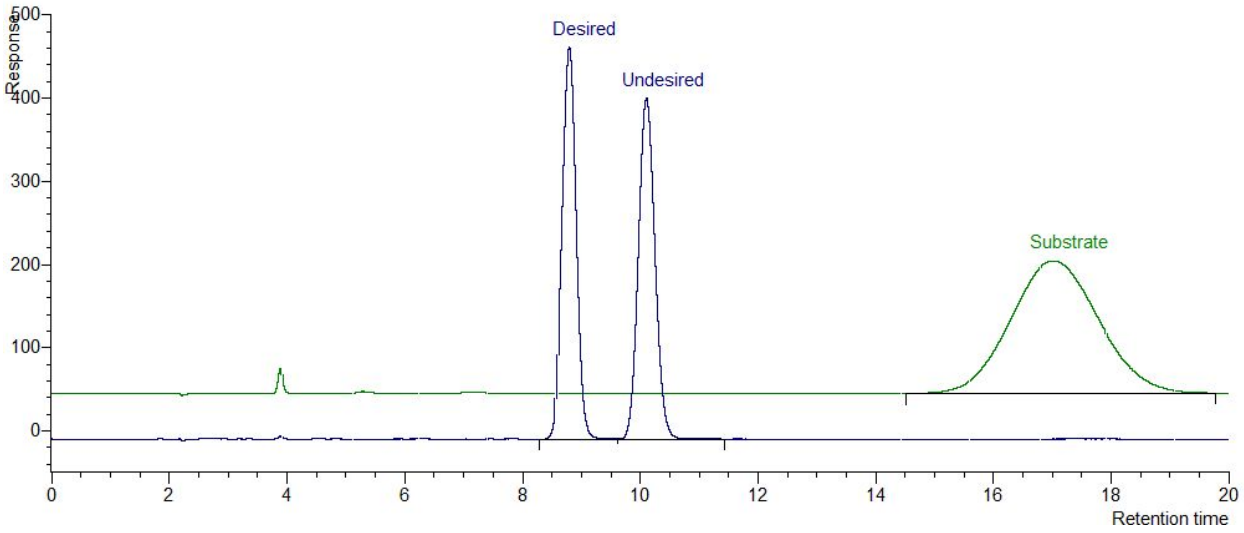
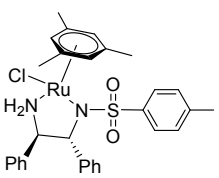


Figure S2. HPLC chromatograms for the reference material

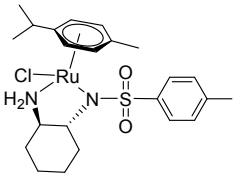
	RT (min)	**RRT**
Desired enantiomer (*S*)	8.81	1.00
Undesired enantiomer (*R*)	10.12	1.15
Substrate	17.03	1.93

3. Asymmetric transfer hydrogenation of 1

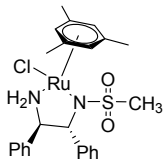
List of catalysts tested in transfer hydrogenation:



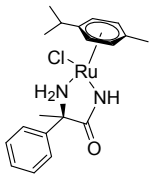
A: RuCl[(R,R)-TsDPen] (mesitylene)



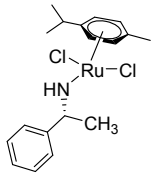
B: RuCl[(R,R)-TsDach] (cymene)



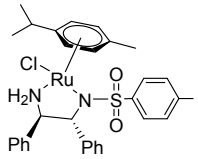
C: RuCl[(R,R)-MsDPen] (mesitylene)



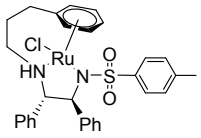
D: RuCl[(R)-2-Ph-2-amino propionamide](cymene)



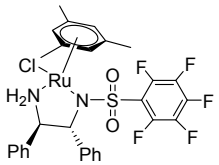
E: $RuCl_2$[(R)-α-Me-Bn-NH2] (cymene)



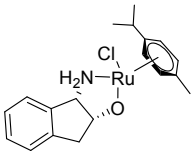
F: RuCl[(R,R)-TsDPen] (cymene)



G: RuCl[(S,S)-teth-TsDPen]



H: RuCl[(R,R)-FsDPen] (mesitylene)



I: RuCl[(1S,2R)-1-amino -2-indanol](cymene)

Catalysts Preparation: Catalysts **A**, **B, C, F** and **G** are commercially available and were used as such. The catalysts **D** and **E** were prepared according to the following procedure: $[RuCl_2cymene]_2$ (61.24 mg, 0.1 mmol) and the ligand (0.2 mmol, (*R*)-2-phenyl propionamide (33 mg, 0.2 mmol) for **D**; (*R*)-α-Me-Bn-NH_2 (24.2 mg, 0.2 mmol) for **E**) are dissolved in DCM (4 mL) containing Et_3N (100 µL) and heated to 50°C for 0.25 hour in a sealed vial. The mixture is cooled to room temperature and extracted with a 4M KOH solution in water (1 mL). The DCM phase was recovered, dried over Na_2SO_4, filtrated. Upon removal of DCM, a dark red crystalline solid is obtained for **D**, a brown viscous oil for **E**. Both catalysts were used as such. The catalysts **H** and **I** were prepared according to the following procedure: $[RuCl_2cymene]_2$ (10 mg, 0.0163 mmol) and the ligand (0.1 mmol) were heated in IPA (0.5 mL) at 50°C for 0.25 hour. 100 µL of the Ru solution (0.00625 mmol) was used as such in the transfer hydrogenation experiments.

Reaction Conditions:

Conditions 1: KOH/MeOH/HCOOH

A 1 M solution of KOH in MeOH (1 mL) was diluted with MeOH (1 mL). The solution was treated by formic acid and added to a 5 mL vial charged with substrate **1** (37.3 mg, 0.1 mmol) followed by the addition of the catalyst (0.00625 mmol). The vial was sealed, degassed by N_2 and heated to 40°C. The substrate was not completely dissolved.

Conditions 2: TEAF/MeOH

A solution of TEAF 1:1 (Et_3N:HCOOH, 85 mg, 0.57 mmol HCOOH) or TEAF 5:2 (49 mg, 0.57 mmol HCOOH) in MeOH (2 mL) was added to a 5 mL vial charged with benzodiazepine **1** (37.3 mg, 0.1 mmol) followed by the addition of the catalyst (0.00625 mmol). The vial was sealed, degassed by N_2 and heated to 40°C. The substrate was not completely dissolved.

Conditions 3: TEAF/CH_2Cl_2

In a 5 mL vial, benzodiazepine **1** (37.3 mg, 0.1 mmol) was dissolved in a mixture of TEAF 1:1 (85 mg, 0.57 mmol HCOOH) and CH_2Cl_2 (2 mL) followed by the addition of the catalyst (0.00625 mmol). The mixture was degassed by N_2 and heated to 40°C. TEAF 1:1 does not properly dissolve (droplets on the vial wall).

Conditions 4: MeOH/H_2O and HCOONa

A solution of HCOONa (1.36 g, 20 mmol) in water (15 mL) was diluted with MeOH (25 mL) giving a homogeneous solution. 2mL of this solution (1 mmol HCOONa) was added to a 5 mL vial charged with benzodiazepine **1** (37.3 mg, 0.1 mmol) followed by the addition of the catalyst (0.00625 mmol). The vial was sealed, degassed by N_2 and heated to 40°C. The substrate does not dissolve entirely.

Conditions 5: Biphasic HCOONa/H_2O and CH_2Cl_2

HCOONa (1.36 g, 20 mmol) was dissolved in water (10 mL). In a 5 mL vial, benzodiazepine **1** (37.3 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1.5 mL) followed by the addition of the aqueous solution of HCOONa (0.5 mL, 1 mmol HCOONa) and catalyst (0.00625 mmol). The mixture was degassed by N_2 and heated to 40°C.

Conditions 6: Biphasic withTEAF/H_2O and CH_2Cl_2

In a 5 mL vial, benzodiazepine **1** (37.3 mg, 0.1 mmol) was dissolved in CH_2Cl_2 (1.5 mL) followed by the addition of TEAF 1:1 (85 mg, 0.57 mmol), water (0.5 mL) and catalyst (0.00625 mmol). The mixture was degassed by N_2 and heated to 40°C.

Conditions 7: IPA/KOtBu

A solution of the Ru-catalyst (0.00625 mmol) in IPA (2 mL) was prepared and treated with KOtBu (2.7 mg, 0.024 mmol). The solution was added to benzodiazepine **1** (37.3 mg, 0.1 mmol, S/C 15) in a 5 mL vial. The vial was sealed, degassed by N_2 and the mixture heated to 80°C for 3 hours.

Conditions 8: Neat in TEAF

In a 5 mL vial, benzodiazepine **1** (37.3 mg, 0.1 mmol) was dissolved in TEAF (2 mL) followed by the addition of catalyst (0.00625 mmol). The mixture was degassed by N_2 and heated to 40°C. The substrate did not dissolve entirely.

Results: (ee's in absolute values; TEAF 52/11 = HCOOH:Et_3N in 5:2/1:1 mol:mol)

Catalyst	Conditions	H-source		solvent	t	e.e. (%)	conv. (%)
			(eq.)		(h)		
F	1	HCOOH	5	MeOH	4.5	0	0
F	1	HCOOH	10	MeOH	4.5	13	5
F	1	HCOOH	15	MeOH	4.5	14	36
C	1	HCOOH	5	MeOH	4	0	0
C	1	HCOOH	10	MeOH	4	42	8
C	1	HCOOH	15	MeOH	4	39	23
F	7	IPA	solvent	IPA	3	79	22
C	2	TEAF11	5.7	MeOH	4	59	15
C	2	TEAF52	5.7	MeOH	4	51	41
A	2	TEAF11	5.7	MeOH	3	54	9
C	2	TEAF11	5.7	MeOH	3	59	14
B	2	TEAF11	5.7	MeOH	3	37	3
I	2	TEAF11	5.7	MeOH	3	28	74
J	2	TEAF11	5.7	MeOH	3	35	19
F	2	TEAF11	5.7	MeOH	3	23	14
K	2	TEAF11	5.7	MeOH	3	7	3
G	2	TEAF11	5.7	MeOH	3	0	6
H	2	TEAF11	5.7	MeOH	3	71	12
A	3	TEAF11	5.7	DCM	17	11	25
C	3	TEAF11	5.7	DCM	17	18	29
B	3	TEAF11	5.7	DCM	17	7	14
I	3	TEAF11	5.7	DCM	17	17	55
J	3	TEAF11	5.7	DCM	17	34	37
F	3	TEAF11	5.7	DCM	17	17	15
K	3	TEAF11	5.7	DCM	17	2	8
G	3	TEAF11	5.7	DCM	17	14	15
H	3	TEAF11	5.7	DCM	17	1	16
A	8	TEAF11	solvent	TEAF11	17	15	1
A	8	TEAF52	solvent	TEAF52	17	7	8
A	6	TEAF11	5.7	H2O/DCM	3	19	5
C	6	TEAF11	5.7	H2O/DCM	3	43	10
B	6	TEAF11	5.7	H2O/DCM	3	15	2
I	6	TEAF11	5.7	H2O/DCM	3	30	5
J	6	TEAF11	5.7	H2O/DCM	3	5	5
F	6	TEAF11	5.7	H2O/DCM	3	48	2
K	6	TEAF11	5.7	H2O/DCM	3	4	1
G	6	TEAF11	5.7	H2O/DCM	3	1	3
H	6	TEAF11	5.7	H2O/DCM	3	0	3
A	5	HCOONa	10	H2O/DCM	3	47	6
H	1	HCOOH	10	MeOH	3	57	19
H	4	HCOONa	10	H2O/MeOH	3	45	2
H	5	HCOONa	10	H2O/DCM	3	36	7
H	2	TEAF52	5.7	MeOH	3	63	29

4. First screening for the enantioselective hydrogenation of 1

Procedure: Inside a N_2 glovebox, the catalysts were prepared from $[Ir(COD)Cl]_2$ (3.34mg, 0.005mmol) in presence of the ligand (1.05 eq/Ir) for 1/2 h at 50°C in DCM (1mL). 0.05mL of the catalyst solution was transferred via a liquid-handling robot into a 5mL vial. For ligand **L12**, 1 eq/Ir of NaBArF was added to generate the cationic complex. Iodine was added via the liquid handling robot from a 0.04M stock solution in DCM (2 eq/Ir). After evaporation of DCM, the substrate **1** was added as a solid (18.6mg, 0.05mmol) followed by the solvent (DCM, THF, TFE, AcOH; 1mL). The vials were capped and placed in the parallel hydrogenation reactor. The reactor was purged with N_2 and pressurized with H_2 (50 bar). The reaction was run overnight at room temperature. The samples for HPLC analysis were prepared by dissolving 100μL of the reaction mixture into 1mL of MeOH:EtOH (1:1 v/v).

Ligand set:

L1: (R)-(+)-2-[2-(Diphenylphosphino)phenyl]-4-isopropyl-2-oxazoline, CAS Number 164858-78-0

L2: (S)-(+)-2-[2-(Diphenylphosphino)phenyl]-4-phenyl-2-oxazoline, CAS Number 148461-15-8

L3: (S)-4-Isopropyl-2-[(S)-2-(bis(2-methoxyphenyl)phosphino)ferrocen-1-yl]oxazoline, Solvias- SL-N012-2

L4: (R)-diMe-PipPhos

L5: (S)-1-[(R)-2-(Dicyclohexylphosphino)ferrocenyl]ethyldiphenylphosphine, SL-J004-2, CAS Number 162291-01-2

L6:(R)-1-Dicyclohexylphosphino-2-[(R)-(N,N-dimethylamino)[2-(dicyclohexylphosphino)phenyl]methyl] ferrocene, SL-T002-1, CAS Number 1156547-61-3

L7: (R)-Phanephos, (R)-(–)-4,12-Bis(diphenylphosphino)-[2.2]-paracyclophane, CAS Number 364732-88-7

L8: (2S,3S)-(−)-Bis(diphenylphosphino)butane, ChiraPhos, CAS Number 64896-28-2

L9: (R)-2,2'-Bis[bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-6,6'-dimethoxy-1,1'-biphenyl, CAS Number 352655-61-9

L10: (2R,3R)-(-)-2,3-Bis(diphenylphosphino)-bicyclo[2.2.1]hept-5-ene, min. 95% (R,R)-NORPHOS, CAS Number 71042-55-2

L11: (1S,1S',2R,2R')-1,1'-Di-tert-butyl-(2,2')-diphospholane, (S,S',R,R')-TangPhos, CAS Number 470480-32-1

L12: was obtained from the group of Pr. A. Pfaltz [See for example: Pauli, L.; Tannert, R.; Scheil, R.; Pfaltz, A. Asymmetric Hydrogenation of Furans and Benzofurans with Iridium–Pyridine–Phosphinite Catalysts. *Chem. Eur. J.*, **2015**, *21*: 1482-1487.

Hydrogenation conditions: Ir (0.0005mmol), I_2 (none or 0.001mmol), substrate **1** (0.05mmol), Solvent (1mL), 50 bar H_2, R.T., 18h.

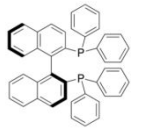
Results: See Scheme 2 in article and below ee (>0 = (S)-major enantiomer).

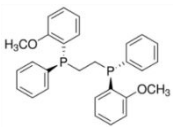
E.e.		**Catalysts**											
Additive	**Solvent**	L1	L2	L3	L4	L5	L6	L7	L8	L9	L10	L11	L12
no I2	DCM	-36	-7	-47	38	-34	0	41	13	3	-22	-23	63
	THF	-27	-10	-13	18	-57	-4	18	1	27	10	-9	-28
	TFE	-21	0	-75	55	22	-18	46	0	-42	-4	-52	-35
	HOAc	0	0	0	-9	0	47	4	9	-19	0	0	0
I2	DCM	-56	-6	-61	-38	2	-3	6	18	6	-13	-39	26
	THF	-22	-15	-22	-22	-2	-3	16	15	-8	-6	-15	-22
	TFE	0	0	0	0	0	12	41	39	-31	-28	0	-36
	HOAc	-40	-27	0	-7	27	-3	-1	-6	-25	-2	-33	0

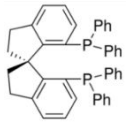
4. 2[d] screening: 48 chiral ligands

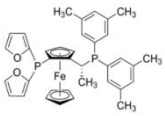
46 chiral ligands combined with $[Ir(COD)Cl]_2$ and 2 preformed Ir(COD)LBArF with UBAPhox (**L47**, **L48**) were tested in DCM as a solvent and with/without iodine as an additive.

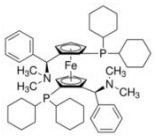
List of ligands:

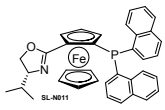

L13-(S)-Binap

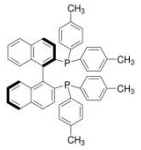

L21-(S, S)-DIPAMP

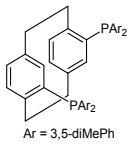

L29-(S)-SDP

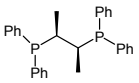

L37-JosiPhos (J015-1)


L45-MandyPhos (M002-2)

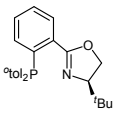

L53-POX-N011-2

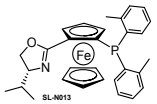

L14-(R)-Tol-Binap

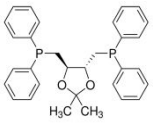

L22-Xylyl-PhanePhos

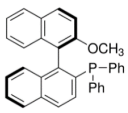

L30-(2S,3S)-ChiraPhos

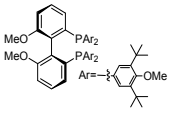

L38-JosiPhos (J212-1)

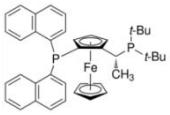

L46-Tol-tBu-Phox

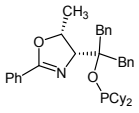

L54-POX-N013-1

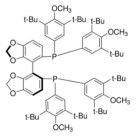

L15-(R, R)-DIOP

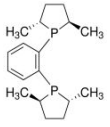

L23-(R)-MOP

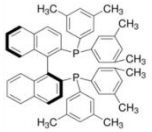

L31-(S)-BiPheP

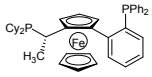

L39-JosiPhos (216-1)

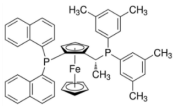

L47-UBAPhox

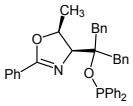

L55-(S)-DTBM-SegPhos

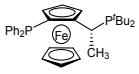

L16-(S, S)-MeDuPhos

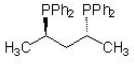

L24-(S)-Xylyl-Binap

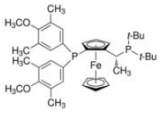

L32-WalPhos (W003-2)

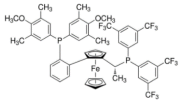

L40-JosiPhos (J404-1)

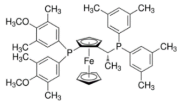

L48-UBAPhox

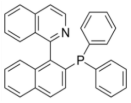

L56-JosiPhos 2-1

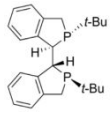

L17-(R, R)-BDPP

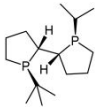

L25-JosiPhos 13-1

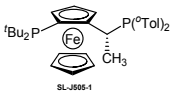

L33-WalPhos (W005-1)

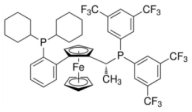

L41-JosiPhos (J418-1)

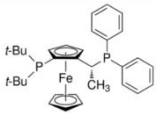

L49-(R)-Quinap

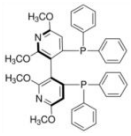

L57-(R,R,S,S)-DuanPhos

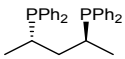

L18-(S,S,R,R)-TangPhos

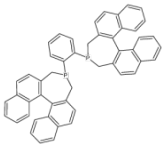

L26-JosiPhos 505-1

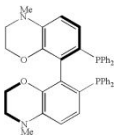

L34-WalPhos (W008-1)

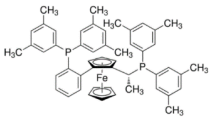

L42-JosiPhos (J502-1)

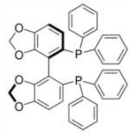

L50-(S)-P-Phos


L58-(2S,4S)-SkewPhos


L19-(S)-BinaPhane


L27-(R)-SolPhos


L35-WalPhos (W009-1)


L43-(R)-SegPhos

L51-POX-N006-2

L59-catASium T1

L20-JosiPhos (J009-1)

L28-MandyPhos M001

L36-WalPhos (W022-1)

L44-(R)-DM-SegPhos

L52-POX-N008-2

L60- (R, R)-QuinoxP*

Procedure: The catalysts were formed as described above. With **L47** and **L48**, the preformed (COD)IrL-BArF complexes were used.

Library layout:

No Iodine						Iodine					
L13	L21	L29	L37	L45	L53	L13	L21	L29	L37	L45	L53
L14	L22	L30	L38	L46	L54	L14	L22	L30	L38	L46	L54
L15	L23	L31	L39	L47	L55	L15	L23	L31	L39	L47	L55
L16	L24	L32	L40	L48	L56	L16	L24	L32	L40	L48	L56
L17	L25	L33	L41	L49	L57	L17	L25	L33	L41	L49	L57
L18	L26	L34	L42	L50	L58	L18	L26	L34	L42	L50	L58
L19	L27	L35	L43	L51	L59	L19	L27	L35	L43	L51	L59
L20	L28	L36	L44	L52	L60	L20	L28	L36	L44	L52	L60

Hydrogenation conditions: Ir (0.0005mmol), I_2 (none or 0.001mmol), substrate **1** (0.05mmol), Solvent (1mL), 50 bar H_2, R.T., 18h.

Results: Conversion (%) and enantiomeric excess (>0 = (S)-major enantiomer).

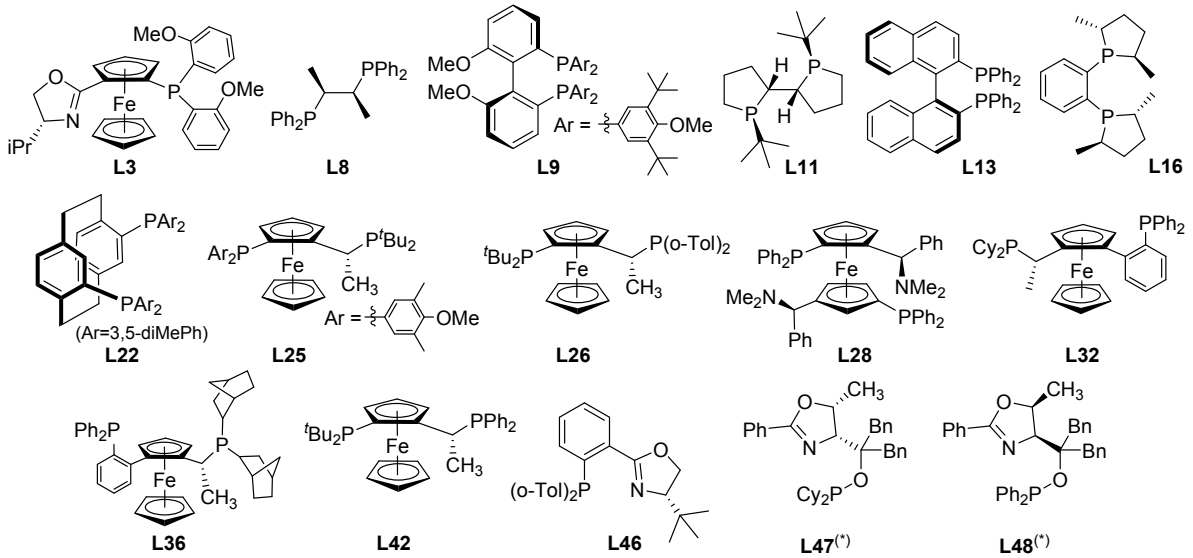
Conversion		No Iodine						Iodine					
		A	B	C	D	E	F	G	H	I	J	K	L
	1	1	3	52	30	10	0	100	81	99	100	22	33
	2	2	49	4	59	1	2	100	13	97	44	35	17
	3	92	1	19	19	33	49	100	22	99	12	51	100
	4	34	12	36	9	10	53	57	100	11	90	94	22
	5	11	38	32	40	0	42	99	19	84	100	16	99
	6	26	36	51	60	4	21	75	19	69	33	99	98
	7	38	11	74	1	3	1	100	100	79	100	100	98
	8	27	5	46	1	4	77	16	95	15	99	100	100

E.e.	No Iodine						Iodine					
	A	B	C	D	E	F	G	H	I	J	K	L
1	-42	-3	26	-22	-3	-10	12	2	-11	-5	1	-39
2	14	39	25	-15	-41	-7	-7	30	20	-24	-52	30
3	7	16	-10	38	71	10	6	1	-2	10	78	23
4	31	13	-83	-33	-55	-41	39	10	-13	-18	-85	-19
5	-26	-32	-16	-41	-16	7	8	-28	19	-35	-17	-21
6	-23	-61	32	-54	8	23	-39	-24	11	-37	41	-8
7	-10	-12	-11	17	11	21	3	-44	5	-47	-57	23
8	9	-51	73	38	8	-38	-5	-38	1	-50	-63	-32

5. 3rd Screening at higher temperature

14 chiral ligands combined with $[Ir(COD)Cl]_2$ and 2 preformed Ir(COD)LBArF with UBAPhox (**L47**, **L48**) were tested in THF, IPA, and EtOAc at 60°C.

List of ligands:



Procedure: The catalysts were formed as described above. With **L47** and **L48**, the preformed (COD)IrL-BArF complexes were used. Hydrogenation conditions: Ir (0.0005mmol), I_2 (none or 0.001mmol), substrate **1** (0.05mmol), Solvent (1mL), 50 bar H_2, 60°C, 18h.

Results: (Positive ee = (S)-product is the major enantiomer)

	THF				IPA				EtOAc			
	No I_2		I_2		No I_2		I_2		No I_2		I_2	
Ligand	*Conv.*	*e.e.*	*Conv.*	*e.e.*	*Conv.*	*e.e.*	*Conv.*	*e.e.*	*Conv.*	*e.e.*	*Conv.*	*e.e.*
L3	20	-13	87	-18	100	-10	76	-22	20	1	87	-20
L8	50	2	100	5	100	3	100	1	42	8	100	9
L9	100	68	100	8	100	72	100	-11	100	62	100	-30
L11	100	25	100	-14	100	36	100	-7	100	29	100	-16
L13	100	-47	100	5	100	-33	100	1	100	-36	100	4
L16	100	38	100	7	100	3	100	3	100	3	100	17
L22	100	38	100	59	91	23	100	-1	94	35	100	55
L25	100	-7	100	-16	87	-9	72	5	100	-4	100	-30
L26	91	-3	100	-11	74	-1	100	-25	97	-3	100	-7
L28	49	6	100	-32	59	5	100	-7	50	-10	100	-23
L32	100	86	100	18	57	3	95	8	100	84	100	27
L36	92	77	100	4	61	0	92	3	100	77	100	11
L42	100	-19	100	-57	54	3	74	-8	100	-39	100	-68
L46	57	-2	100	0	86	10	82	0	32	-14	100	-7
L47	100	30	100	38	100	32	100	66	100	32	100	31
L48	100	-38	100	-61	100	-28	100	-60	100	-28	100	-67

6. Optimization of Ir/WalPhos

During this study, both hands of WalPhos 003 were used indifferently as the focus was the catalyst activity and robustness. As a consequence, absolute values of ee's are given in the table below. WalPhos 003-1 is needed to produced the (*S*)-enantiomer of **2**.

Substrate to catalyst ratio

Hydrogenation conditions: Ir (x mmol), substrate **1** (0.05mmol), Solvent (1mL), 50 bar H_2, 60°C, 18h.

#	S/C	Solvent	e.e. (%)	conv. (%)
1	100	THF	92	99
2	200	THF	90	71
3	500	THF	80	14
4	1000	THF	65	3
5	100	toluene	91	100
6	200	toluene	91	83
7	500	toluene	90	43
8	1000	toluene	81	9

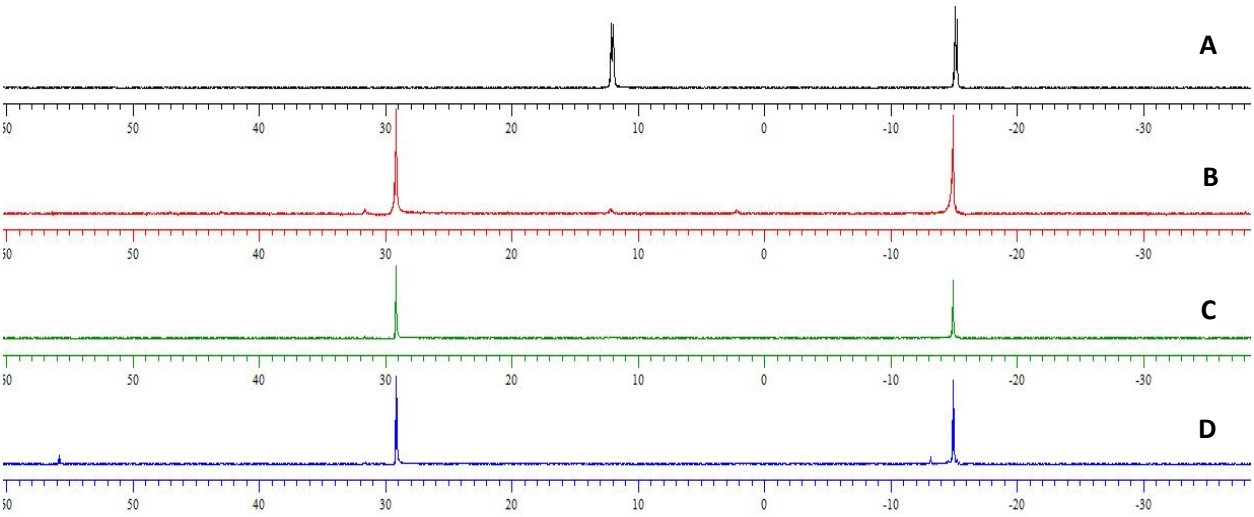
Acid screening

Hydrogenation conditions: Ir (0.0005mmol), substrate **1** (0.05mmol), Solvent (1mL), 50 bar H_2, RT, 18h.

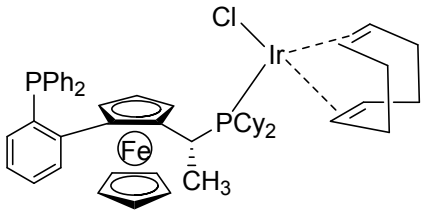
#	Acid (eq/1)	Solvent	e.e. (%)	conv. (%)
1	AcOH (1 eq.)	THF	92	54
2	Piv acid (1 eq.)	THF	90	14
3	HCOOH (1 eq.)	THF	90	39
4	*p*-Tos-OH (1 eq.)	THF	22	95
5	$B(O^iPr)_3$ (1 eq.)	toluene	96	52
6	$B(Et)_3$ (1 eq.)	toluene	95	70
7	$Ti(O^iPr)_4$ (1 eq.)	toluene	N/a	0
8	$Al(TFE)_3$ (1 eq.)	toluene	39	65
9	$MeSO_3H$ (1 eq.)	THF	81	91

7. NMR study of the catalyst formation

The formation of the precatalyst was studied by ^{31}P NMR. The following spectra in undeuterated DCM were acquired:
Spectrum A: Walphos in DCM ($^{31}P\{^1H\}$ (300 Mhz, DCM, 298K) 12.08 (PCy_2), -15.13 (PPh_2))
Spectrum B: $[Ir(COD)Cl]_2$ + Walphos @ RT for 10 min ($^{31}P\{^1H\}$ (300 Mhz, DCM, 298K) 29.12 (PCy_2), -15.01 (PPh_2))
Spectrum C: $[Ir(COD)Cl]_2$ + Walphos @ 50°C for 0.5h ($^{31}P\{^1H\}$ (300 Mhz, DCM, 298K) 29.12 (PCy_2), -15.01 (PPh_2))
Spectrum D: $[Ir(COD)Cl]_2$ + Walphos @ 50°C for 15h ($^{31}P\{^1H\}$ (300 Mhz, DCM, 298K) 29.12 (PCy_2), -15.01 (PPh_2), -13.194, 55.708)



Remarkably, we can observe that the formation of the chelate does not happen even after one night at 50°C. After 10 min at room temperature, a new Ir complex is formed where only the $–PCy_2$ moiety of the ligand is bound to the Ir (shift of the signal from 12.08ppm to 29.12ppm while the $–PPh_2$ signal remained unchanged) such as shown on the proposed structure below.



The complete chelation of the ligand may occur under H_2 after removal of the COD. An additional spectrum taken after addition of substrate (5 eq) and Boc anhydride (5 eq) did not show any change either.

8. Production campaign

After transfer to Bayer, a set of scale-up experiments confirmed that this catalytic asymmetric hydrogenation reaction could be a cost-efficient method to cleanly convert **1** to target compound *S*-**2** in good enantioselectivity (enantiomeric ratio 96:4).

H_2O was detrimental to the reaction in THF, but did not lead to significant catalyst deactivation in toluene. Using Boc anhydride as additive, catalyst performance was increased (S/C ratio). Toluene is also a preferred solvent for a robust hydrogenation process at high dilution.

However, THF increases solubility of reaction components. Upon scale-up, THF therefore seemed better suited for running more concentrated hydrogenation reactions. In addition, the lower boiling point of THF allowed for larger option space for solvent exchange. Although S/C ratio was not optimal, we believe that the catalyst is sufficiently robust to be used for multi-kg scale production.

Sufficient stability of the reaction components allowed processing in the hydrogenation plant without prior preparation and addition of the catalyst solution under inert atmosphere. All solids were combined (starting material, Ligand and Ir-precatalyst), suspended in THF and transferred to the autoclave without special precaution to exclude air contact. Inertisation took place in the autoclave before introduction of hydrogen. The catalyst was only activated by hydrogenation of COD after complete inertisation.

For the ease of processing, telescoping conversion to the desired product by hydrogenation in THF and subsequent crystallization from isopropanol was chosen for scale-up.

Optimized procedure

Hydrogenation (2x)

Benzodiazepine[2] **1** (1.200 kg), Walphos SL-W003-1 (33.2 g, 1.5 mol%, Solvias) and $[Ir(COD)Cl]_2$ (16.3 g, 0.75 mol%, Umicore) were placed in a stirable vessel at ambient temperature. THF (9 L) was added and the vessel was inertized with nitrogen. The resulting thin suspension was transferred to a 20 L pressure reactor (Büchi, Hastelloy®), additional THF (3 L) was added to complete transfer of solids from transfer lines. The reactor was pressurized with hydrogen (80 bar), and the mixture was heated to 50°C. After 16 hours, the reactor was cooled to 23°C, the atmosphere was exchanged to nitrogen and the crude hydrogenation solution (**2**: 93.8 % area, enantiomeric ratio 96.1: 3.9 (S:R) by HPLC) was transferred to a storage vessel.

Crystallization

The crude hydrogenation solutions from two pressure reactions were combined for crystallization in a 36 L stainless steel reactor.

After filtration, the solvent was distilled (40°C / 200 mbar) to ca. 7.2 kg solution (ca. 3-fold solution in THF). The solution was cooled to 23-27°C, and *i*-PrOH (14.4 L, ca. 6-fold) was slowly added (ca. 175 mL/min) over 90 min. The resulting suspension was stirred for 16 h, filtered, washed with *i*-PrOH (3 times 1.2 L) and dried (50°C, vacuum) to yield 1.677 kg of (*S*)-**2** in (70% yield, enantiomeric ratio 99.5:0.5 by HPLC, 99% ee) as off-white crystalline solid.

Analytical data

(4*S*)-1-(4-bromophenyl)-7,8-dimethoxy-4-methyl-4,5-dihydro-3H-2,3-benzodiazepine (*S*-**2**):

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.13 (d, *J*=6.4 Hz, 3 H) 2.62 (dd, *J*=13.7, 6.5 Hz, 1 H) 2.86 (dd, *J*=13.8, 3.0 Hz, 1 H) 3.55 (s, 3 H) 3.80 (s, 3 H) 3.82 - 3.98 (m, 1 H) 6.51 (s, 1 H) 6.89 (s, 1 H) 7.05 (d, *J*=3.3 Hz, 1 H) 7.37 (m, *J*=8.4 Hz, 2 H) 7.51 (m, *J*=8.4 Hz, 2 H).

LCMS: Rt = 9.62 min; MS (ESIpos): m/z = 375.0666 $(M+H)^+$

MS: ThermoFisherScientific LTQ-Orbitrap-XL; HPLC: Agilent 1200SL; column: Agilent, POROSHELL 120, 3 x 150 mm, SB – C18 2.7 µm; Eluent A: 1 l water + 0.1% trifluroacetic acid; Eluent B: 1 l acetonitrile + 0.1% trifluroacetic acid; Gradient: 0.0 min 2% B → 1.5 min 2% B → 15.5 min 95% B → 18.0 min 95% B; Oven: 40° C; Flow: 0.75 ml/min; UV-detection: 210 nm

REFERENCES

(1) This reactor was developed by Premex in cooperation with DSM. See: www.premex-reactorag.ch/e/spezialloesungen/produkteneuheiten/

(2) Preparation of **1**: Siegel, S.; Baeurle, S.; Cleve, A.; Haendler, B.; Fernandez-Montalvan, A. E.; Moenning, U.; Krause, S.; Lejeune, P.; Busemann, M.; Kuhnke, J. Bicyclo 2,3-benzodiazepines and spirocyclically substituted 2,3-benzodiazepines PCT Int. Appl. WO 2014/128067 A1, **28 August 2014**, Example 45A.