15 JAN 07

Enantio- and regioselective Iridium-catalyzed allylic substitution - Mechanism and Development

Björn Bartels and Günter Helmchen

Universität Heidelberg

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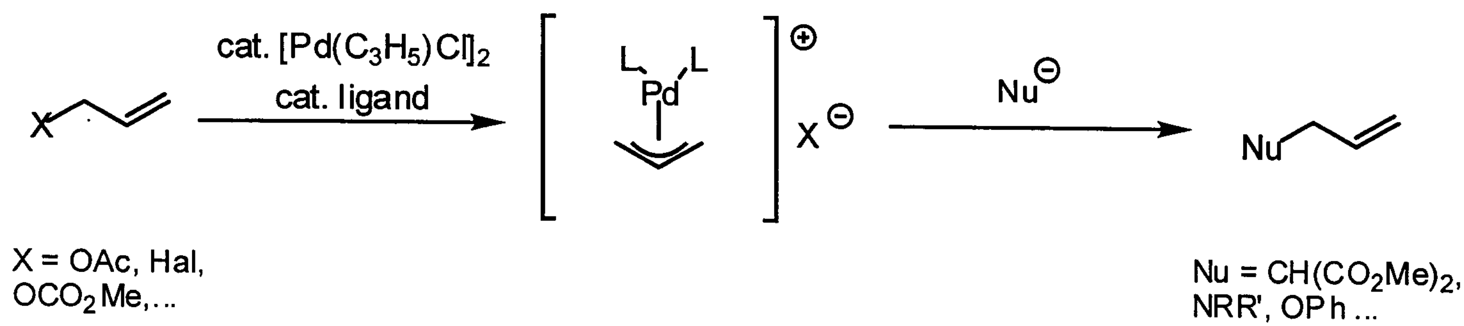
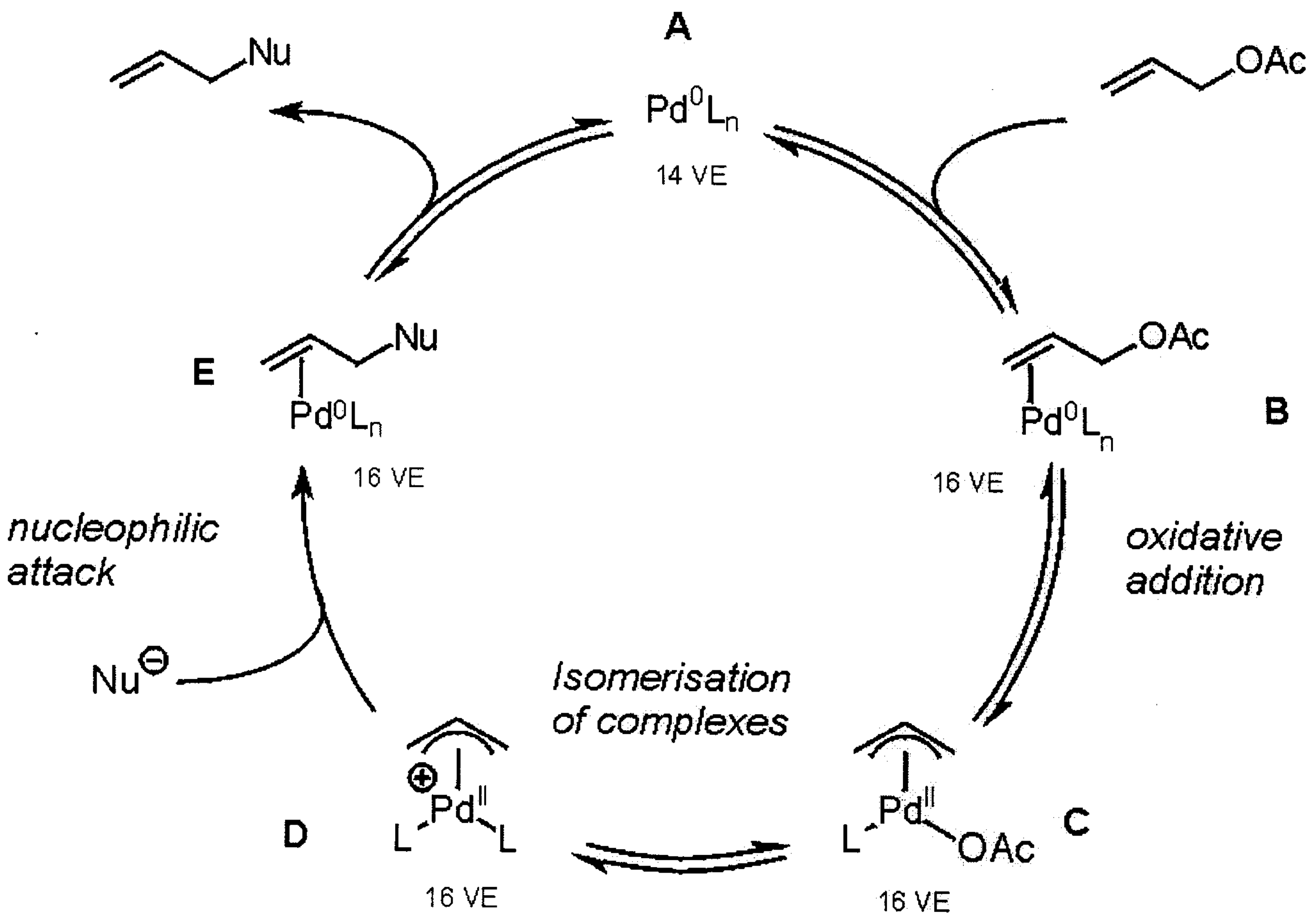
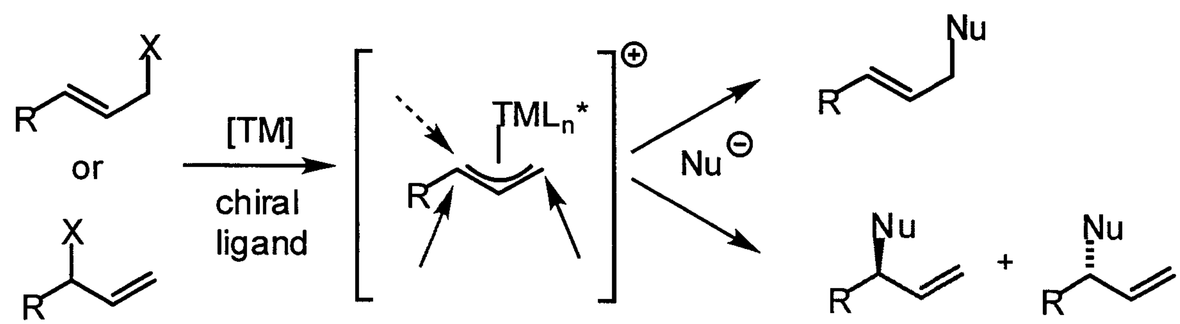
Introduction - allylic substitution



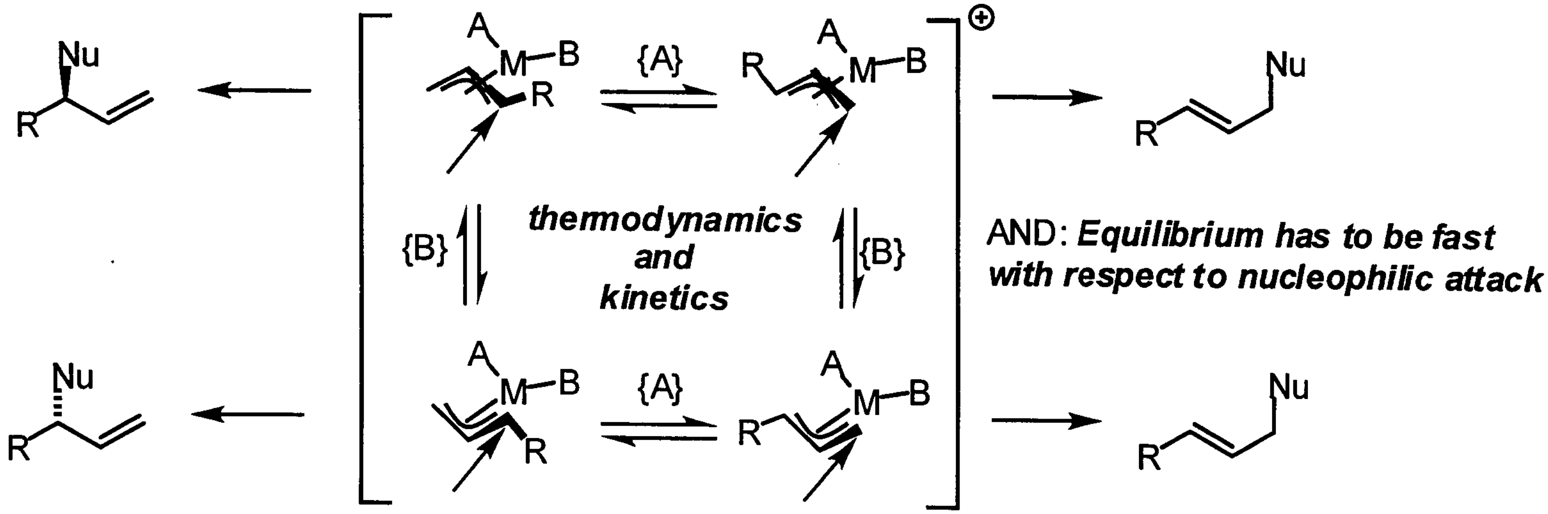
Introduction - mechanism



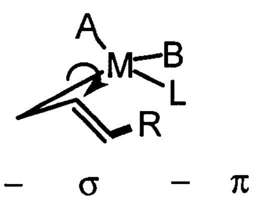
Introduction - unsymmetrically substituted substrates



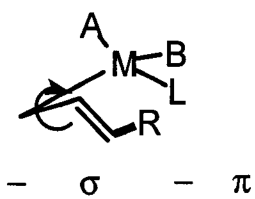
Introduction - basic problem



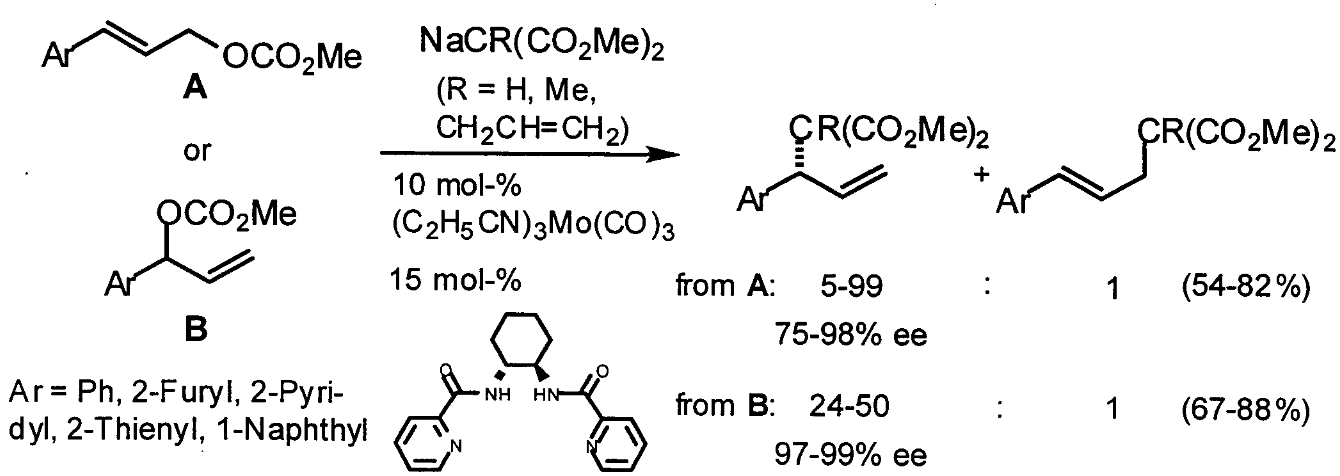
{A}: *via*



{B}: *via*

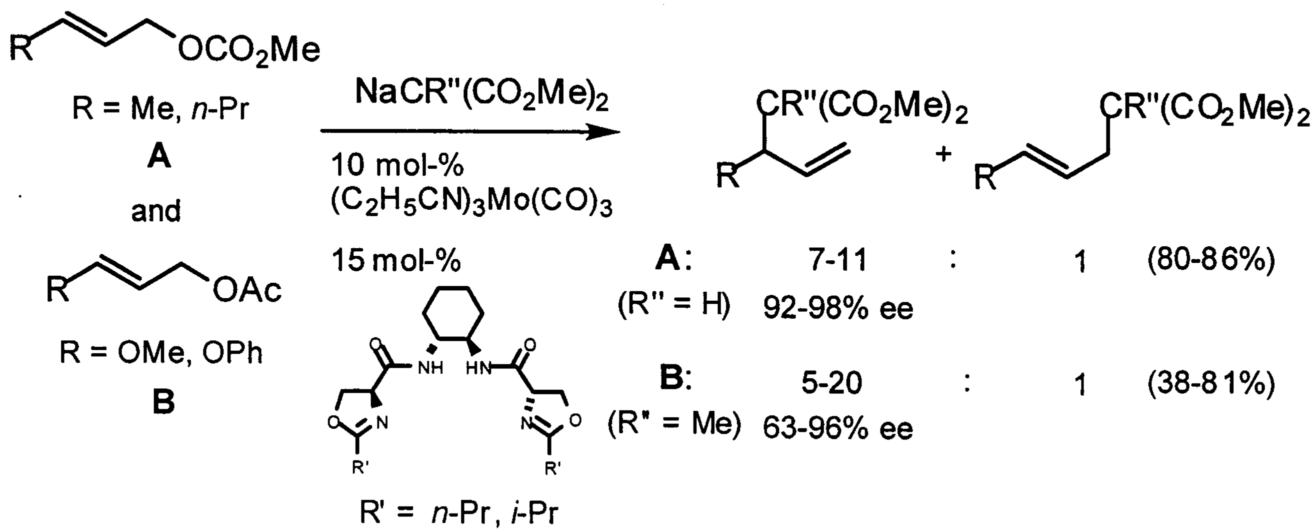


Introduction - leading papers



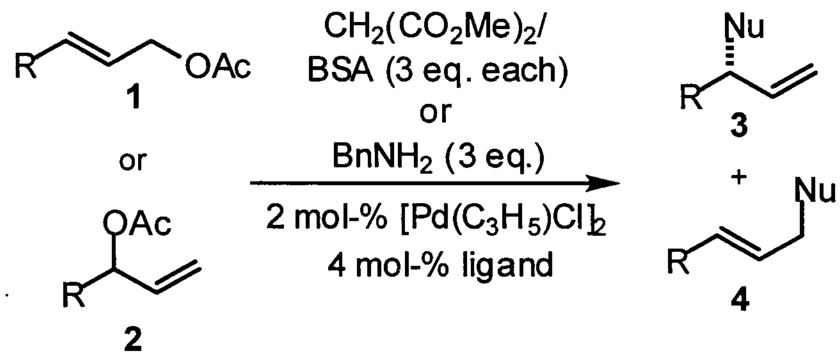
B. M. Trost, I. Hachiya, *J. Am. Chem. Soc.* **1998**, *120*, 1104-1105.

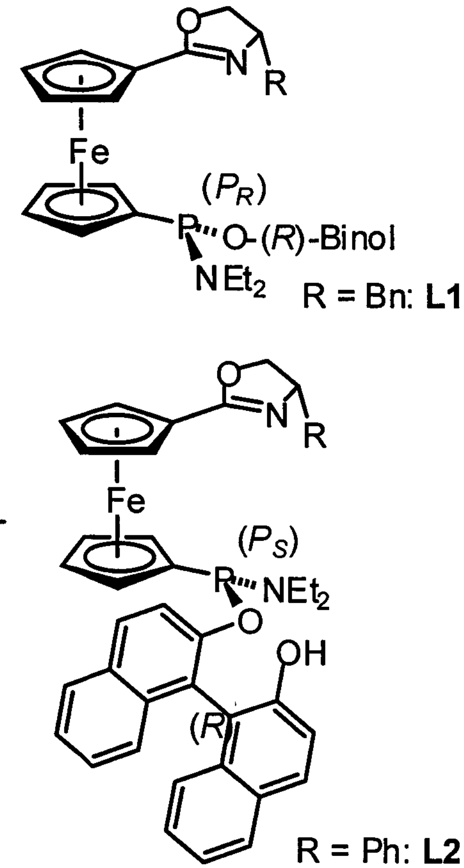
Introduction - leading papers



F. Glorius, A. Pfaltz, *Org. Lett.* **1999**, *1*, 141-144

Introduction - leading papers

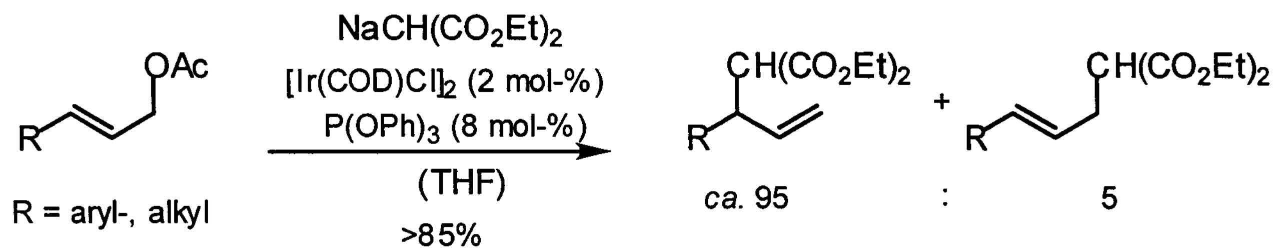




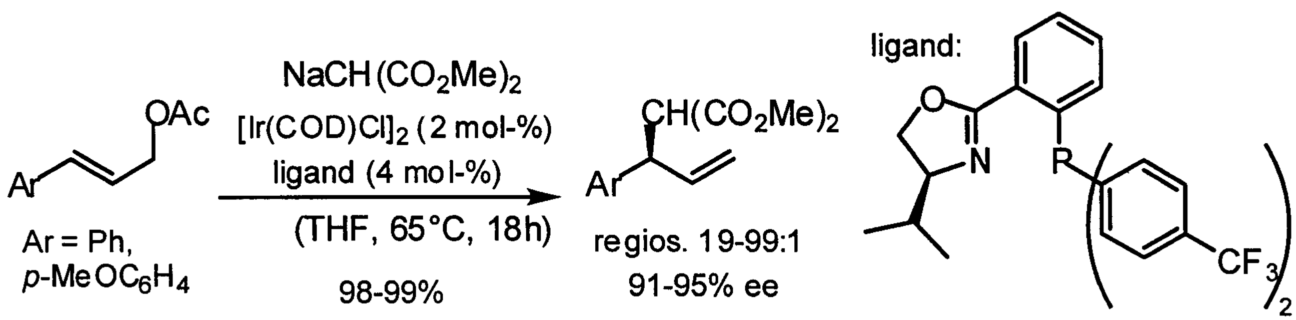
Nu	substr.	R	ligand	yield	**3**:**4**	*ee* of **3**
$CH(CO_2Me)_2$	**1**	Ph	**L1**	98%	95:5	95%
$CH(CO_2Me)_2$	**1**	Me	**L1**	83%	>97:3	94%
NHBn	**2**	Ph	**L2**	94%	94:6	98%
NHBn	**2**	Me	**L2**	78%	>97:3	84%

S.-L. You, X.-Z. Zhu, Y.-M. Luo, X.-L. Hou, L.-X. Dai, *J. Am. Chem. Soc.* **2001**, *123*, 7471-7472

Introduction - preliminary work

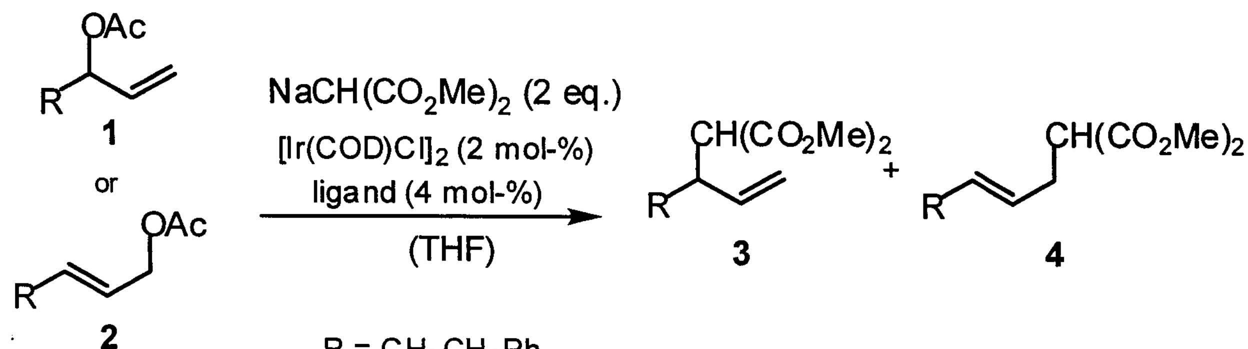


R. Takeuchi, M. Kashio, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 263-265



J. P. Janssen, G. Helmchen, *Tetrahedron Lett.* **1997**, *38*, 8025-8026

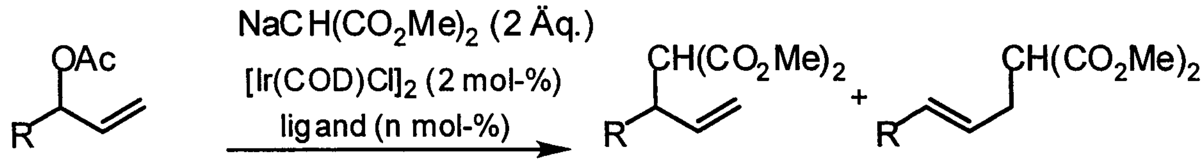
Mechanism - ligand acceleration



R = CH_2CH_2Ph

entry	substrate	ligand	temp. [°C], time [h]	yield [%]	regiosel. **3:4**
1	**1**	$P(OPh)_3$	25, 3	99	95:5
2	**1**	[none]	25, 3	66	89:11
3	**1**	PPh_3	25, 3	0	-
4	**2**	$P(OPh)_3$	25, 3	99	95:5
5	**2**	[none]	25, 3	0	-
6	**2**	PPh_3	25, 3	0	-

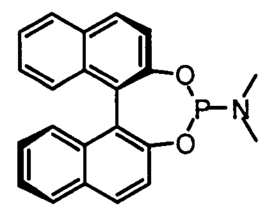
Mechanism - variation of Ir/ligand ratio



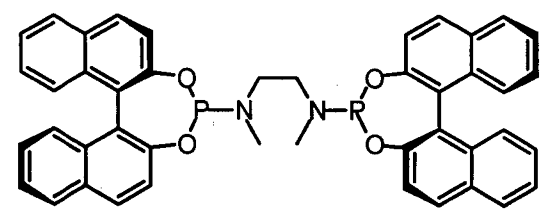
1 **3** **4**

R = CH_2CH_2Ph

entry	ligand	n	Lig./Ir	temp. [°C], time [h]	yield [%]	regiosel. **3:4**	ee [%] (*Config.*)
1	(*R*)-**L2**	4	1:1	25, 3	92	98:2	69 (*R*)
2	(*R*)-**L2**	8	2:1	25, 3	66	98:2	68 (*R*)
3	(*R*)-**L2**	16	4:1	25, 3	5	n. d.	n. d.
4	(*R,R*)-**L3**	2	0.5:1	25, 3	41	79:21	8 (*S*)
5	(*R,R*)-**L3**	4	1:1	25, 66	63	74:26	16 (*S*)

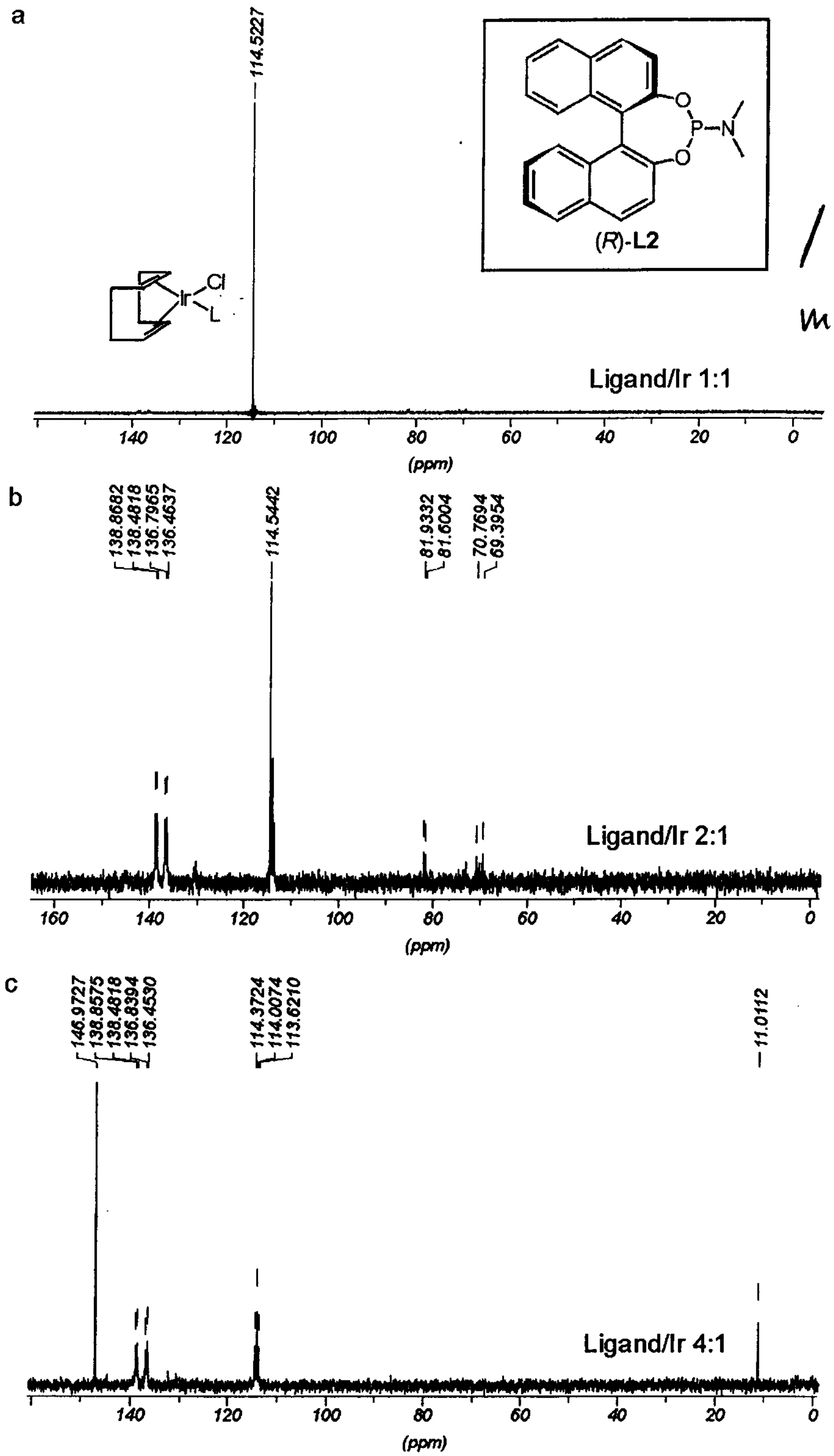


(*R*)-**L2**

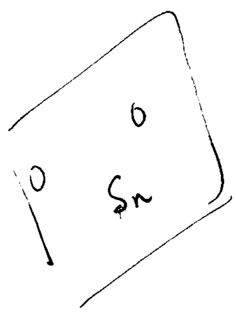


(*R,R*)-**L3**

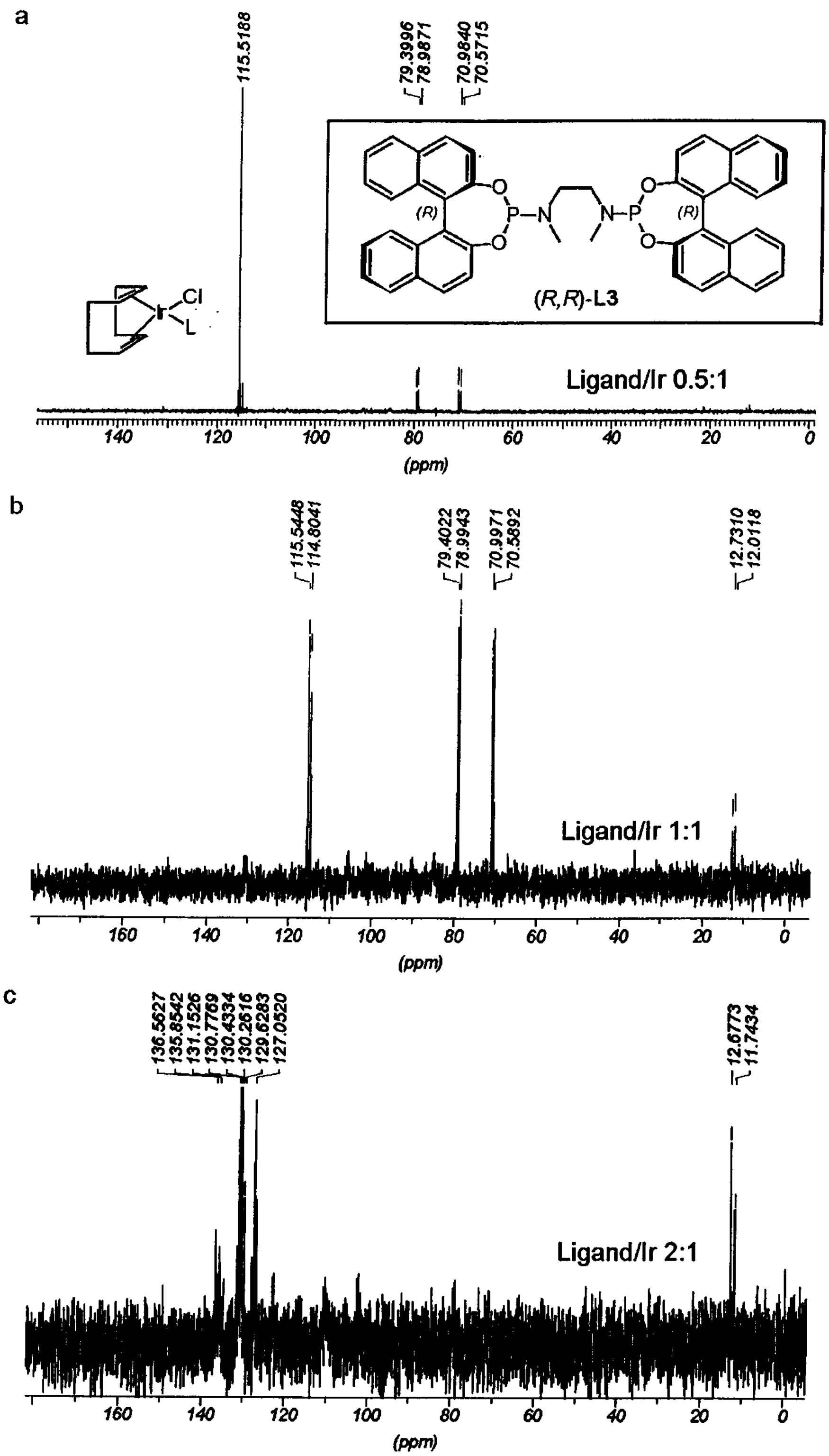
Mechanism – variation of the Ir/ ligand ratio



/ $[Ir(COD)Cl]_2$ mixtures

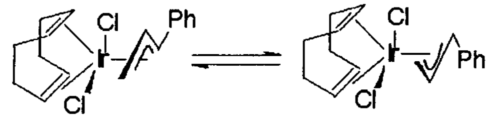


Mechanism – variation of the Ir/ ligand ratio

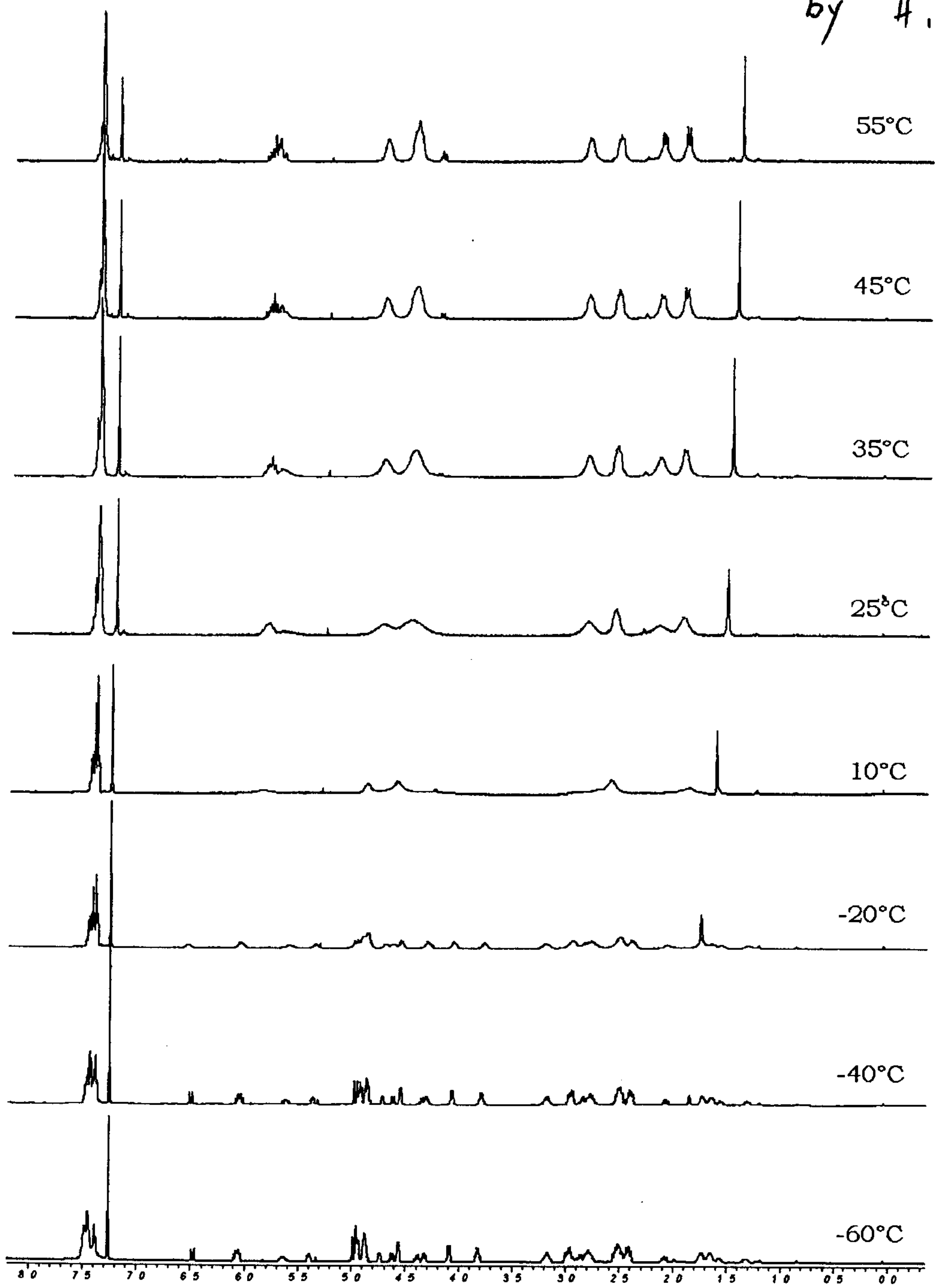


/ $[Ir(COD)Cl]_2$ - mixtures

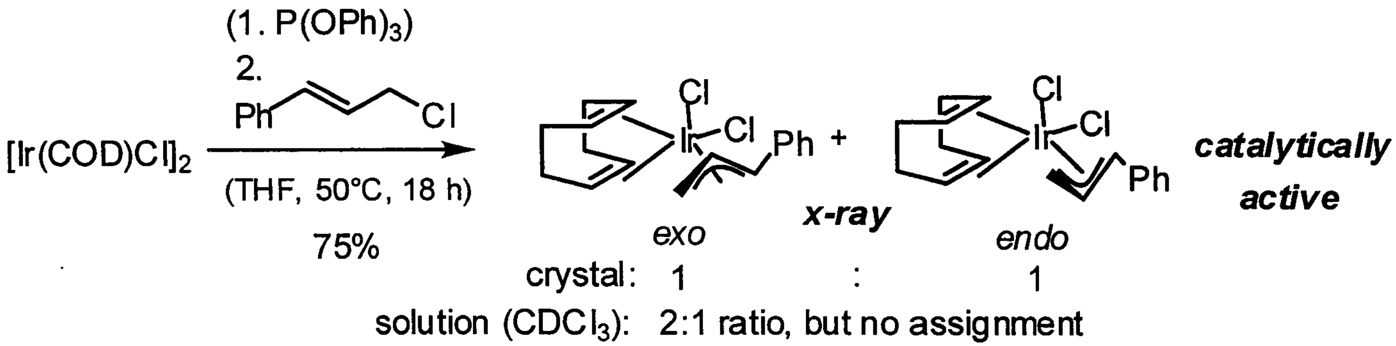
Mechanism – dynamics of allyl complex

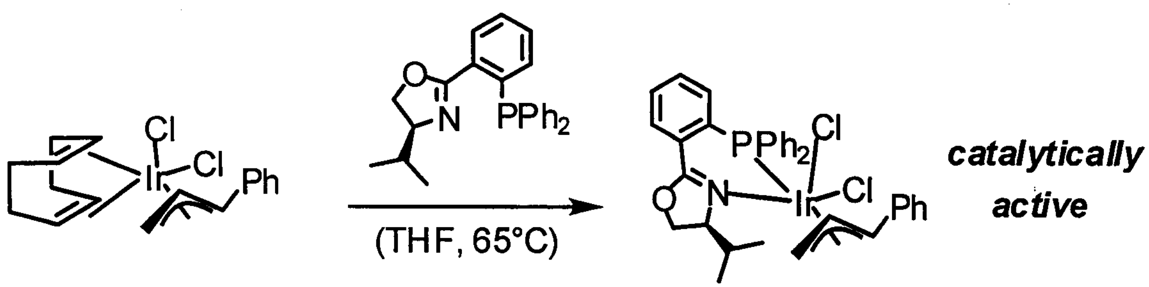


$k \simeq 4\ s^{-1}$ at $-40°C$
by $^1H,^1H$ - Exsy



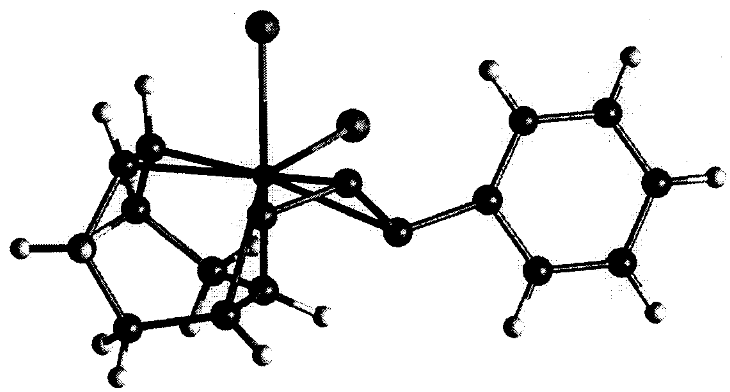
Mechanism - synthesis of Ir-complexes





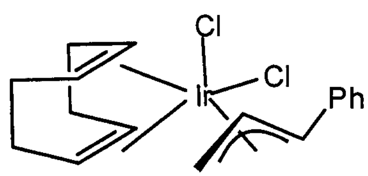
(Dr. Cristina Garcia-Yebra)

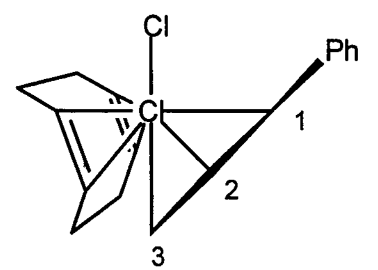
Mechanism - X-Ray of Ir-Complex



Exo-form:

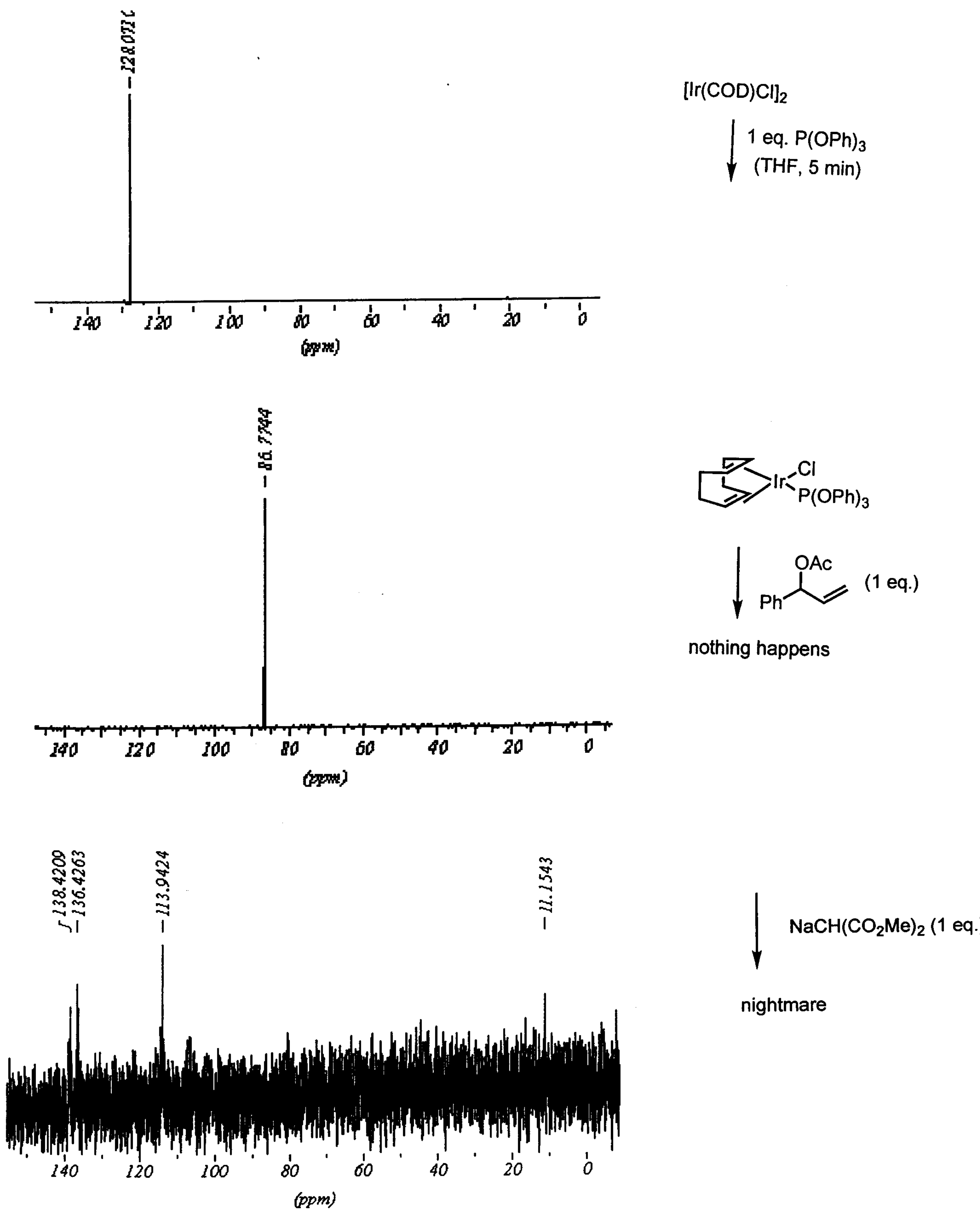
Ir-C1: 2.450(9) Å
Ir-C2: 2.244(18) Å
Ir-C3: 2.11(3) Å
C1-C2: 1.348(18) Å
C2-C3: 1.436(13) Å





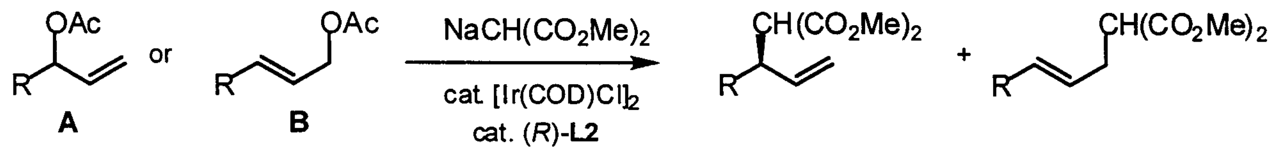
trans-effect: ═ better π-acceptor than Cl

Mechanism – ^{31}P n.m.r. of catalysis



Mechanism - memory effects

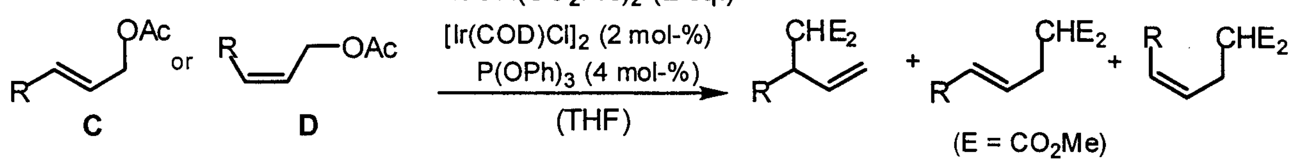
I Regiochemical substitution pattern of substrate



R = CH_2CH_2Ph

from **A**:	(92%)	98 (69% ee) :	2
from **B**:	(54%)	95 (43% ee) :	5

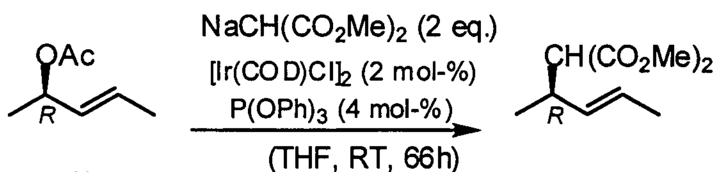
II Double bond geometry



R = CH_2CH_2OMOM

from **C**:	(95%)	97	:	3	:	0
from **D**:	(80%)	12	:	0	:	88

III Configuration

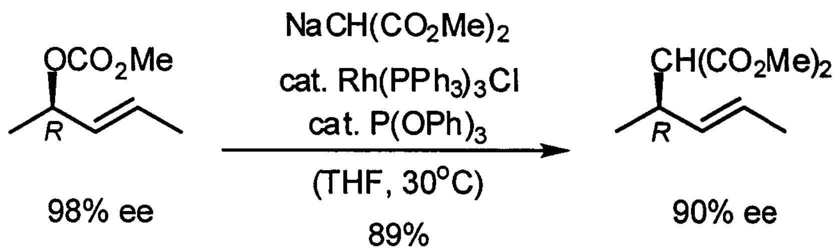


99% ee

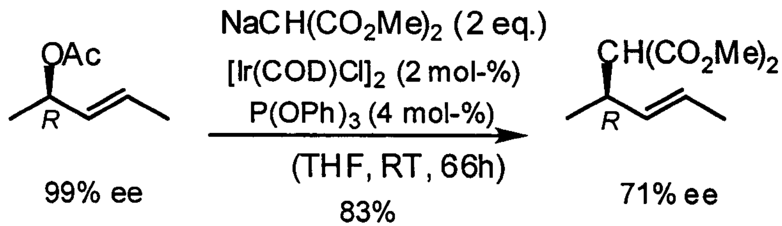
83%

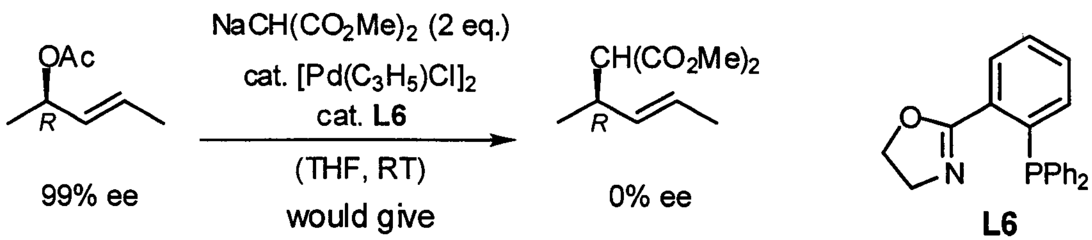
71% ee

Mechanism - Comparison of memory effect



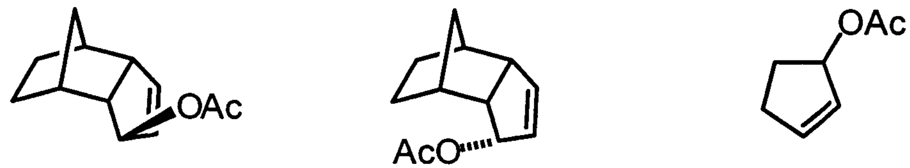
P. A. Evans, J. D. Nelson, *J. Am. Chem. Soc.* **1998**, *120*, 5581-5582





L6

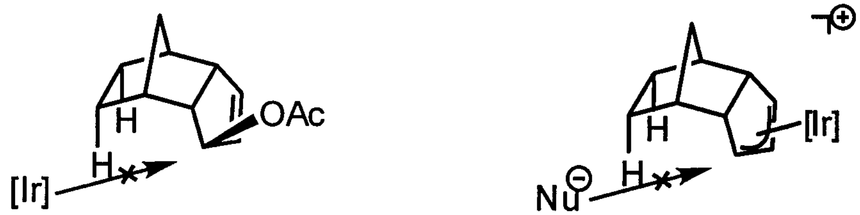
Mechanism - stereochemical course



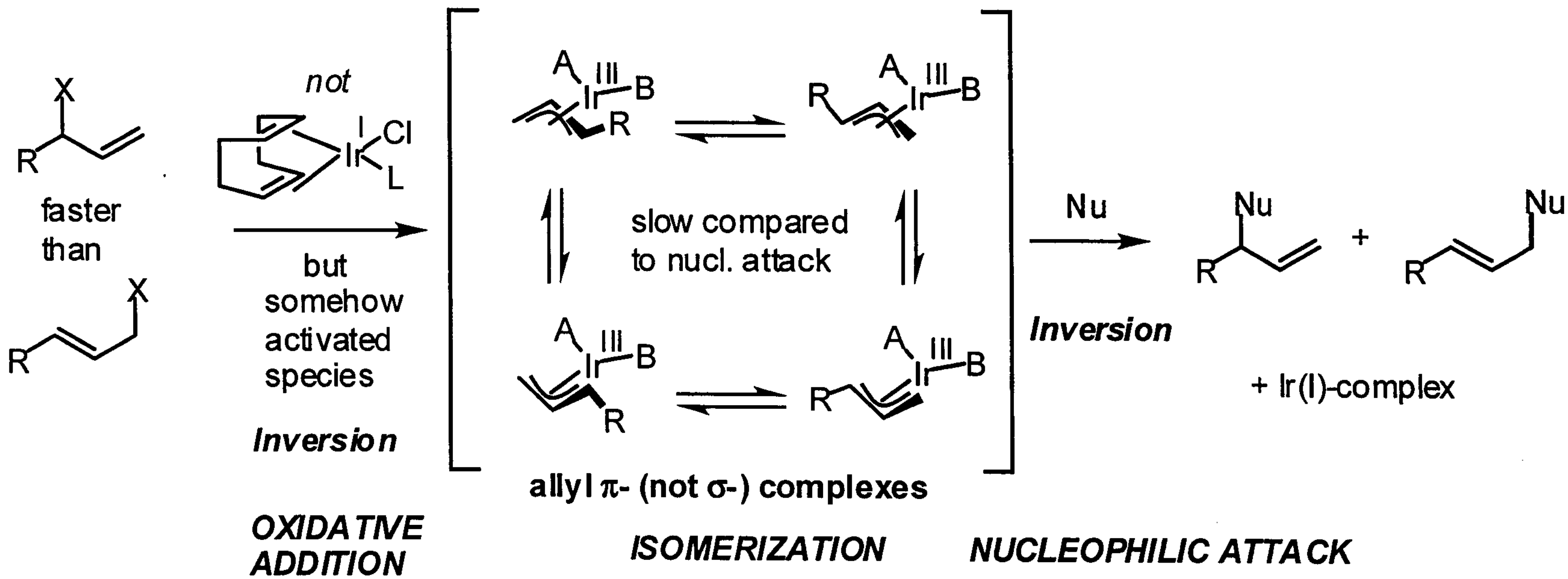
<5% Conversion <5% Conversion 100% Conversion

(conditions: THF, 65°C, 18h, 2 mol-% $[Ir(COD)Cl]_2$, 4 mol-% $P(OPh)_3$, 2 eq. $NaCH(CO_2Me)_2$)

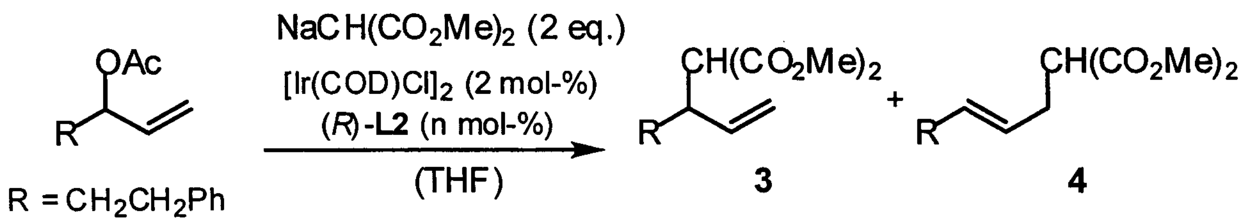
suggests mechanism *via* **double Inversion:**



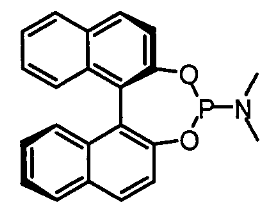
Mechanism - summary



Development - variation of Ir/lig. ratio

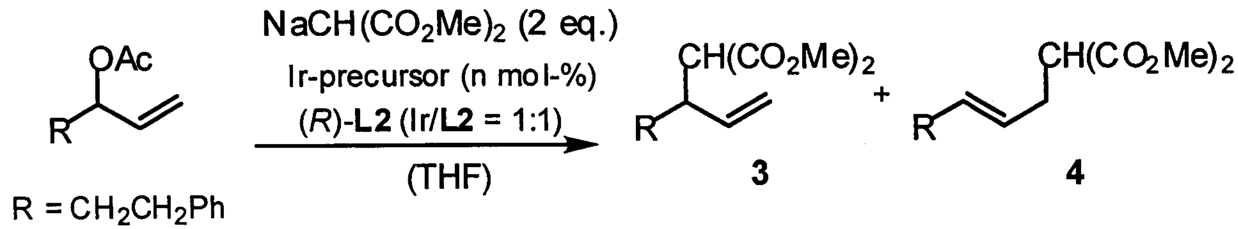


entry	n	Lig./Ir	temp. [°C], time [h]	yield [%]	regiosel. **3:4**	ee [%] (*Config.*)
1	4	1:1	25, 3	92	98:2	69 (*R*)
2	8	2:1	25, 3	66	98:2	68 (*R*)
3	16	4:1	25, 3	5	n. d.	n. d.



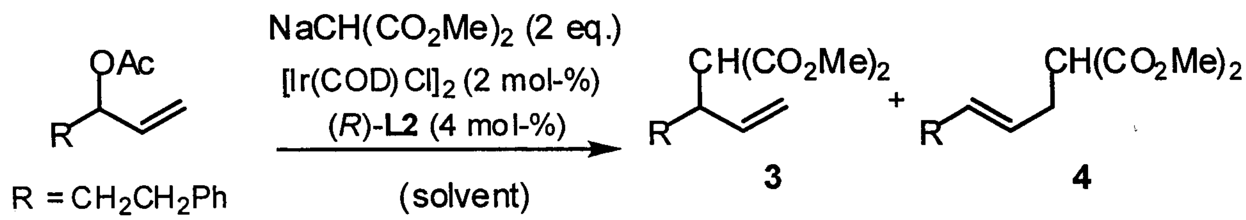
(*R*)-**L2**

Development - variation of catalyst



entry	Ir-precursor	n mol-%	temp. [°C], time [h]	yield [%]	regiosel. **3:4**	ee [%] (*Config.*)
1	$[Ir(COE)_2Cl]_2$	2	25, 3	16	76:24	9 (*R*)
2	$Ir(PPh_3)_2COCl$	4	65, 24	81	73:27	29 (*R*)
3	$[Ir(COD)Cl]_2$	0.5	25, 3d	21	92:8	33 (*R*)
4	$[Ir(COD)Cl]_2$	1	25, 3d	37	96:4	41 (*R*)
5	$[Ir(COD)Cl]_2$	2	25, 3	92	98:2	69 (*R*)
6	$[Ir(COD)Cl]_2$	4	25, 1	99	99:1	51 (*R*)

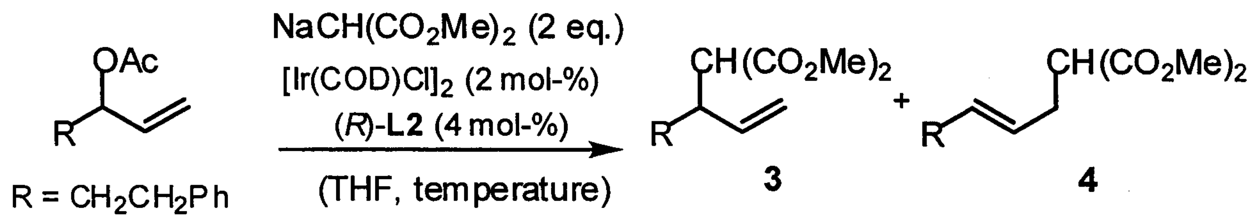
Development - variation of solvent



entry	solvent	ε[a]	temp. [°C], time [h]	yield [%]	regiosel. **3:4**	ee [%] (*Config.*)
1	toluene	2.7	25, 72	91	98:2	0
2	ether	4.2	25, 72	65	99:1	25 (*R*)
3	THF	7.4	25, 3	92	98:2	69 (*R*)
4	CH_2Cl_2	8.9	25, 72	10	-[b]	25 (*R*)
5	DMF	37	25, 72	44	96:4	67 (*S*)
6	CH_3CN	38	25, 72	28	76:24	28 (*R*)

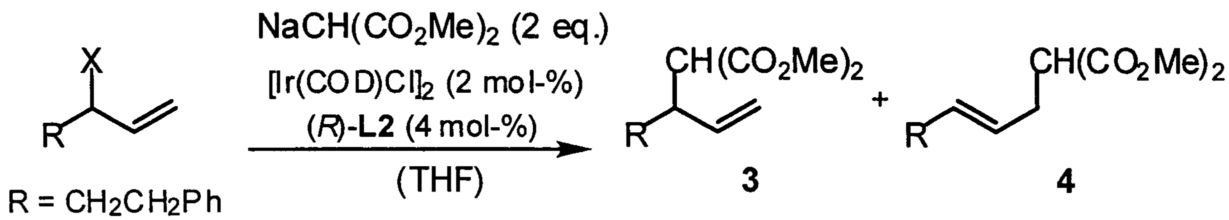
[a] dielectric constant. [b] linear isomer not detected (GC/MS).

Development - variation of temperature



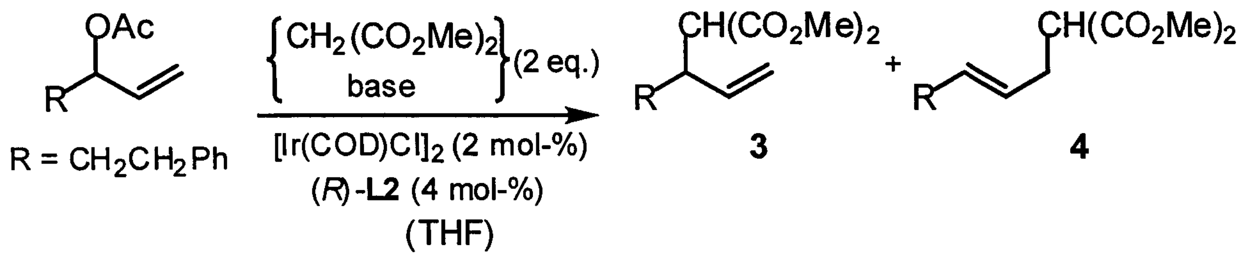
entry	temp. [°C], time [h]	yield [%]	regiosel. **3:4**	ee [%] (*Config.*)
1	0, 6	74	99:1	47 (*R*)
2	25, 3	92	98:2	69 (*R*)
3	45, 1	99	98:2	67 (*R*)
4	65, 1	98	98:2	68 (*R*)

Development - variation of leaving group



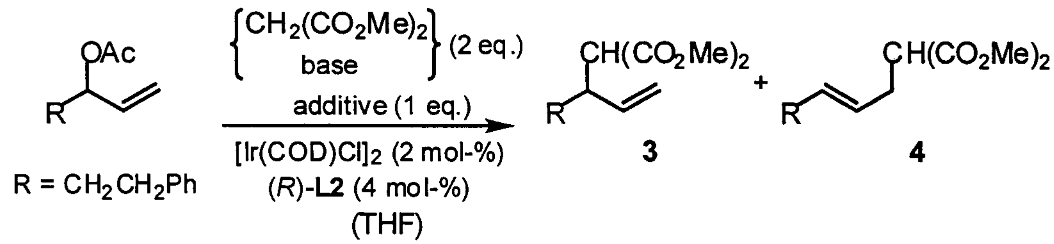
entry	leaving group X	temp. [°C], time [h]	yield [%]	regiosel. **3:4**	ee [%] (*Config.*)
1	Cl	25, 3	88	60:40	0
2	OCOMe	25, 3	92	98:2	69 (*R*)
3	OCO_2Et	25, 3	47	85:15	25 (*R*)
4	$OPO(OEt)_2$	25, 3	41	82:18	0
5	OH	65, 24	0	-	-

Development - variation of counter ion



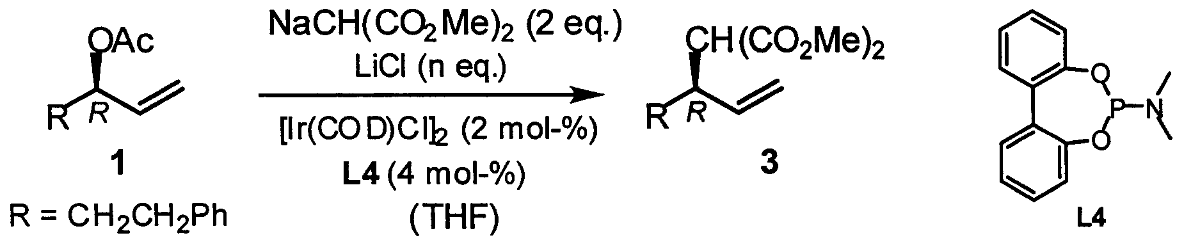
entry	base	temp. [°C], time [h]	yield [%]	regio-sel. **3**:**4**	ee [%] (*Config.*)
1	*n*-BuLi	25, 3	30	98:2	60 (*R*)
2	NaH	25, 3	92	98:2	69 (*R*)
3	Cs_2CO_3	25, 3	76	99:1	29 (*R*)
4	$ZnEt_2$	25, 7d	8	44:56	9 (*R*)
5	BSA	25, 5d	13	-	20 (*R*)

Development - variation of additives



entry	base	additive	temp. [°C], time [h]	yield [%]	regio-sel. **3**:**4**	ee [%] (*Config.*)
1	*n*-BuLi	$ZnCl_2$	25, 7d	91	86:14	3 (*R*)
2	NaH	NMe_4Br	25, 3	95	99:1	49 (*R*)
3	NaH	NBu_4Cl	25, 3	15	99:1	25 (*R*)
4	NaH	LiF	25, 3	99	99:1	58 (*R*)
5	NaH	LiCl	25, 3	83	99:1	**86 (*R*)**
6	NaH	LiBr	25, 3	69	98:2	83 (*R*)
7	NaH	LiI	25, 3	57	99:1	5 (*R*)
8	NaH	$ZnCl_2$	25, 7d	29	88:12	15 (*R*)

Development - origin of LiCl-effect

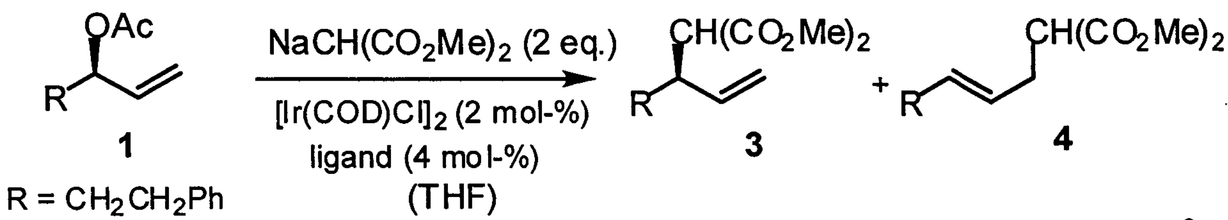


entry	ee of **1** [%] (*Conf.*)	equiv. LiCl	temp. [°C], time [h]	yield [%]	regios. **3:4**	ee [%] (*Config.*)	ret.[a] [%]
1	91 (*R*)	0	25, 3	96	99:1	44 (*R*)	48
2	91 (*R*)	0.5	25, 3	81	92:8	33 (*R*)	36
3	91 (*R*)	1	25, 3	61	79:21	34 (*R*)	37
4	91 (*R*)	2	25, 3	41	79:21	13 (*R*)	14

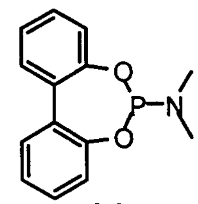
[a] Retention or Cee-value (Conservation of enantiomeric excess) is defined as ee(produkt)/ee(sm)×100.

Reviews about additives in transition metal catalysis: E. M. Vogl, H. Groeger, M. Shibasaki, *Angew. Chem. Int. Ed.* **1999**, *38*, 1570-1577; especially halides: K. Fagnou, M. Lautens, *Angew. Chem. Int. Ed.* **2002**, *41*, 26-47.

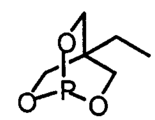
Ligand Screening - achiral ligands



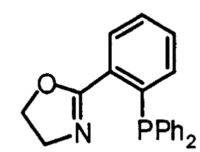
entry	ee of **1** [%] (*conf.*)	ligand	temp. [°C], time [h]	yield [%]	regios. **3:4**	ee [%] (*conf.*)	ret. [%]
1	91 (*R*)	$P(OPh)_3$	25, 3	91	95:5	51 (*R*)	56
2	98 (*S*)	$P(NMe_2)_3$	25, 18	0	-	-	-
3	91 (*R*)	**L4**	25, 3	98	99:1	39 (*R*)	43
4	98 (*S*)	**L5**	25, 18	99	84:16	70 (*S*)	71
5	91 (*R*)	**L6**	25, 3	93	53:47	66 (*R*)	73
6	98 (*S*)	[none]	25, 18	67	91:9	85 (*S*)	87



L4

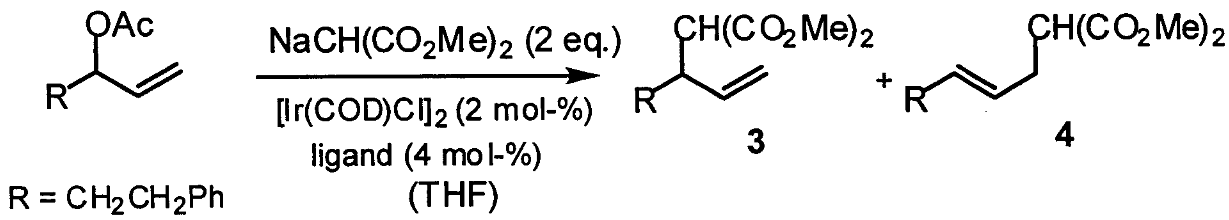


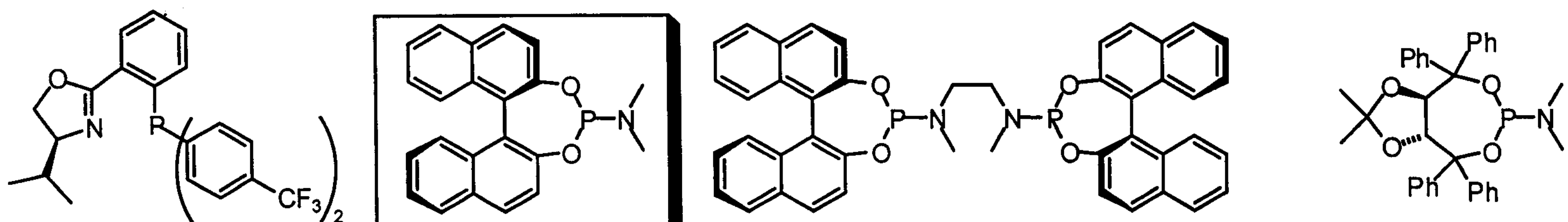
L5



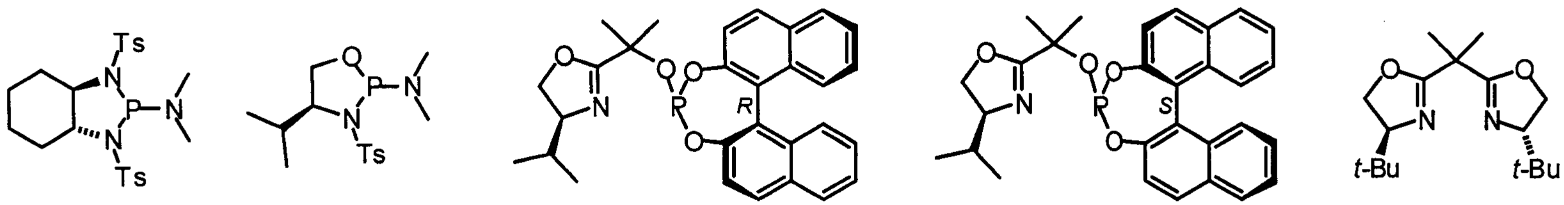
L6

Ligand Screening I - branched substrate



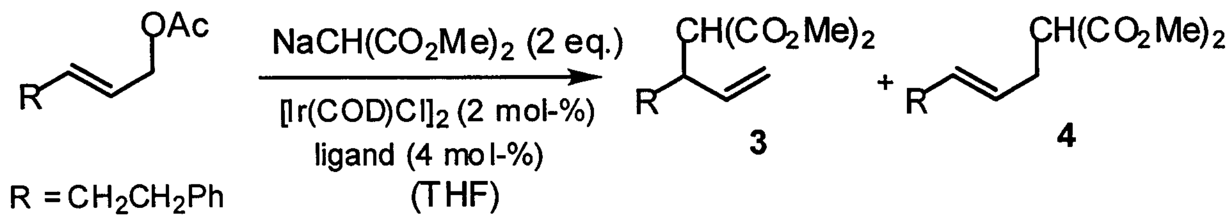


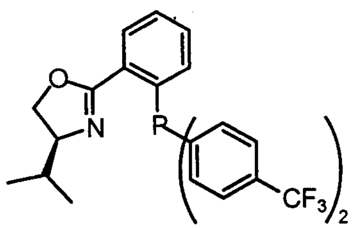
95:5, 8% ee (*S*) | 98:2, **69% ee** (*R*) | 74:26, 8% ee (*S*) | 84:16, 5% ee (*R*)



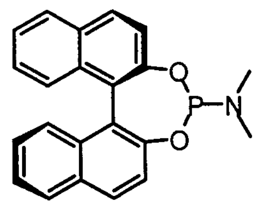
89:11, 0% ee | 96:4, 9% ee (*R*) | 94:6, 63% ee (*R*) | 95:5, 62% ee (*S*) | 92:8, 0% ee

Ligand Screening I - linear substrate

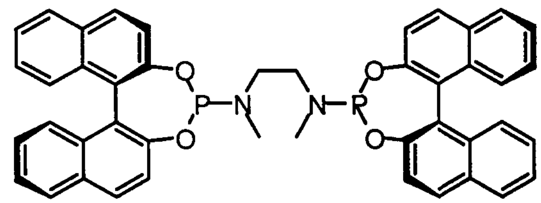




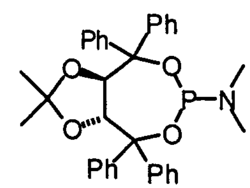
62:38, 78% ee (*R*)



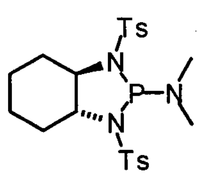
95:5, 43% ee (*R*)



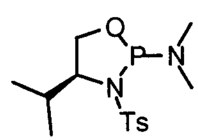
76:24, 15% ee (*R*)



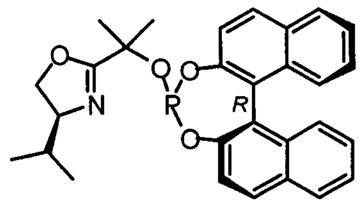
21:79, 8% ee (*R*)



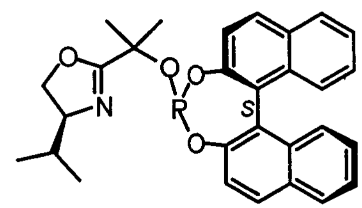
23:77, 5% ee (*R*)



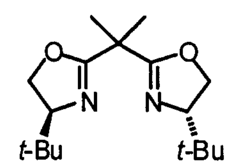
39:61, 7% ee (*S*)



45:55, 10% ee (*S*)

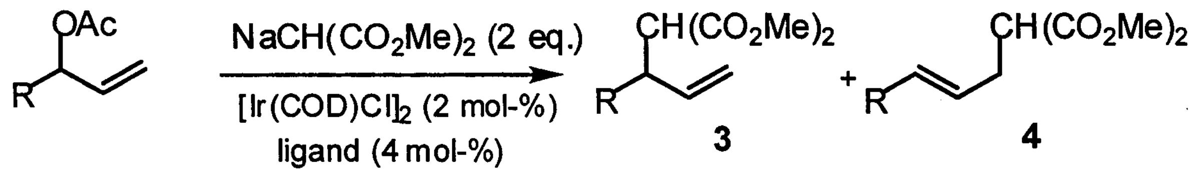


47:53, 22% ee (*R*)

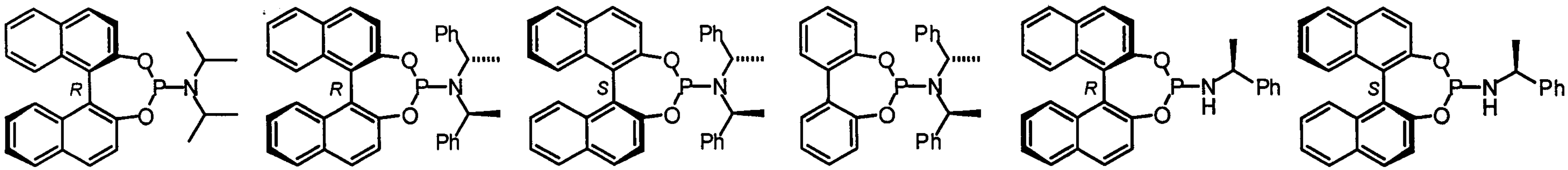


11:89, 7% ee (*S*)

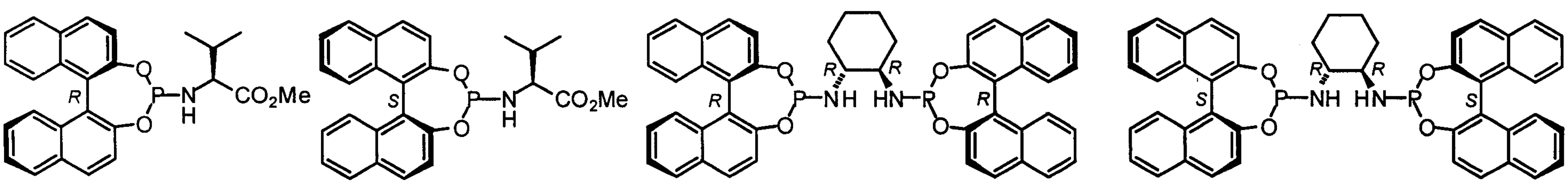
Ligand Screening II - branched substrate



R = CH_2CH_2Ph 3 4

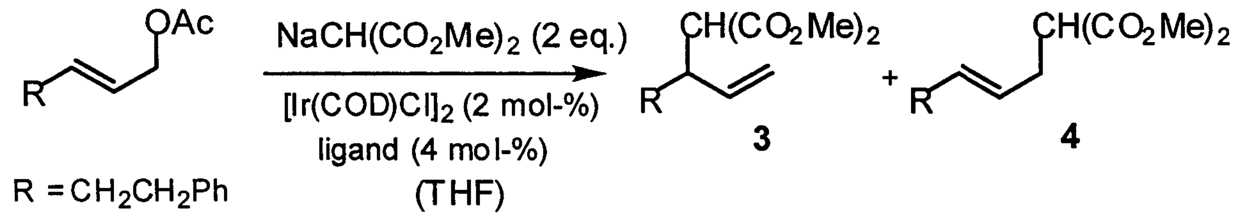


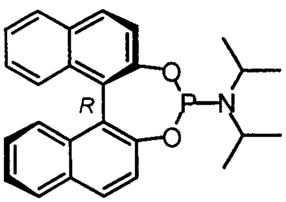
85:15, 21% ee (*S*) 86:14, 27% ee (*R*) 89:11, 24% ee (*R*) 89:11, 7% ee (*R*) 99:1, 64% ee (*R*) 96:4, 27% ee (*S*)



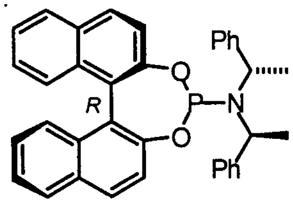
98:2, 31% ee (*R*) 98:2, 19% ee (*S*) 86:14, 24% ee (*R*) 92:8, 23% ee (*S*)

Ligand Screening II - linear substrate

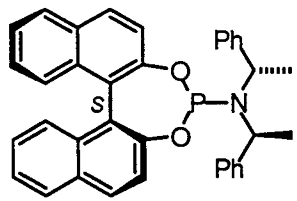




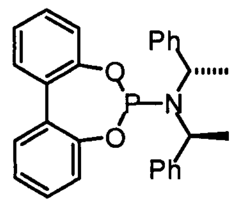
28:72, 12% ee (*S*)



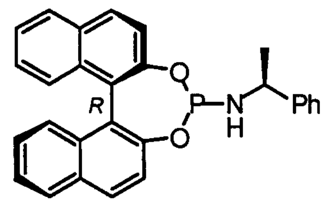
30:70, 23% ee (*S*)



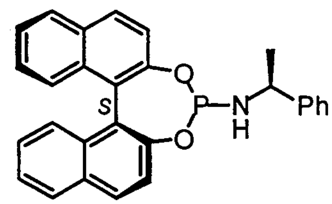
53:47, **77% ee (*R*)**



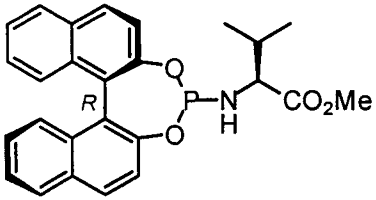
53:47, 61% ee (*R*)



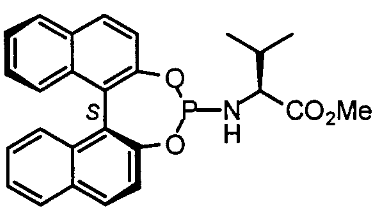
83:17, 57% ee (*R*)



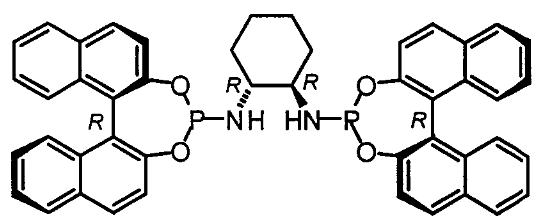
88:12, 38% ee (*S*)



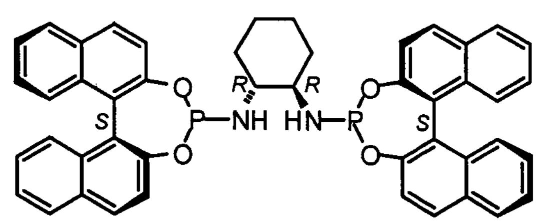
90:10, 24% ee (*R*)



72:28, 39% ee (*S*)

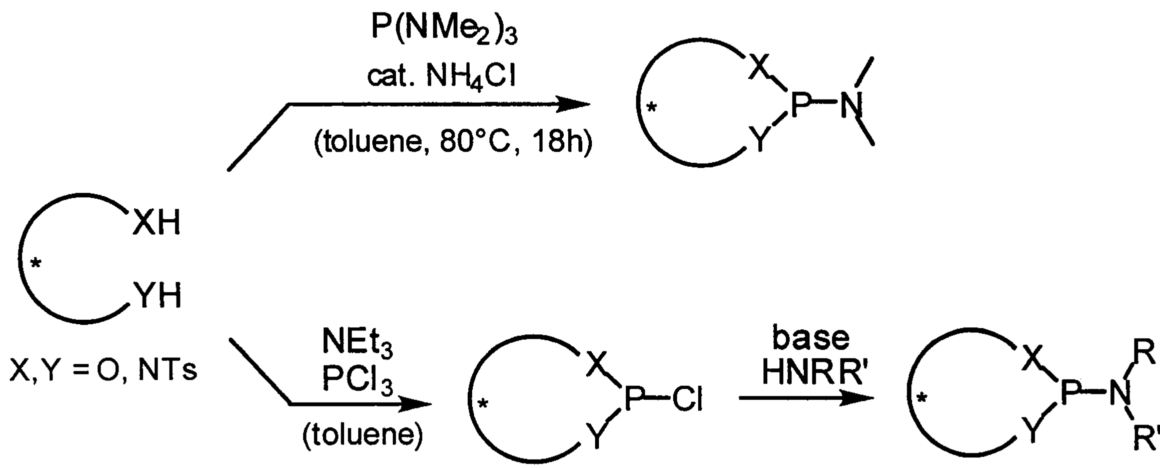


32:68, 23% ee (*R*)

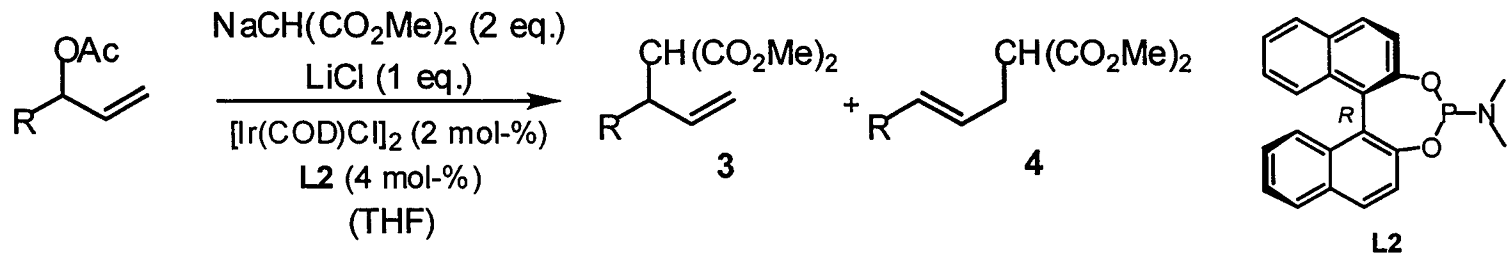


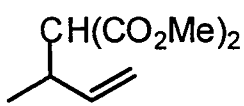
75:25, 20% ee (*S*)

Ligand Synthesis

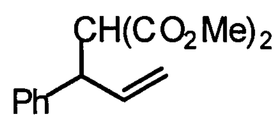


Variation of Substrate - branched

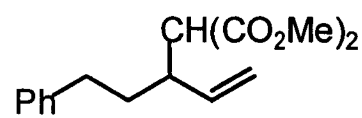




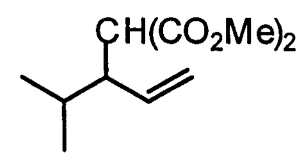
94:6, 57% ee (*R*)



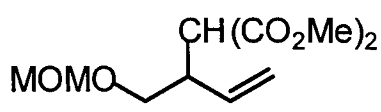
98:2, 4% ee (*R*)



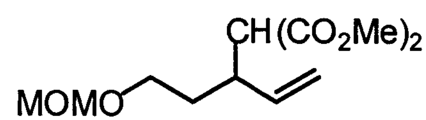
99:1, 86% ee (*R*)



99:1, 74% ee (*R*)

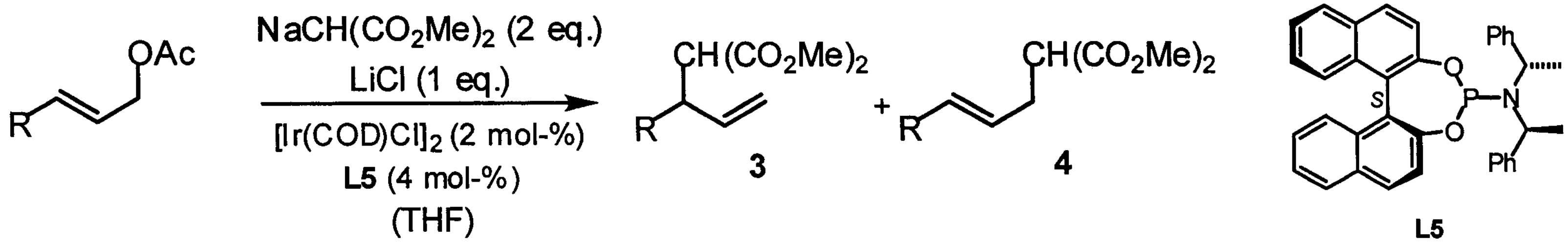


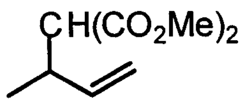
95:5, 78% ee (*R*)



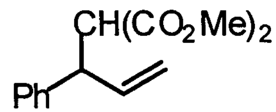
98:2, 70% ee (*R*)

Variation of Substrate - linear

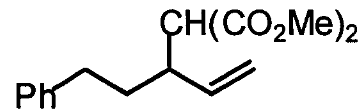




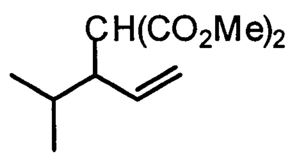
75:25, 82% ee (*R*)



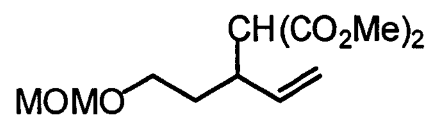
91:9, 86% ee (*R*)



65:35, 92% ee (*R*)

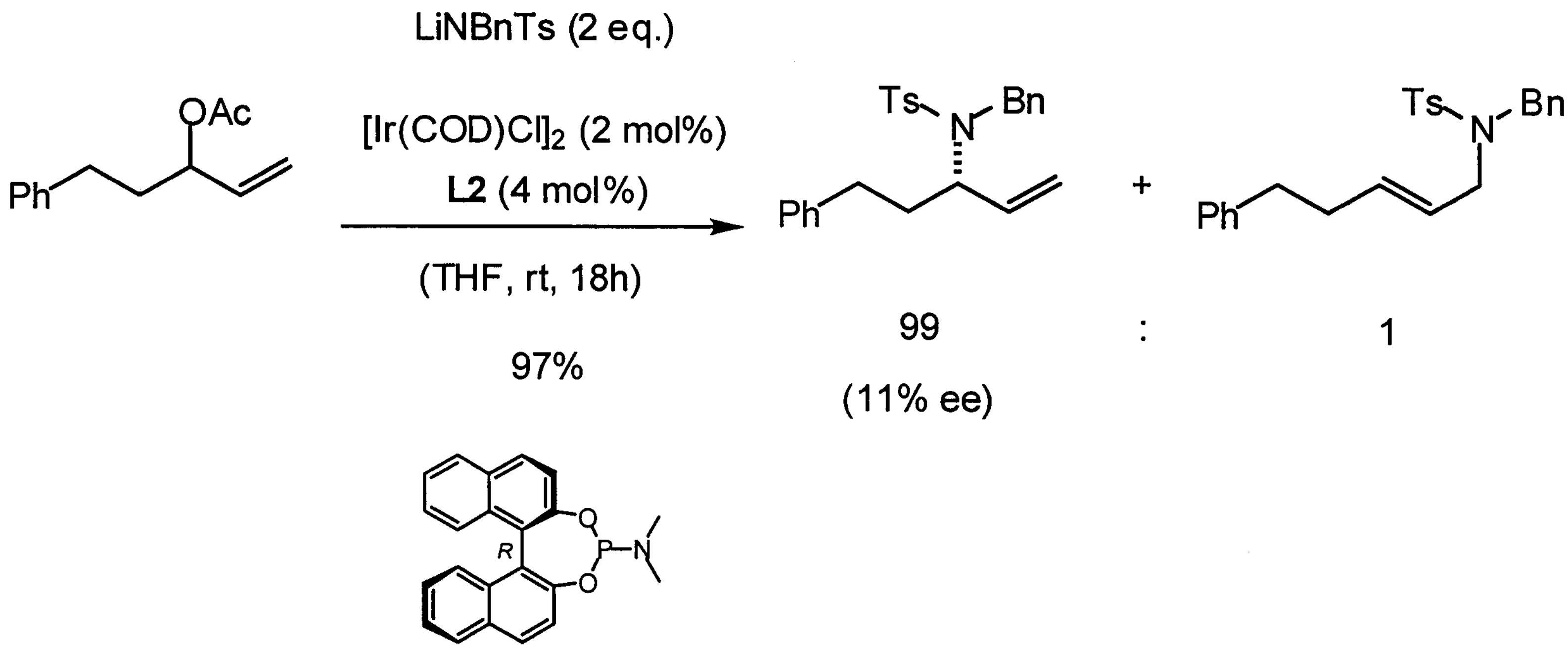


55:45, 94% ee (*R*)



65:35, 83% ee (*R*)

Variation of Nucleophile - amination



L2

Summary

- Basic properties of Iridium-allyl complexes have been investigated (hapticity, isomerization, memory effects).
- Enantioselective alkylation has been developed giving rise to enantio-selectivities up to 94% ee.
- Part of the work has been published in B. Bartels, G. Helmchen, *Chem. Commun.* **1999**, 741-742.

Outlook

- Still unsolved: structure of catalytically active Ir-complex bearing allyl fragment *and* monodentate phosphorus containing ligand.
- Further variation of ligand structure might lead to more selective product formation, especially in the case of the amination reaction.

Acknowledgements

- Prof. G. Helmchen
- Members of Helmchen and Kazmaier groups
- Graduiertenkolleg for financial support