



Recent Advances in the Asymmetric NH(K)
Catalytic in Chromium
(Nozaki-Hiyama-Kishi)

Keith Korthals



First Example (sub-stoichiometric)

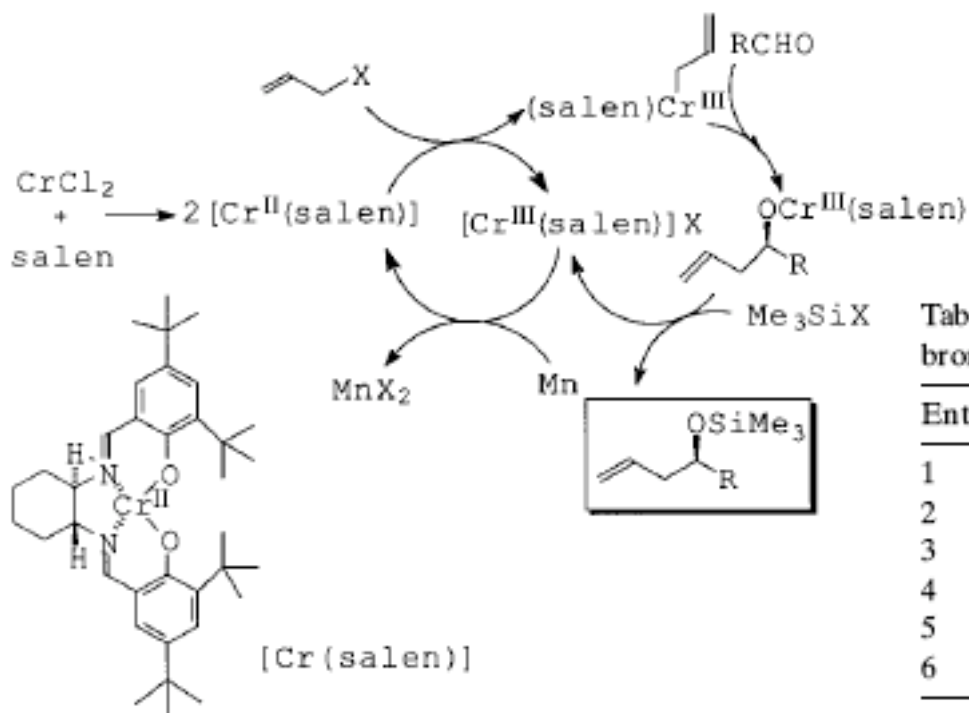


Table 1. Influence of bases on the enantioselective addition of allyl bromide to PhCHO catalyzed by [Cr(salen)] complex.

Entry	Base ^[a]	Yield [%] ^[b]	ee [%] ^[c]
1	–	56	21
2	K ₂ CO ₃	51	47
3	K ₂ CO ₃ ^[d]	52	25
4	Et ₃ N	65	65
5	Et ₃ N ^[e]	50	50
6	(<i>t</i> Bu) ₂ Py	20	58

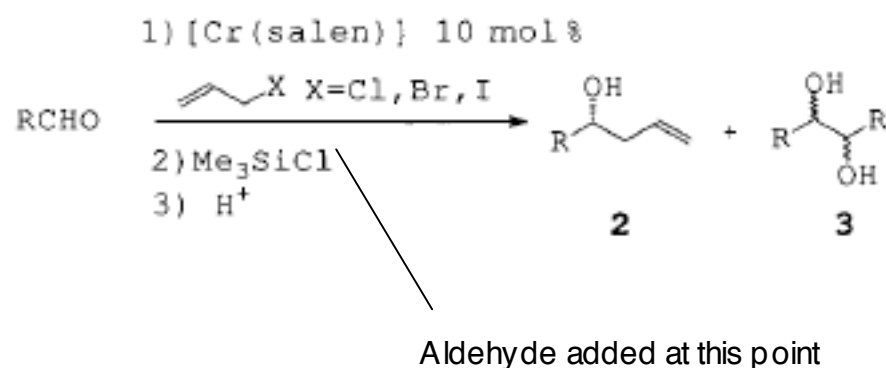
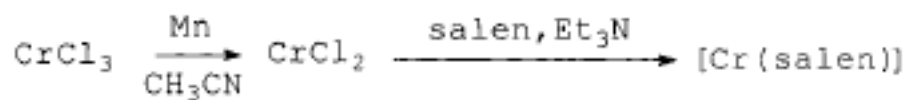
[a] All the bases were added to a suspension of salen and CrCl₂ in CH₃CN. All the reactions, except for that in entry 1, were carried out with 20 mol % of base. [b] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [c] The *ee* value was evaluated with a cyclodextrin Megadex 5.25 mt chiral column. The absolute configuration of the isolated homoallylic alcohol was assigned by comparison of the GC analysis trace with that of the known product.^[5a] [d] The reaction was carried out at 40 °C. [e] 10 equivalents of Et₃N were employed.

Bandini, Marco; Cozzi, Pier Giorgio; Melchiorre, Paolo; Umani-Ronchi, Achille. *Angew. Chem., Int. Ed.* **1999**, *38*(22), 3357-3359.

Who took this journal? The journal fairy??



First Example



Allyl bromide and iodide gives modest or no ee.
Substitution of allyl substrate tends toward low ee.

Table 2. Enantioselective addition of various allyl halides to PhCHO catalyzed by $[\text{Cr}(\text{salen})]$ complex.

Entry	RX	Yield [%] ^[a]	ee [%] ^[b]
1		67	84 (R)
2		65	65 (R)
3		70	0
4		62	42 (R) ^[c]
5		60	43 (R) ^[c]
6		85	70 (nd) ^[d]

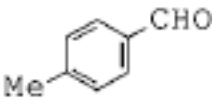
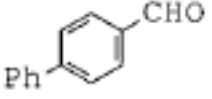
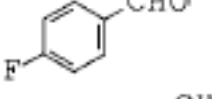
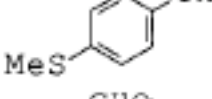
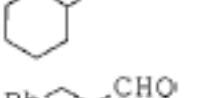
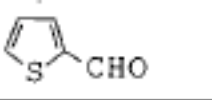

[a] Yield of isolated product after desilylation (HCl/THF) and flash chromatography. [b] Determined with a cyclodextrin Megadex 5.25 mt chiral column. The absolute configuration of the isolated homoallylic alcohol was assigned by comparison of the GC analysis trace with that of the known product.^[5a] [c] Determined with a cyclodextrin Megadex 5.25 mt chiral column on the corresponding O-methyl ether. The absolute configuration was assigned by comparing the optical rotation with that of the known product: $[\alpha]_{\text{D}} = +6.3$ ($c = 0.51$ in C_6H_6); literature value: *R* isomer, $[\alpha]_{\text{D}} = +50.2$ ($c = 1.16$ in C_6H_6).^[11a]



First Example



Table 3. Enantioselective addition of allyl chloride to aldehydes catalyzed by [Cr(salen)] complex.

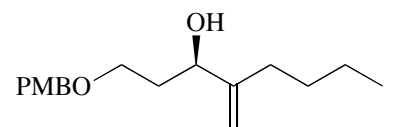
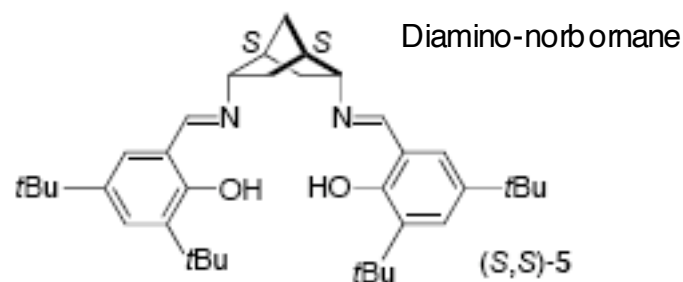
Entry	R'CHO	Yield of 2 [%] ^[a]	Yield of 3 [%] ^[b]	ee of 2 [%] ^[d]
1		NHK 67	Pinacol coupling 16	78 (<i>R</i>) ^[e]
2		54	35	82 (<i>R</i>) ^[e]
3		41	40	77 (<i>R</i>) ^[e]
4		46	40	78 (<i>R</i>) ^[e]
5		42 ^[e]	0 ^[h]	89 (<i>R</i>) ^[f]
6		45 ^[e]	13	77 (<i>S</i>) ^[g]
7		40	40	65 (<i>R</i>) ^[e]

Side reaction of the pinacol problematic.

Bandini, Marco; Cozzi, Pier Giorgio; Melchiorre, Paolo; Umani-Ronchi, Achille. *Angew. Chem., Int. Ed.* **1999**, *38*(22), 3357-3359.



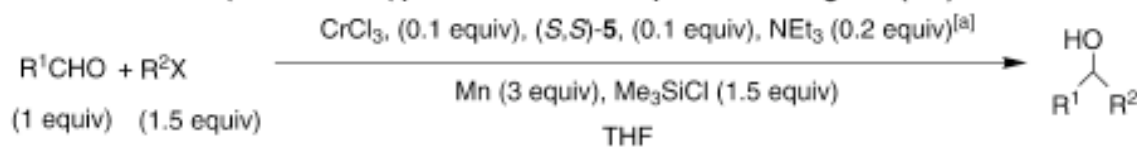
Another Ligand of the Same Type

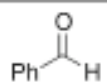

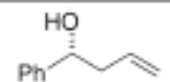
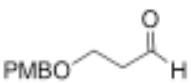

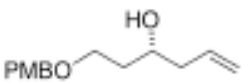


From triflate with NiCl₂
Furstner, N.

61 % ee, 54 % yield 20 °C^(a)

Table 1: Catalytic, enantioselective Nozaki–Hiyama–Kishi-type additions in the presence of ligand (*S,S*)-5.



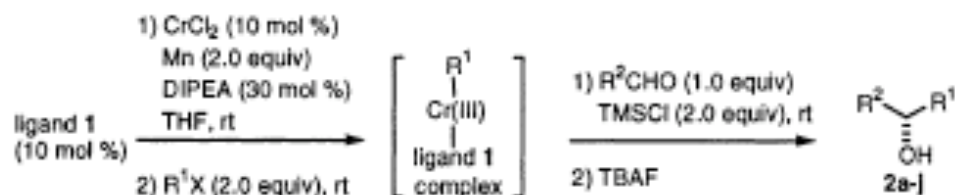
Entry	Aldehyde	Halide	Product	ee [%]	Yield [%] ^[b]	Reaction temperature ^[c]
1				90 ^[d,e]	72	5 °C
6				92 ^[e,h]	69 ^[i]	10 °C

[a] For entries 7 and 8, the reaction was run in the presence of 0.02 equiv of NiCl₂. [b] Yield after flash chromatography. [c] Reaction temperature was optimized for entries 1, 2, 5, 6, 7, and 8. [d] Enantiomeric excess was determined by gas chromatography (GC) of the corresponding TMS ethers on a chiral stationary phase (Macherey–Nagel: Lipodex A, 95 °C). [e] Absolute configurations were assigned by comparison of optical rotations with literature data.^[5d,11,12] [f] Absolute configuration based on GC/HPLC data (that is, comparison of the products of entries 2 and 1 and of the products of entries 3 and 5 on an analytical scale). [g] Not determined. [h] Enantiomeric excess determined by HPLC on a chiral phase (Daicel: Chiralcel OD-H). [i] Some debenzoylation occurred as a side reaction. [j] Absolute configuration determined by 1) oxidative cleavage (ozonolysis), 2) reduction to 1,2,4-butanetriol, 3) GC co-injection with a sample of known absolute configuration.^[13] [k] Reaction was performed with (*R,R*)-5. [l] Assignment of absolute configuration in analogy to entry 7.

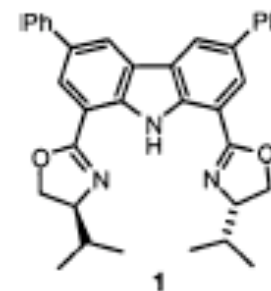
Berkessel*, A.; Menche, D.; Sklorz, C. A.; Schroder, M.; Paterson, I. *Angew. Chem., Int. Ed.* **2003**, *42*(9), 1032-1035.



Bis(oxazoliny)carbazole



entry	product	R ¹	X	R ²	ee(%) ^{a,b}	yield(%) ^c	time(h)
1	2a	allyl	Br	Ph	90(<i>S</i>) ^f	93	12
2 ^d	2a	allyl	Br	Ph	93(<i>S</i>) ^f	89	12
3	2a	allyl	Cl	Ph	89(<i>S</i>) ^f	95	16
4	2a	allyl	I	Ph	64(<i>S</i>) ^f	52	12
5	2b	allyl	Br	<i>p</i> -BrPh	92(<i>S</i>) ^g	87	12
6	2c	allyl	Br	PhCH=CH	95(<i>S</i>) ^h	87	12
7 ^d	2d	allyl	Br	PhCH ₂ CH ₂	86(<i>R</i>) ⁱ	91	12
8	2e	allyl	Br	<i>c</i> -C ₆ H ₁₁	94(<i>S</i>) ^f	95	12
9	2e	allyl	Cl	<i>c</i> -C ₆ H ₁₁	93(<i>S</i>) ^f	88	12



Bis(oxazoliny)carbazole ligand

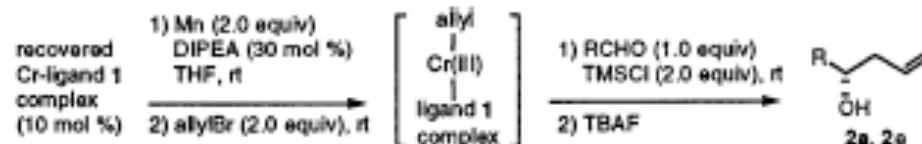
^a Ee determined by HPLC except **2j**. For HPLC conditions, see Supporting Information. ^b Absolute configuration determined by comparison of optical rotation to known literature value. ^c Isolated yields. ^d Reaction was carried out at 0 °C. ^e Ee determined by 600 MHz ¹H NMR of the corresponding MTPA ester. For further details, see Supporting Information. ^f See ref 19a. ^g See ref 19b. ^h See ref 1a. ⁱ See ref 4f. ^j See ref 19c. ^k See ref 19d. ^l See ref 19e. ^m See ref 19f. ⁿ See ref 19g.



Bis(oxazoliny)carbazole



- Recovery of Ligand



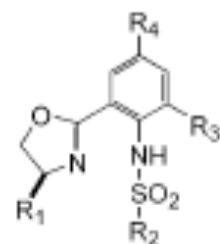
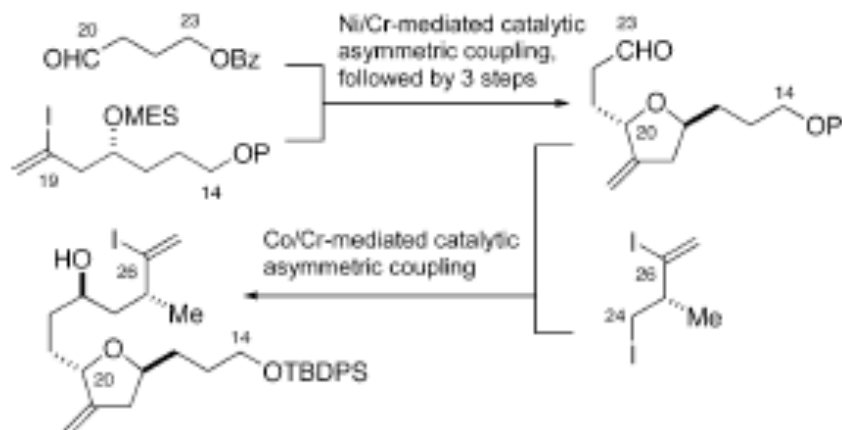
entry	product	R	ee(%) ^{a,b}	yield(%) ^c	time(h)	recycling
1 ^d	2a	Ph	92(<i>S</i>) ^e	86	24	first time
2 ^d	2a	Ph	93(<i>S</i>) ^e	79	24	second time
3	2e	<i>c</i> -C ₆ H ₁₁	95(<i>S</i>) ^e	84	16	first time
4	2e	<i>c</i> -C ₆ H ₁₁	94(<i>S</i>) ^e	90	16	second time

- Enantioselective Crotylation of Benzaldehyde



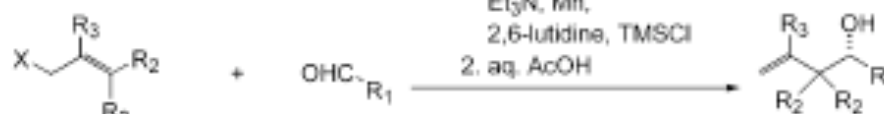
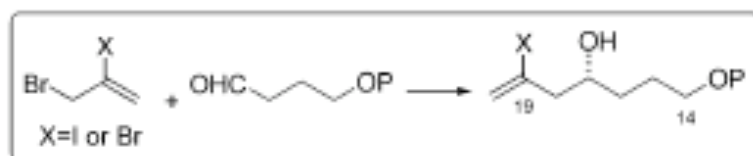


Fe/Cr- and Co/Cr- Mediated 2-Haloallylation



- 1a** : R₁=i-Pr, R₂=Me, R₃=Me, R₄=H
1b : R₁=t-Bu, R₂=2-naphthyl, R₃=Me, R₄=H
1c : R₁=i-Pr, R₂=Me, R₃=H, R₄=H
1d : R₁=t-Bu, R₂=Bn, R₃=H, R₄=H
1e : R₁=t-Bu, R₂=Bn, R₃=H, R₄=Me
1f : R₁=t-Bu, R₂=Bn, R₃=H, R₄=n-Bu

Sulfonamides: no result provided for other derivatives



- 2a** : X=Br, R₂=R₃=H
2b : X=Br, R₂=Me, R₃=H
2c : X=I, R₂=H, R₃=Me

- 3a** : R₁=(CH₂)₅Me
3b : R₁=(CH₂)₃O-TBDPS

- 4a** : R₁=(CH₂)₅Me, R₂=R₃=H
4b : R₁=(CH₂)₃O-TBDPS, R₂=R₃=H
4c : R₁=(CH₂)₃O-TBDPS, R₂=Me, R₃=H
4d : R₁=(CH₂)₃O-TBDPS, R₂=H, R₃=Me

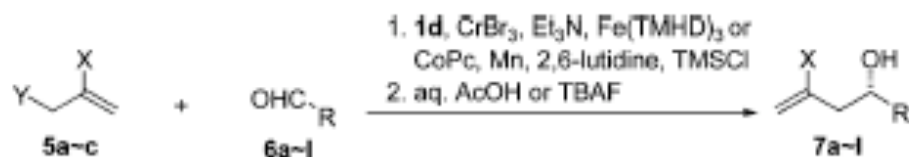
2,6-lutidine was added to improve ee. Its role is not clear. Also tried 2,6-di-*tert*-butylpyridine, quinoline, and acridine. Only 2,6-lutidine worked.

Entry	2a-c	+ 3a,b	→ 4a-d	ee (%) ^b	yield (%)
1	2a	3a	4a	93	93
2	2a	3b	4b	92	90
3	2b	3b	4c	94	94
4	2c	3b	4d	93	91 ^c

^a All reactions were done with 10 mol% of the catalyst at 0 °C. ^b *Ee* of the products was established by ¹H-NMR analysis of its Mosher ester. ^c The reaction completed within 12 h.



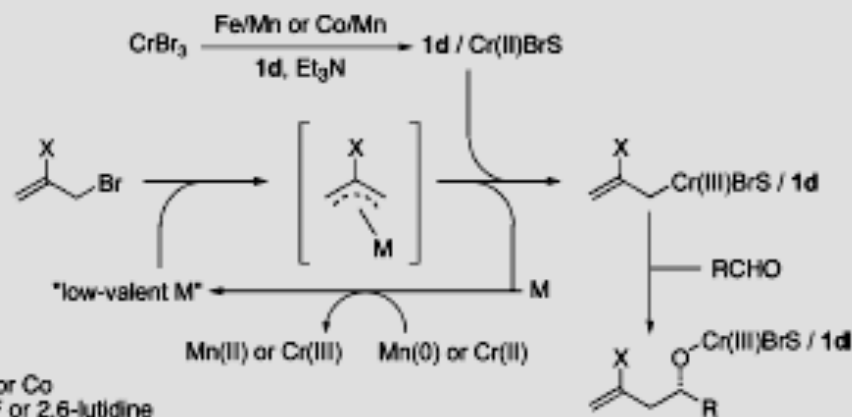
Fe/Cr- and Co/Cr- Mediated 2-Haloallylation



Entry	5a-c	6a-l	7a-l	yield	ee ^d
1 ^{b,f}	5a: X=Y=Br	6a: R=(CH ₂) ₃ Me ^f	7a: X=Br, R=(CH ₂) ₃ Me	75%	93%
2 ^b	5a: X=Y=Br	6b: R=(CH ₂) ₃ O-TBDPS ^f	7b: X=Br, R=(CH ₂) ₃ O-TBDPS	75	92
3 ^b	5a: X=Y=Br	6c: R=(CH ₂) ₃ O-TBS	7c: X=Br, R=(CH ₂) ₃ O-TBS	60	91
4 ^b	5a: X=Y=Br	6d: R=(CH ₂) ₂ CH(SET) ₂	7d: X=Br, R=(CH ₂) ₂ CH(SET) ₂	70	90
5 ^b	5a: X=Y=Br	6e: R=cyclohexyl	7e: X=Br, R=cyclohexyl	70	90
6 ^b	5a: X=Y=Br	6f: R=CH=CH(CH ₂) ₂ Me ^g	7f: X=Br, R=CH=CH(CH ₂) ₂ Me	75	87
7 ^b	5a: X=Y=Br	6g: R=CH=CHPh	7g: X=Br, R=CH=CHPh	75	83
8 ^b	5a: X=Y=Br	6h: R=Ph	7h: X=Br, R=Ph	86	84
9 ^{b,f}	5b: X=I, Y=Br	6b: R=(CH ₂) ₃ O-TBDPS	7i: X=I, R=(CH ₂) ₃ O-TBDPS	50	93
10 ^c	5b: X=I, Y=Br	6b: R=(CH ₂) ₃ O-TBDPS	7j: X=I, R=(CH ₂) ₃ O-TBDPS		
11 ^b	5c: X=Cl, Y=Br	6b: R=(CH ₂) ₃ O-TBDPS	7k: X=Cl, R=(CH ₂) ₃ O-TBDPS		
12 ^d	5c: X=Cl, Y=Br	6b: R=(CH ₂) ₃ O-TBDPS	7l: X=Cl, R=(CH ₂) ₃ O-TBDPS		

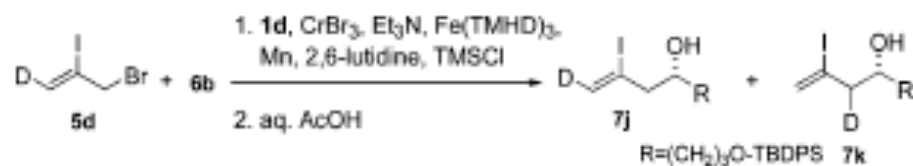
^a All reactions were done with 10 mol% Fe(TMHD)₃ was used. ^c Co(Pc) was used. ^d The conditions specified in Table 1. ^e ee of the chiral HPLC analysis or by ¹H NMR analysis determination of absolute chemistry, see Supplementary information. ^f The aldehyde was not completely converted. ^g 6b = 3b.

Scheme 2. Proposed Mechanism for the Fe/Cr- or Co/Cr-Mediated Reactions





Fe/Cr- and Co/Cr- Mediated 2-Haloallylation



metallootropic rearrangement

1 : 2.6

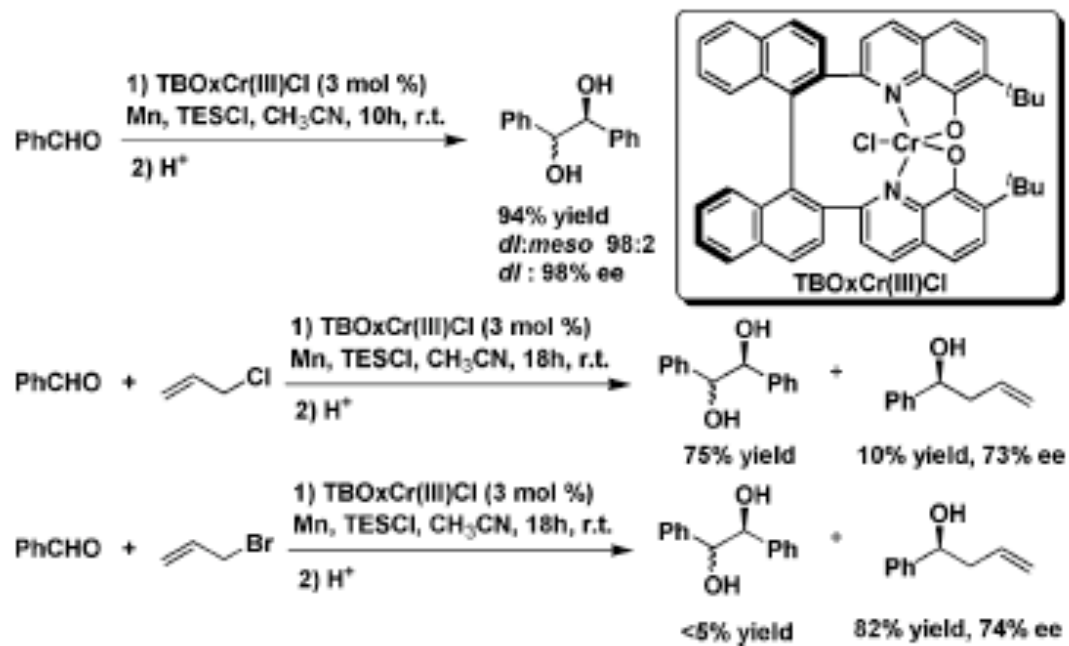
2

Kurosu, M.; Lin, M.H.; Kishi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 12248 - 12249.

Choi, Hyeong-wook; Nakajima, Katsumasa; Demeke, Dantew; Kang, Fu-An; Jun, Hyuk-Sang; Wan, Zhao-Kui; Kishi, Yoshito. *Org. Lett.* **2002**, *4*(25), 4435-4438.

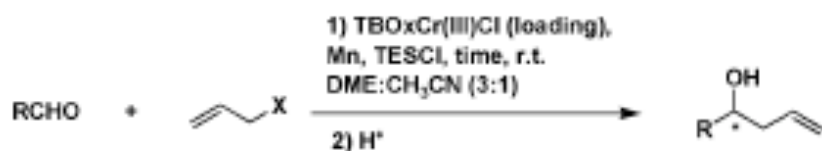


Bis(8-quinolinolato) (TBOx) Chromium





Bis(8-quinolinolato) (TBOx) Chromium



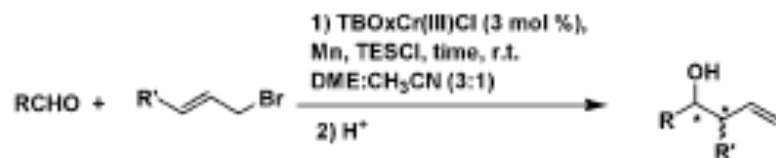
entry	RCHO	X	loading (mol %)	time (h)	yield ^a (%)	ee ^b (%) (config.) ^c
1		Br	0.5	48		
2		Br	1	24		
3		Br	3	18		
4		Br	10	8		
5		Br	3	18		
6		Br	3	18		
7 ^d		Br	3	24		
8 ^d		Br	3	24		
9		Br	3	24		
19		Br	3	40	89	97 (S)
20		Cl	3	40	76	98 (S)
21		Br	3	18	81	97 (S)
22		Cl	3	24	79	97 (S)
23		Br	3	24	81	94 (R)
24		Cl	3	40	77	95 (R)
25 ^e		Br	3	40	68	97 ^f (R)
26 ^e		Cl	3	60	54	98 ^f (R)
14 ^e		Br	3	18	89	96 (R)
15		Br	1	40	79	96 (R)
16		Br	3	40	90	98 (R)
17		Cl	3	40	68	98 (R)
18		Br	10	24	88	98 (R)

^a Isolated yield after chromatographic purification. ^b Enantiomeric excess was determined by chiral HPLC analysis. ^c Assigned by comparison of the sign of optical rotation with reported value. ^d CH₃CN:toluene (1:1) was used as solvent. ^e Crude products were treated with TBAF in THF. ^f Enantiomeric excess was determined by ¹⁹F NMR of the corresponding MTPA ester.



Crotyl Systems

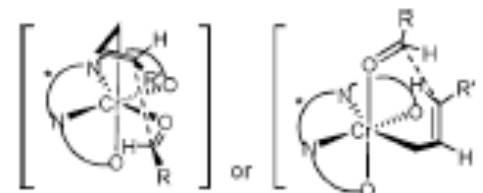
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entry	RCHO	R'	time (h)	yield ^a (%)	<i>anti</i> : <i>syn</i> ^b	ee[%] ^c <i>anti</i> / <i>syn</i>
1 ^e		CH ₃	36	84	4.4:1	97 / 97
2 ^{d,e}		CH ₃	36	76	5.5:1	95 / 96
3 ^d		<i>n</i> -C ₃ H ₇	48	71	8.4:1	91 / 91
4 ^d		<i>n</i> -C ₅ H ₁₁	60	65	10.3:1	90 / 87

5		CH ₃	60	73	6.3:1	96 / 97
6 ^f		CH ₃	36	88	4.2:1	94 / 94

^a Isolated yield of a mixture of *anti* and *syn* product after chromatographic purification. ^b Determined by ¹H NMR of crude product. ^c Enantiomeric excess was determined by chiral HPLC analysis. ^d EtOCH₂CH₂OEt was used as solvent instead of DME. ^e The absolute configuration of the major *anti* isomer was determined to be *R,R*.⁷ ^f The absolute configuration of the major *anti* isomer was determined to be *S,R*.⁸





The End



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- The End!
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