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The Development of the Asymmetric Nozaki–Hiyama–Kishi Reaction

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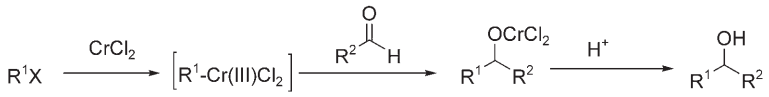
Abstract: This review collates the literature to date on the development of the Nozaki–Hiyama–Kishi (NHK) reaction into an important chromium-mediated, carbon-carbon bond forming process. The initial research employed stoichiometric quantities of chromium and this was exploited in the key steps of a range of total syntheses. Thereafter, the NHK reaction was further developed with the discovery of the catalytic variant. The focus of recent investigations is on the application of this reaction in asymmetric synthesis. The asymmetric NHK typically employed a range of salen- and oxazoline-derived chiral ligands and tethered bis(8-quinolinato)-chromium complexes. To date, good to high enantioselectivities have been obtained in a variety of NHK-type processes, including allylation, crotylation, methallylation, allenylation, propargylation and vinylation of a range of aldehydes, with limited examples employing ketones as substrates. Selected examples of the asymmetric NHK in total synthesis will also be described.

Keywords: allylation; asymmetric catalysis; chromium; crotylation; Nozaki–Hiyama–Kishi reaction

1 Introduction

The Nozaki–Hiyama–Kishi reaction, first reported in the late 1970s, has become an important and versatile carbon-carbon bond forming process, involving the nucleophilic addition of organochromium(III) reagents to carbonyl compounds (Scheme 1).[1]

Nozaki–Hiyama–Kishi (NHK) reactions combine many unique and important features: i) pronounced chemoselectivity of the organochromium(III) reagents for aldehydes, even in the presence of ketones; ii) a wide range of substrates including allyl, propargyl, alkenyl, alkynyl, and aryl halides, alkenyl triflates, and sulfonates and phosphates, are suitable precursors for the formation of organochromium intermediates; iii) compatability with an array of functional groups in both reaction partners; iv) unique stereochemical characteristics, for example, γ-mono-substituted allylchromium reagents in general lead to the corresponding homoallyl alcohols with excellent *anti* selectivity, independent of whether the starting halide is (*E*)- or (*Z*)-configurated; v) alkenyl halides react with complete retention of their double bond geometry.



Scheme 1.

Pat Guiry graduated with an Honours BSc. degree in Chemistry from University College Dublin (UCD) in 1986. He stayed at UCD for his PhD working under the supervision of Professor Dervilla Donnelly on the application of aryllead triacetates to the synthesis of natural products. During his PhD he also worked in Marseille in 1988 under the supervision of Dr. Jean-Pierre Finet (Cu-catalysed *N*-arylation) and at Texas A&M in 1989 with Professor Sir Derek Barton (mechanistic studies of arylation/phenol arylation). He received his PhD degree in 1990 and moved to the group of Dr. John Brown, FRS at the Dyson Perrins Laboratory, Oxford University for postdoctoral studies in the area of asymmetric catalysis. He returned to UCD as a College Lecturer in 1993 where he started his independent research. His research interests are the design and preparation of chiral ligands and their application in a broad range of asymmetric catalytic transformations. He was a visiting researcher in the group of Professor Andreas Pfaltz at the MPI at Mülheim ander-Ruhr in 1996. He was the recipient of a President's Research Award in 1996 and a President's Teaching Award in 2000 from UCD. He was promoted to Senior Lecturer in 2002, to Associate Professor of Synthetic Organic Chemistry in 2003 and to Professor of Synthetic Organic Chemistry in 2006. He was the Merck Frosst Visiting Professor at the University of Toronto in early 2004. He was appointed as the Chief Executive of the Conway Institute of Biomolecular and Biomedical Sciences at UCD 2004–5 and Director of the Synthesis and Chemical Biology in 2006. A keen tennis player, he represented Ireland in 2007 in the Trabert Cup (ITF World Team Competition) in Turkey where he was team captain.

Gráinne Hargaden was born in Dublin, Ireland. She studied at University College Dublin and received a BSc (Honours) degree in chemistry in 2003. Working in the group of Professor Pat Guiry she has recently completed her PhD studies in which she researched the application of new oxazoline-containing ligands in the catalytic enantioselective Nozaki–Hiyama–Kishi reaction. During her PhD she also worked in the laboratory of Professor P. G. Cozzi at the University of Bologna applying oxazoline-containing ligands in new chromium-catalysed asymmetric processes. She completed her studies in July 2007 and is now a postdoctoral researcher in the group of Professor Tim Donohoe at Oxford.

These features combine to render the NHK reaction particularly well suited for application in total synthesis. Chromium-induced inter- or intramolecular carbon-carbon bond formations have been used as key steps in the synthesis of many complex targets with examples including epothilone D **1**, analogues of phomactin **2** and halichondrin B **3** (Figure 1).[2]

2 Development of a Catalytic Nozaki–Hiyama–Kishi Reaction

Although displaying such attractive features, the one main drawback of the early NHK reactions was that they were performed using stoichiometric amounts of chromium(II) chloride. Since chromium(II) is a one-electron donor, a large excess of toxic chromium(II) salts was required. This difficulty was overcome, and

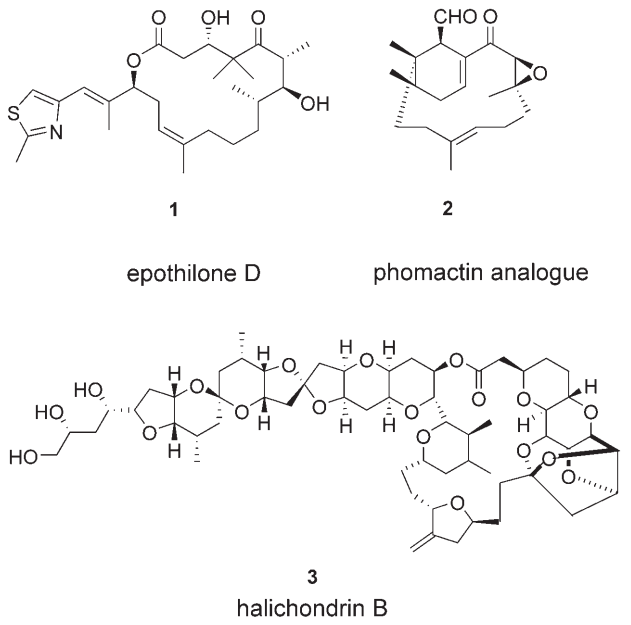
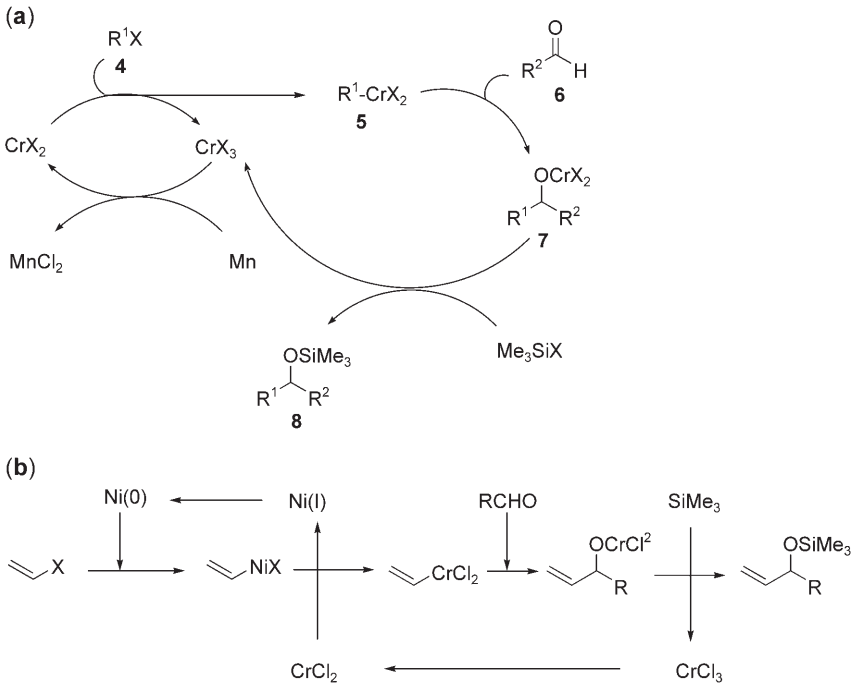


Figure 1.

the synthetic utility of the reaction thus greatly enhanced, by Fürstner's development of a catalytic redox process. In this system chromium(II) is recycled from chromium(III) which allows for reduced quantities of chromium salts, thereby rendering the reaction more environmentally benign.[3]

In Fürstner's catalytic system [Scheme 2 (**a**)], the organic halide **4** reacts with two equivalents of $CrCl_2$ to form the organochromium(III) reagent **5** and one equivalent of CrX_3. The nucleophile then adds to the aldehyde **6** to from a stable chromium(III) alkoxide intermediate **7**. The high stability of the $O–Cr^{3+}$ bond serves as the thermodynamic sink which drives the conversion but impedes catalysis. This is overcome by silylation of **7** by oxophilic chlorotrimethylsilane to form trimethylsilyl ether **8**, which may be readily cleaved using acid to provide the free alcohol product. The chromium(III) salt is released from the organic product, and is then reduced to chromium(II) by the stoichiometric reductant managanese, thus regenerating the active species and completing the catalytic cycle. Commercially available manganese powder is ideally suited for this purpose as it forms an efficient redox couple with chromium(III), is inexpensive, easy to handle and incapable of reacting directly with organic compounds.

The catalytic process can be initiated from either catalytic amounts of chromium(II) chloride or chromium(III) chloride. Chromium(III) chloride is preferred as it is cheap, relatively insensitive to oxygen and moisture and is easy to manipulate. There have also been reports of Nozaki–Hiyama–Kishi reactions using tetrakis(dimethylamino)ethylene as an organic reducing agent, with the use of electrochemical driving forces also possible.[4] Miller has developed an apparatus for carrying out redox-coupled chromium-



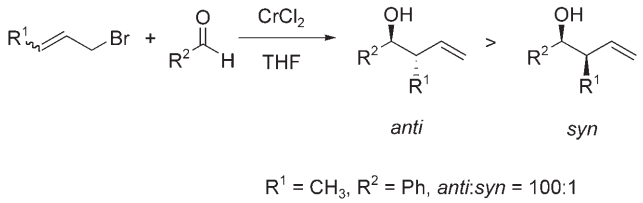
Scheme 2.

manganese reactions on solid-supported substrates which allows recycling of the stoichiometric reductant.[5] Kurosu reports a different source of Cr salt using supported CrF_2.[6]

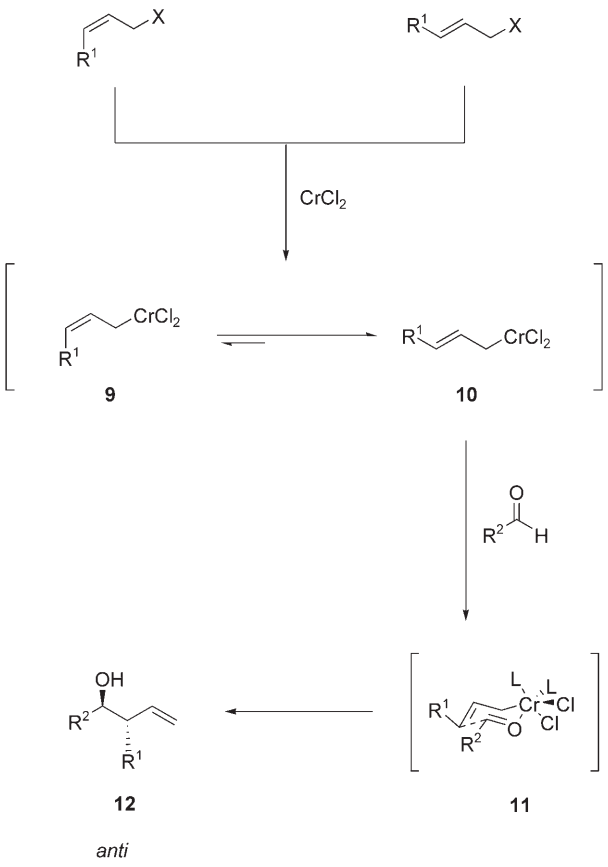
There had been very few reports of stoichiometric NHK reactions with aryl halides but this catalytic procedure was also successfully applied to these reagents. In addition, alkenyl iodides and alkenyl triflates were successfully utilised. Efficient reaction of these substrates required doping with $NiCl_2$ [Scheme 2 (**b**)].[3b]

3 Diastereoselectivity in Reactions with Monosubstituted Allylic Halides

One of the attractive features of the Nozaki–Hiyama–Kishi reaction is that crotyl bromide and other γ-monosubstituted allylic halides usually react with aldehydes to form homoallylic alcohols with a high degree of *anti*-selectivity (Scheme 3).



Scheme 3.



Scheme 4.

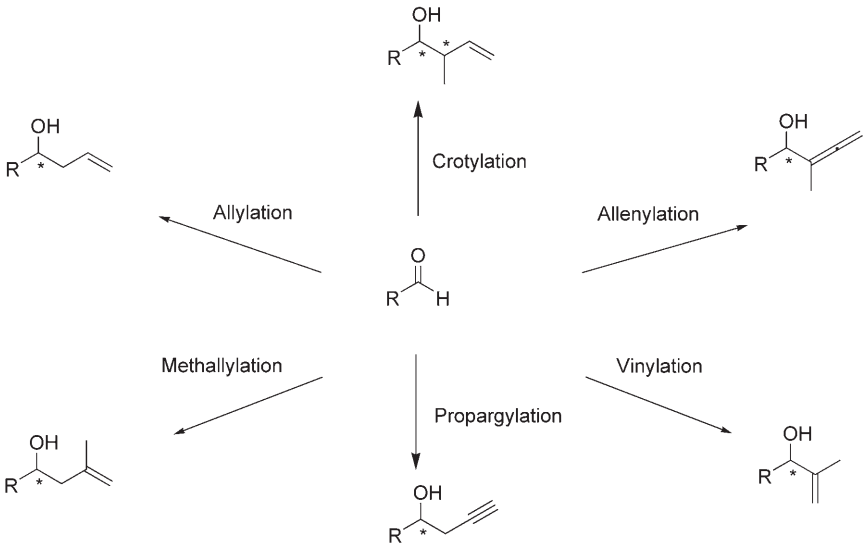
This preference for the *anti*-product is independent of the double bond configuration of the starting halide.[7] This diastereoselectivity may be explained by a rapid equilibration of the (*E*)- and (*Z*)-allylchromium(III) intermediates **9** and **10**, which are preferentially σ-bound to chromium at the primary allyl position. The (*E*)-allylchromium species **6** is more highly favoured and is thought to add to the aldehyde *via* a Zimmerman–Traxler transition state **11**, in which both the γ-substituent of the allylic system and the aldehyde substituent prefer equatorial positions, thus forming the *anti*-product **12** (Scheme 4). An exception to this remarkable *anti*-selectivity arises with the reaction of γ-monosubstituted allylic halides with very bulky aldehydes, for example *t*-BuCHO, which may force the transition state to adopt a twist-boat rather than a chair conformation thus favouring the *syn*-product.

Knochel has shown that, in contrast to γ-monosubstituted allylic halides which add in a stereoconvergent fashion to an aldehyde in the presence of CrC_2, γ-disubstituted allylic phosphates or chlorides and a β,γ-disubstituted allylic phosphate react in a stereodivergent fashion.[8] It is suggested that this difference in behaviour may be due to a very slow isomerisation of the intermediate γ-disubstituted allylic chromium(III) species compared to the addition of the aldehyde.

4 Catalytic Enantioselective Nozaki–Hiyama–Kishi Reaction

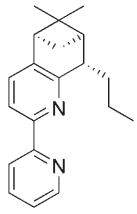
Considering the unique features which the Nozaki–Hiyama–Kishi reaction possesses and its undoubted potential in the synthesis of complex natural products, the development of an efficient enantioselective version to control the absolute stereochemical outcome for a range of processes was highly desirable (Scheme 5). However, due to difficulties such as ligand coordination and specificity combined with the tendency of chromium(II) to form dimers or clusters with polydentate ligands, relatively few reports of an enantioselective variant had been reported.

The first somewhat successful enantioselective version relied on over stoichiometric amounts (up to 400%) of chiral ligands. For example, Kishi reported the application of the chiral bipyridine ligand **13** in the allylation and alkenylation of benzaldehyde and obtained enantioselectivities of 28–74% *ee*.[9] Kibaya-



Scheme 5. Nozaki-Hiyama-Kishi processes.

shi's *N*-benzoylprolinol ligand **14** gave enantioselectivities of up to 98% for the reaction of allyl bromide with a range of aldehydes.[10]



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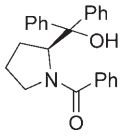
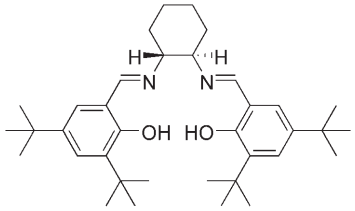


14

5 Application of Salen-Derived Ligands in the Enantioselective Nozaki–Hiyama–Kishi Reaction

The first effective catalytic enantioselective Nozaki–Hiyama–Kishi reaction was developed by Cozzi and co-workers in 1999 using chromium complexes (10 mol%) of the commercially available chiral salen ligand **15**.[11]



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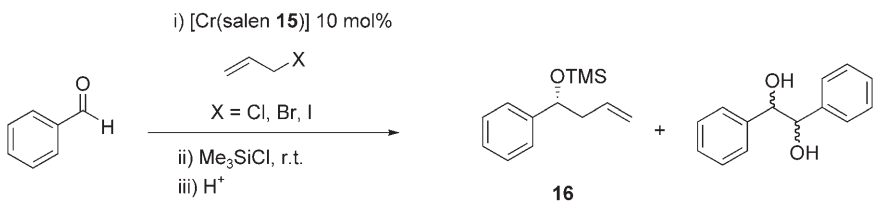
The chiral organometallic allyl-Cr(salen **15**) was prepared *in situ* by the addition of anhydrous $CrCl_2$ to a solution of **15** in THF, followed by addition of allyl bromide. Subsequent addition of Mn, Me_3SiCl and benzaldehyde at room temperature gave the silylated homoallylic alcohol **16** in a yield of 15%, with the main product being the pinacol product (Scheme 6). Further investigation revealed that formation of this pinacol side product was minimised by using acetonitrile as the solvent. The optimum reaction conditions were found to be as follows; $CrCl_2$ being formed *in situ* by the manganese-promoted reduction of $CrCl_3$, preparation of the [Cr(salen)**15**] complex in acetonitrile with the reaction being carried out in the presence of a base capable of deprotonating the salen ligand. Interestingly, the nature of the base had a dra-



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Scheme 6.

matic influence on the enantioselectivity achieved (Table 1).

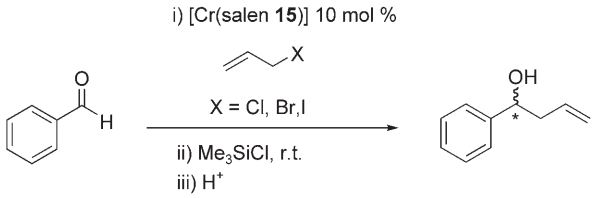
Table 1. Influence of bases on enantioselective addition of allyl bromide using **15**.

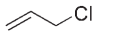
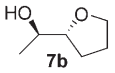
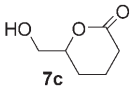
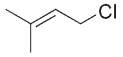
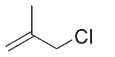
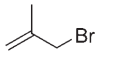
Entry	Base (20 mol%)	Yield [%]	*ee* [%]
1	-	56	21
2	K_2CO_3	51	47
3[a]	K_2CO_3	52	25
4	Et_3N	65	65
5	Et_3N (10 equivs.)	50	50
6	(2,6-di-*t*-Bu)Pyr	20	58

[a] Reaction carried out at 40 °C.

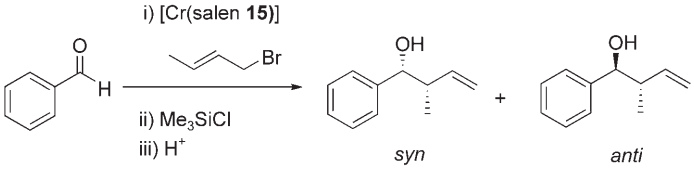
The highest enantioselectivity of 84% (*R*) was obtained in the reaction of benzaldehyde with allyl chloride (Table 2, entry 1). Using the more reactive allyl iodide (Table 2, entry 3) resulted in racemic product, most likely due to the reaction of the iodide with Mn, affording an achiral allylation species. Changing silylating agents was reported to have no influence on the asymmetric induction of the process.

Table 2. Enantioselective additions of various allyl halides to benzaldehyde catalysed by [Cr(**15**)] complex.

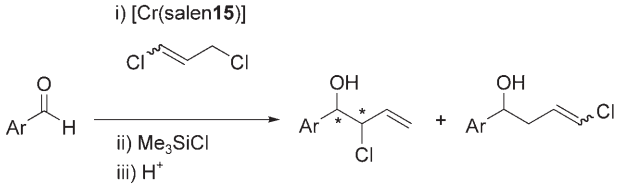


Entry	RX	Yield [%]	*ee* [%] (Configuration)
1		67	84 (*R*)
2	 **7b**	65	65 (*R*)
3	 **7c**	70	0
4		62	42 (*R*)
5		60	43 (*R*)
6		85	70 (nd)

The enantioselective addition of crotyl bromide to aromatic aldehydes using ligand **15** was subsequently studied with unexpected results reported (Scheme 7). Cozzi et al. reported that by changing the amount of salen ligand **15** it was possible to switch the diastereoselection from *anti* to *syn*.[12]



Scheme 7.



Scheme 8.

Using 10 mol% of [Cr(salen)**15**] gave the homoallylic alcohol in moderate yield (50%) but with a low degree of diastereoselectivity [*anti*:*syn* = 67:33, *anti* = 5% *ee*, *syn* = 78% *ee*]. Further research revealed that enhanced diastereoselection could be obtained by increasing the amount of salen ligand, with the highest diastereoselection [*anti*:*syn* = 83:17] obtained when a 2:1 salen:chromium salt ratio was utilised. In addition the *syn* product was obtained with excellent enantiomeric excess (ee_{syn} = 89%, ee_{anti} = 36%). Normally reactions of aldehydes with stereogenic allylchromium reagents afford homoallylic alcohols with an excellent degree of *anti*-selectivity. The model proposed to explain the observed *syn*-selectivity involves the formation of an acyclic transition state in which the aldehyde is coordinated by the manganese salts or by a [Cr(salen)**15**)] complex (Figure 2).[13]

This work was extended to other prochiral substrates, with the chiral chromium complex of **15** catalysing the addition of 1,3-dihalopropenes to a range

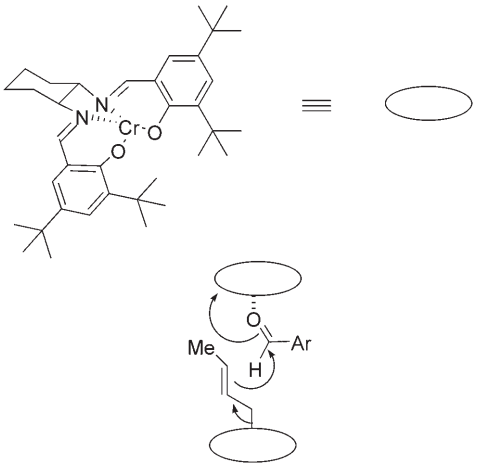
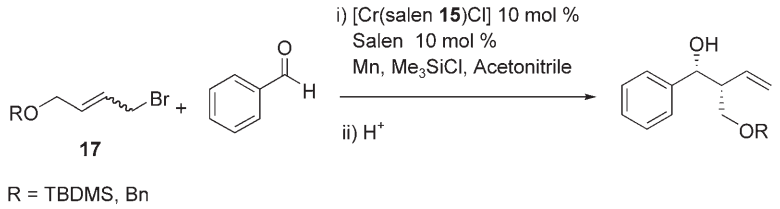


Figure 2.

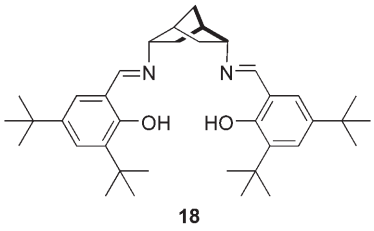


Scheme 9.

of aromatic aldehydes (Scheme 8). The best result was obtained using *p*-F-C_6H_4CHO which gave a *syn: anti* ratio of 90:10 and ee_{syn} of 83%. The products are useful synthetic intermediates and were readily converted to their corresponding optically active vinyl epoxides.[14]

In a further development of this methodology, Cozzi et al. successfully reacted functionalised allyl bromides **17** with benzaldehyde in the presence of [Cr(salen)**15**]Cl (10 mol%) and free salen ligand **15** (10 mol%), in moderate yields with good diastereoselectivity (up to 83:17 *syn*) and enantioselectivity (up to 81%) for the reaction with benzyloxy-substituted allyl (Scheme 9).[15]

Berkessel modified the previously successful salen ligand **15** by increasing the separation between the nitrogen atoms.[16] Dianane-derived ligands **18** which contain a novel C_2-symmetric diamine based on the

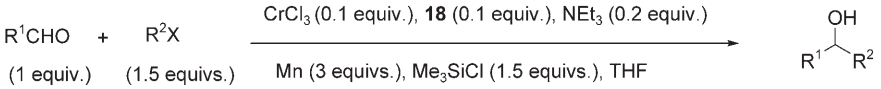


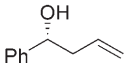
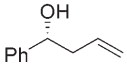
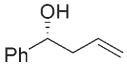
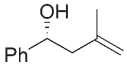
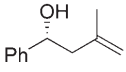
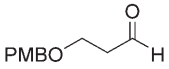
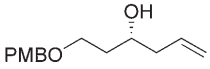
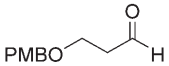
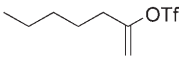
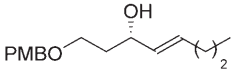
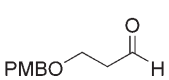
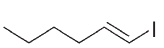
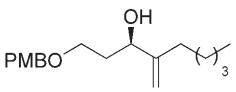
18

rigid bicyclo[2.2.1]heptane, were prepared and applied in a range of NHK additions (Table 3).[17]

An optimum enantioselectivity of 90% was observed for the allyl bromide/benzaldehyde system at 5°C (Table 3, entry 1). In contrast to ligand **15**, the new modified salen ligand **18** was also able to effect an enantioselective addition of allyl iodide (Table 3, entry 1). The related β-methallyl halides (Table 3, entries 4 and 5) reacted as smoothly as the allyl halides although the enantioselectivities were lower. To dem-

Table 3.



Entry	Aldehyde	Halide or Triflate	Product	% *ee* (Yield)	Temperature
1				90 (72)	5°C
2				31 (nd)	r.t.
3				79 (76)	r.t.
4				54 (78)	r.t.
5				64 (nd)	r.t.
6				92 (69)	10°C
7[a]				75 (59)	15°C
8[a]				61 (54)	20°C

[a] Reaction was run in the presence of 0.02 equiv. of $NiCl_2$.

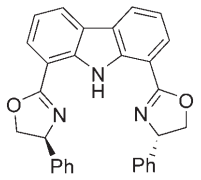
onstrate the applicability of this methodology to polyketide natural-product synthesis, PMB-protected 3-hydroxypropanal was coupled with allyl bromide in an excellent enantioselectivity of 92% (Table 3, entry 6). Finally, vinyl iodides and triflates were used as substrates, with 2 mol% of Ni(II) required for efficient coupling. The addition of *E*-1-iodohex-1-ene to PMB-protected 3-hydroxypropanal afforded the corresponding *E*-allylic alcohol adduct in 75% *ee* (Table 3, entry 7). The vinyl triflate (Table 3, entry 8) added to this aldehyde with 61% *ee* being obtained. These two reactions are among few examples of synthetically useful levels of asymmetric induction being obtained for catalytic, enantioselective NHK reactions using vinylic halides and triflate substrates.

6 Application of Oxazoline-Containing Ligands in the Catalytic Enantioselective Nozaki–Hiyama–Kishi Reaction

Ligands containing a chiral oxazoline ring have been applied with considerable success in the catalytic enantioselective Nozaki–Hiyama–Kishi reaction.

Nakada developed a tridentate C_2-symmetric bis-(oxazolinyl)carbazole ligand **19** and proposed that this tridentate ligand would provide enhanced enantioselectivities due to stabilisation of the allyl-Cr(III)-ligand complex owing to the presence of a σ-bond with the carbazole nitrogen and two coordination bonds to the oxazoline nitrogens, which leaves a vacant coordination site at which an aldehyde can bind.[18]

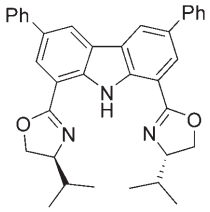
It was found that THF was the best solvent, with no pinacol formation being observed. Yields and enantioselectivities were reduced significantly using Et_2O, MeCN and DMF.



19

Pyridine, DIPEA, TEA and K_2CO_3 as the base all resulted in excellent isolated yields without dramatic changes in enantioselection (Table 4, entries 2, 3, 6 and 8). As has been found previously allyl iodide and allyl chloride were not satisfactory halides.

In an extension to this work, a similar tridentate carbazole ligand **20a** was prepared in which two



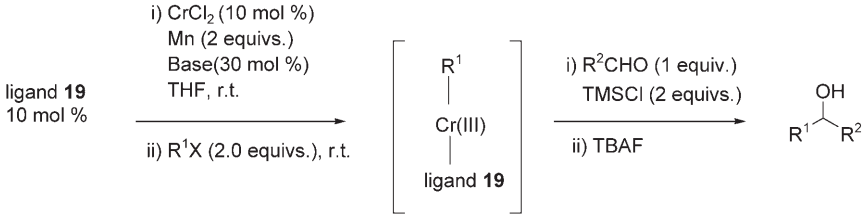
20a

phenyl rings have been placed *meta* to the oxazoline rings on the carbazole backbone thus resulting in an electronically and sterically different environment for the binding of chromium. This modified ligand provided superior enantioselectivities in a range of NHK processes (Table 5).[19]

The reaction of allyl bromide with benzaldehyde proceded with both excellent yield (93%) and enantioselectivity of 93 (*S*) at 0 °C (Table 5, entry 1).

Allyl chloride provided a similar results (Table 5, entry 3), but again allyl iodide gave a lower enantiose-

Table 4. Application of ligand **19** in the NHK reaction.



Entry	Base (equivs.)	X	*ee* [%] (Configuration)	Yield [%]	Temperature [°C]	Time [h]
1	-	Br	71 (*S*)	63	r.t.	63
2	Pyr (0.2)	Br	69 (*S*)	96	r.t.	12
3	TEA (0.2)	Br	71 (*S*)	96	r.t.	12
4	TEA (0.2)	Br	61 (*S*)	62	-10	40
5	TEA (0.2)	I	68 (*S*)	74	r.t.	1
6	DIPEA	Br	68 (*S*)	92	r.t.	12
7	$NaHCO_3$	Br	73 (*S*)	74	r.t.	12
		Br	71 (*S*)	93	r.t.	12

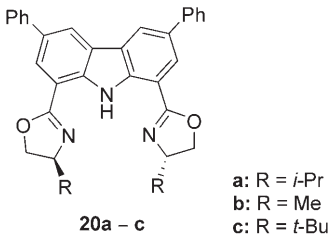
Table 5. Enantioselective NHK using ligand **20a**.

Entry	R^1	X	R^2	*ee* [%] (Configuration)	Yield [%]	Time [h]
1	allyl	Br	Ph	90 (*S*)	93	12
2[a]	allyl	Br	Ph	93 (*S*)	89	12
3	allyl	Cl	Ph	89 (*S*)	95	16
4	allyl	I	Ph	64 (*S*)	52	12
5	allyl	Br	*p*-BrPh	92 (*S*)	87	12
6	allyl	Br	PhCH=CH	95 (*S*)	87	12
7	allyl	Br	*c*-C_6H_{11}	94 (*S*)	95	12
8	allyl	Cl	*c*-C_6H_{11}	93 (*S*)	88	12
9	allyl	Br	*n*-C_6H_{11}	92 (*R*)	83	12
10	methallyl	Br	Ph	46 (*S*)	77	16
11	methallyl	Cl	Ph	95 (*S*)	96	16
12	methallyl	Cl	PhCH=CH	90 (*S*)	50	16
13	methallyl	Br	*c*-C_6H_{11}	96 (*S*)	96	16
14	methallyl	Cl	*c*-C_6H_{11}	95 (*S*)	98	16
15	methallyl	Br	*n*-C_6H_{11}	79 (*R*)	65	16
16	methallyl	Cl	*n*-C_6H_{11}	96 (*R*)	83	16

[a] Reaction was carried out at 0 °C.

lectivity (Table 5, entry 4). The allylation of other aldehydes including saturated and unsaturated aliphatic aldehydes all resulted in high yields, with excellent enantioselecitivity (86–95%) (Table 5, entries 5–9) showing the broad applicability of ligand **20a**. Additionally, the Cr-ligand complex **20** was recycled with the *ee* being decreased by just 1%. Furthermore, the reaction was successfully extended to the methallylation of aldehydes with high yields and excellent enantioselectivities observed (Table 5, entries 10–16).

In 2004, Nakada reported the successful application of ligands **20a–c**in the catalytic asymmetric propargylation of aldehydes.[20] Ligands **20c** provided the highest enantioselectivity of 71% (*R*) for the propargylation of benzaldehyde (Table 6, entry 5). This ligand was then applied in the propargylation of a range of aldehydes with an enantioselectivity of 98% (*R*) being obtained for *t*-BuCHO.

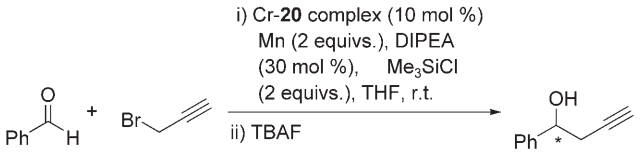


20a – c

a: R = *i*-Pr
b: R = Me
c: R = *t*-Bu

More recently, Nakada has reported the first enantioselective Nozaki–Hiyama–Kishi allenylation of terminally silylated propargyl halides using ligands **20a–c**.[21]

Table 6. Asymmetric NHK propargylation using ligands **20a–c**.



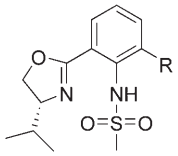
Entry	Ligand	Time [h]	Yield [%]	*ee* [%]
1	**20a**	16	94	26 (*S*)
2	**20a**	16	78	24 (*S*)
3	**20b**	18	80	28 (*S*)
4	**20b**	24	74	24 (*S*)
5	**20c**	60	75	71 (*R*)

The reaction with ligand **20a** took 8 h to complete and again generated the (*R*) product with 52% *ee* (Table 7, entry 1). The reaction with ligand **20b** was complete after 6 h and generated the (*R*) product in 90% yield with 64% *ee* (Table 7, entry 2). Interestingly, the reaction using ligand **20c** led to a lowering and reversal of enantioselectivity to 29% (*S*) (Table 7, entry 3). Screening of solvents and bases showed propionitrile and DIPEA to give the best results (Table 7, entries 4–12). Decreasing the reaction temperature to 0 °C led to a longer reaction time but an increase in enantioselection (Table 7, entry 9). The silyl group of the propargyl halide also affected the enantioselectivity, with the bulkier TES, TIPS, DMPS and MDPS groups not enhancing enantioselecitivity (Table 7, entries 13–16) but the smaller DMS group affording the highest enantioselectivity of 80% (Table 7, entry 17).

A range of additives were then screened with the presence of DMI (1 equiv.) leading to an increase in both yield (97%) and enantioselectivity (83%). Applying the optimal reaction conditions to the allenylation of a range of aldehydes did not result in enhanced enantioselectivities, with the highest *ee* of 82% being obtained with *p*-ClC_6H_5CHO.

Kishi has carried out extensive studies of this reaction using the oxazoline/sulfonamide ligand **21**, with the development of a catalytic process using ligands **21a** and **21b** for Ni/Cr-mediated reactions was reported (Scheme 10).[22]

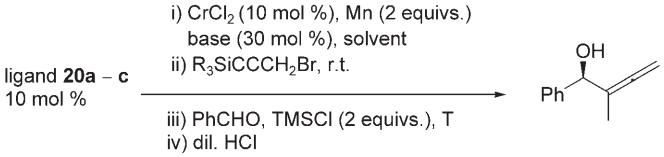
The results indicate that the asymmetric reaction developed in the stoichiometric process is translated



21

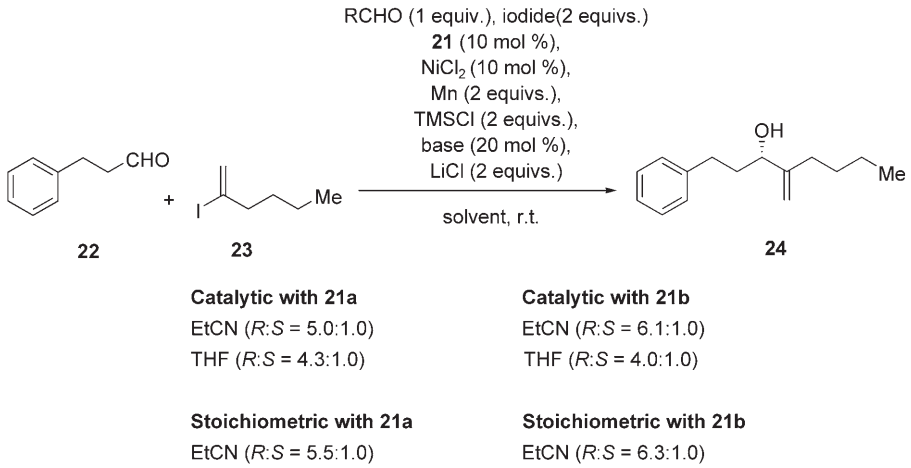
21a: R = Me
21b: R = OMe

Table 7. Asymmetric NHK allenylation of benzaldehyde.



Entry	Ligand	Solvent	Temperature [°C]	Base	R_3Si	Time [h]	Yield [%]	*ee* [%] (*R*)
1	**20a**	THF	r.t.	DIPEA	TMS	8	92	52
2	**20b**	THF	r.t.	DIPEA	TMS	6	90	64
3	**20c**	THF	r.t.	DIPEA	TMS	12	92	29[a]
4	**20b**	DME	r.t.	DIPEA	TMS	12	72	61
5	**20b**	MeCN	r.t.	DIPEA	TMS	12	74	60
6	**20b**	EtCN	r.t.	DIPEA	TMS	12	83	71
7	**20b**	CH_2Cl_2	r.t.	DIPEA	TMS	24	49	57
8	**20b**	DMF	r.t.	DIPEA	TMS	48	56	74
9	**20b**	EtCN	0	DIPEA	TMS	16	80	76
10	**20b**	EtCN	0	DIPEA	TMS	16	72	76
11	**20b**	EtCN	0	γ-collidine	TMS	16	65	76
12	**20b**	EtCN	0	pyridine	TMS	30	64	65
13	**20b**	EtCN	0	DIPEA	TES	24	81	74
14	**20b**	EtCN	0	DIPEA	TIPS	30	49	66
15	**20b**	EtCN	0	DIPEA	DMPS	24	66	73
16	**20b**	EtCN	0	DIPEA	MDPS	30	79	73
17	**20b**	EtCN	0	DIPEA	DMS	16	81	80

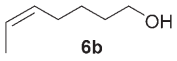
[a] (*S*) product.



Scheme 10.

well into the catalytic asymmetric process. They propose that the transmetalation takes place at the Cr(II) oxidation state which is formed through the chemical reduction of a **21** by Mn(0). [Scheme 11 (**a**)]. In addition the process contains a catalytic cycle centred on the Ni salt which is coupled with the Cr catalytic cylcle, and thus with the Mn redox cycle [Scheme 11 (**b**)].[23]

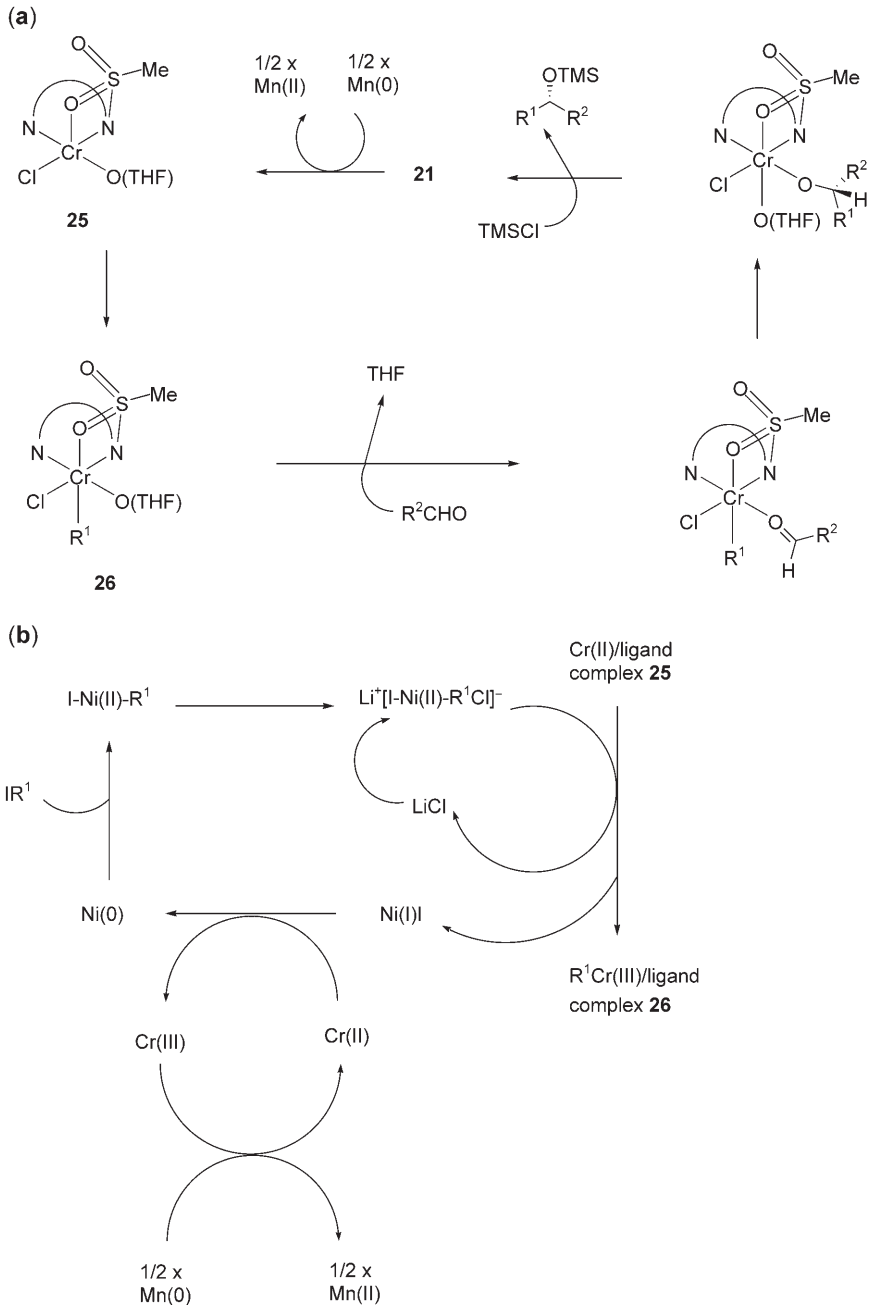
The structurally related ligand **27** was applied in the asymmetric allylation of aldehydes using more



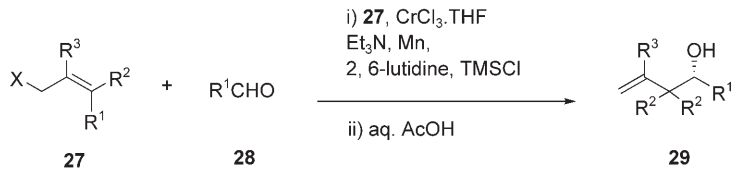
6b

complex substrates than previously utilised (Scheme 12).[24]

The conversions and yields are excellent in all cases. Most noteworthy is the yield and enantioselectivity obtained using methallyl iodide (91 % and 93 % respectively) (Table 8, entry 4). As mentioned previ-



Scheme 11.



28a: X = Br, $R^2 = R^3 = H$
28b: X = Br, R^2 = Me, $R^3 = H$
28c: X = I, $R^2 = H$, R^3 = Me

30a: $R^1 = (CH_2)_5Me$, $R^2 = R^3 = H$
30b: $R^1 = (CH_2)_3OTBDPS$, $R^2 = R^3 = H$
30c: $R^1 = (CH_2)_3OTBDPS$, R^2 = Me, $R^3 = H$
30b: $R^1 = (CH_2)_3OTBDPS$, $R^2 = H$, R^3 = Me

29a: $R^1 = (CH_2)_5Me$
29b: $R^1 = (CH_2)_3OTBDPS$

Scheme 12.

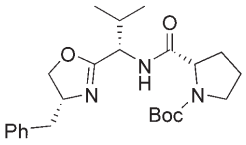
Table 8. NHK allylation of **28a–c** with **29a**, **b** using ligand **27**.

Entry	**28a–c**	**29a, b**	**30a–d**	*ee* [%]	Yield [%]
1	**28a**	**29a**	**30a**	93	93
2	**28a**	**29b**	**30b**	92	90
3	**28b**	**29b**	**30c**	94	94
4	**28c**	**29b**	**30d**	93	91

ously, iodo-halides are prone to the formation of a racemic intermediate, resulting in low levels of stereoinduction.

In an attempt to overcome the widely reported problem of NHK reactions not proceeding to completion due to the formation of TMS-enol ethers of aldehydes, Kishi proposed replacing the TMSCl with an alternative dissociating agent. It was found that the overall efficiency of the process is significantly better using $ZrCp_2Cl_2$.[25] Additionally, they have reported that the rate of the reaction is dramatically accelerated in the presence of 3,3′-dimethyl-2,2′-dipyridyl.[26]

In 2005, Sigman reported the synthesis of a new ligand class **31** containing an oxazoline ring linked to



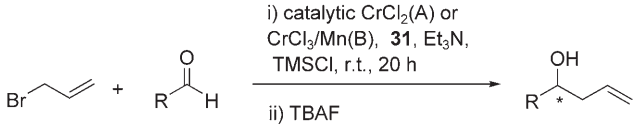
31

a chiral proline unit by an amide bridge. The ligands were applied in the NHK allylation of benzaldehyde with ligand **31** providing the highest yield of 95% and enantioselectivity of 92%. This ligand was subsequently applied in the allylation of a range of aldehydes using both $CrCl_2$ (Method A) and Fürstner's catalytic $CrCl_3$/Mn system (Method B) (Table 9).[27]

Using both the catalytic $CrCl_2$ method (A) and $CrCl_3$/Mn method (B) led to consistent reaction outcomes with little variation in observed enantioselectivity. Aryl aldehydes proved to be excellent substrates, highlighted by a 94% *ee* for benzaldehyde (Table 9, entry 2) and a 92% *ee* for furaldehyde (Table 9, entries 7 and 8). Poorer *ee*s were observed for aliphatic aldehydes (Table 9, entries 9 and 10).

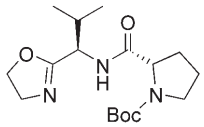
To further explore substrate scope methallyl bromide and *trans*-crotyl bromide were used as substrates in the allylation of benzaldehyde. The crotylation yielded an *anti:syn* ratio of 2.3:1, with both *anti* and *syn* diastereomers having a high enantiomeric excess of 91% and 95%, respectively. Methallylation proceeded with an excellent *ee* of 91%. These results highlight the insensitivity of ligand **31** to the nature of the allylic bromide.

Table 9. NHK allylation of a range of aldehydes using **31**.



Entry	R	Method	Yield [%]	*ee* [%]
1	C_6H_5	A	95	92
2		B	89	94
3	4-BrC_6H_4	A	87	91
4		B	73	90
5	4-$MeOC_6H_4$	A	95	89
6		B	98	89
7	2-Furyl	A	73	92
8		B	61	92
9	$PHCH_2CH_2$	A	94	46
10		B	98	48
11	C_6H_{11}	A	81	89
12		B	64	87

More recently, Sigman has reported the application of structurally related ligand **32** in the first enantioselective allylation of ketones (Table 10).[28]



32

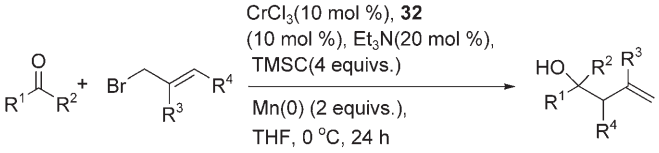
Aryl ketones were found to be excellent substrates for this transformation, with the naphthyl group resulting in the highest enantioselectivity of 92% (Table 10, entry 6). The nature and position of the substituent on the aromatic ring had little effect on the enantioselective outcome of the reaction (Table 10, entries 1–6). Methallyl and crotyl bromide were successfully added to acetophenone with very good enantioselectivities reported, although the addition of crotyl bromide resulted in a modest diastereoselection (Table 10, entries 8 and 9).

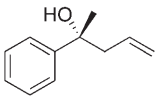
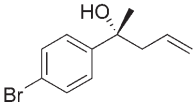
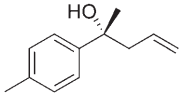
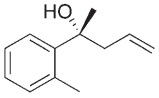
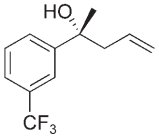
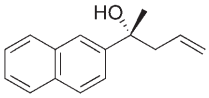
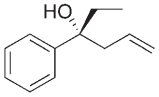
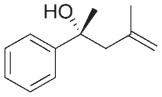
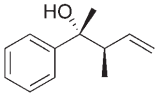
Guiry has reported the application of new tridentate bis(oxazoline) ligands **33** in the Nozaki–Hiyama–Kishi allylation and crotylation of aldehydes.[29] The ligands are structurally similar to Nakada's ligand **19** but contain an *N*-phenylaniline unit linking the two chiral oxazoline rings. The ligands were prepared using a palladium-catalysed Buchwald–Hartwig aryl amination which allowed for the preparation of both symmetric and non-symmetric ligands (**33a–j**).[30]

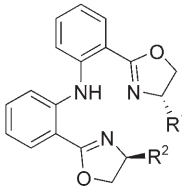
The ligands were initially applied in the allylation of benzaldehyde (Table 11).

The reactions proceeded with excellent conversions after 16 h at room temperature, with no by-products

Table 10. NHK allylation of a range of ketones using **32**.



Entry	Product	Yield [%]	*ee* [%]
1		82	92
2		73	90
3		94	86
4		83	87
5		63	91
6		95	92
7		77	93
8		73	91
9		69	88 (*anti*), 70 (*syn*)



33a: R^1 = Bn, R^2 = Bn
33b: R^1 = *i*-Pr, R^2 = *i*-Pr
33c: R^1 = Ph, R^2 = Ph
33d: R^1 = *t*-Bu, R^2 = *t*-Bu
33e: R^1 = Ph, R^2 = Bn
33f: R^1 = *t*-Bu R^2 = Bn
33g: R^1 = *t*-Bu, R^2 = *i*-Pr
33h: R^1 = *i*-Pr R^2 = Ph
33i: R^1 = *t*-Bu, R^2 = Ph
33j: R^1 = Bn, R^2 = *i*-Pr

33

detected. Of the four symmetric ligands only the diisopropyl-substituted ligand (**33b**) afforded a significant level of enantioselectivity of 69% (Table 11, entry 2). Interestingly, the highest enantioselectivities were obtained using the non-symmetric ligands **33f** and **33g**, 87% and 71% respectively (Table 11, entries 6 and 9). Both the extent and sense of the asymmetric induction is highly dependent on the nature and combination of the substituents on the oxazoline rings, with small changes in structure translating into large variations in enantiodiscrimination.

The optimal ligand **33f** was then used in the allylation of a range of aliphatic and aromatic aldehydes, with enantioselectivities of 87–91% reported, the best aldehyde substrate being the linear aliphatic heptaldehyde.

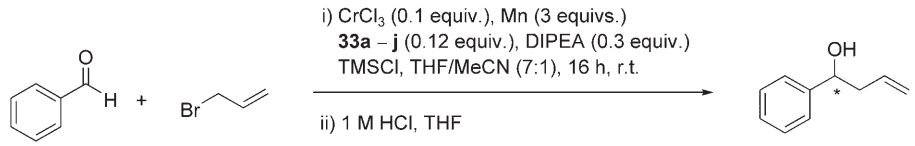
Application in the crotylation of a range of aldehydes resulted in *syn:anti* ratios of up to 80:20 with *para*-methoxybenzaldehyde and heptaldehyde affording excellent enantiomeric excesses of up to 92%. The *tert*-butyl/phenyl-substituted ligand **33i** afforded the highest *anti:syn* selectivity of 88:12 (Table 12, entry 4). As was observed for the reactions with allyl bromide, the highest level of enantiodiscrimination was achieved using the non-symmetric *tert*-butyl/benzyl-substituted ligand **33f** which afforded 82% *ee* (1*R*, 2*R*) for *anti*-2-methyl-1-phenylbut-3-en-1-ol and 90% *ee* (1*R*, 2*S*), for the *syn* diastereomer.

More recently, ligand **33f** has been applied in the methallylation of a range of aldehydes.[31] The methallylation of benzaldehyde using methallyl bromide resulted in an *ee* of 95%, In an effort to increase the efficiency of the reaction TMSCl was replaced by $ZrCp_2Cl_2$ as the dissociating agent following Kishi's findings. Although the reaction went to completion and the isolated yield was significantly enhanced the enantioselectivity dropped to 50%. The reaction using methallyl chloride resulted in an *ee* of 99.5% (Scheme 13). This is the highest enantioselectivity reported to date for this NHK process. The optimum aliphatic aldehyde was again heptaldehyde, affording an enantioselectivity of 89%.[28]

Guiry and Hargaden have recently extended the range of oxazoline-containing ligands for the Nozaki–Hiyama–Kishi transformation by preparing ligand class **34a–p** which incorporate an oxazoline ring linked by an amide bond to a chiral protected proline unit.[32] These ligands were tested in the allylation of benzaldehyde and a selection of the results are given in Table 13.

Of the Cbz-protected ligands **34a–h**, the highest enantioselectivity of 57% (*S*) was obtained with complete conversion and high isolated yield using ligand **34f** (entry 4), derived from (*R*)-proline and the phenyl-substituted oxazoline. Diastereomeric ligand **34b** led to both a reversal and a lowering of the enantioselectivity to 32% (*R*). In contrast to the results obtained with ligand **33**, where the dominant element was the oxazoline chiral centre, it is more difficult to determine the key controlling factor in this ligand class. However, the highest enantioselectivities are those that follow the trend: (*R*)-proline gives the (*S*)-

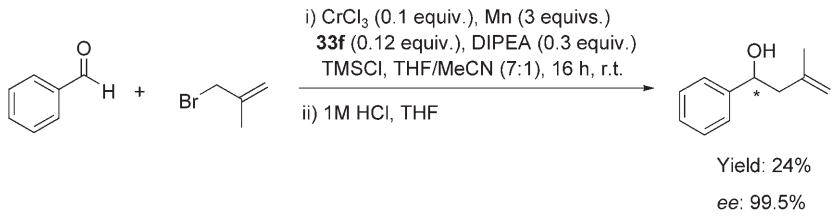
Table 11. NHK allylation of benzaldehyde using ligands **33a–j**.



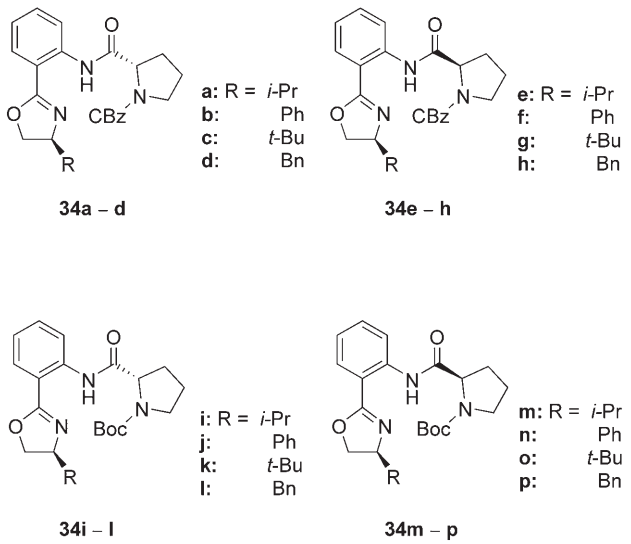
Entry	Ligand	R^1	R^2	X	Yield [%] (Conv.)	*ee* [%] (Configuration)
1	**33a**	Bn	Bn	Br	75 (79)	10 (*R*)
2	**33b**	*i*-Pr	*i*-Pr	Br	78 (96)	69 (*S*)
3	**33c**	Ph	Ph	Br	60 (99)	44 (*S*)
4	**33d**	*t*-Bu	*t*-Bu	Br	63 (88)	11 (*S*)
5	**33f**	Ph	Bn	Br	78 (98)	3 (*S*)
6	**33f**	*t*-Bu	Bn	Br	87 (100)	87 (*R*)
7	**33f**	*t*-Bu	Bn	Cl	10 (19)	74 (*R*)
8	**33f**	*t*-Bu	Bn	I	88 (98)	80 (*R*)
9	**33g**	*t*-Bu	*i*-Pr	Br	97 (100)	71 (*R*)
10	**33h**	*i*-Pr	Ph	Br	90 (100)	18 (*R*)
11	**32i**	*t*-Bu	Ph	Br	65 (100)	*Rac*
12	**33j**	Bn	*i*-Pr	Br	75 (100)	8 (*R*)

Table 12. NHK crotylation of benzaldehyde using ligands **33**.

Entry	Ligand	Yield [%] (Conversion)	*anti:syn*	*ee* (%) (Configuration) *anti*	*syn*
1	**33c**	74 (98)	87:13	64 (1*S*, 2*S*)	7 (1*S*, 2*R*)
2	**33f**	77 (94)	77:23	82 (1*R*, 2*R*)	90 (1*R*, 2*S*)
3	**33g**	79 (100)	77:23	56 (1*R*, 2*R*)	66 (1*R*, 2*S*)
4	**33i**	80 (88)	88:12	4 (1*R*, 2*R*)	48 (1*R*, 2*S*)



Scheme 13.



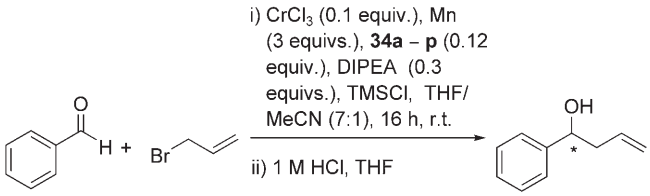
product and (*S*)-proline gives the (*R*)-product although the oxazoline substituent does also play a role, particularly when it is aromatic.

7 Application of Tethered Bis(8-quinolinato)-Chromium Complexes in the Catalytic Enantioselective Nozaki–Hiyama–Kishi Reaction

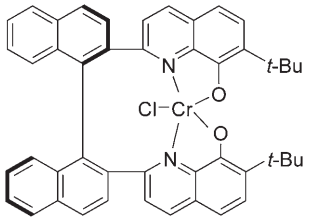
Yamamoto has applied the axially chiral tethered bis-(8-quinolinolato) (TBOx) chromium catalyst **35** in the NHK allylation of a range of aldehydes (Table 14).[33]

The allylation of benzaldehyde using allyl bromide resulted in an enantiomeric excess of 99% (*R*), with a yield of 95% after 8 h at room temperature (entry 2).

Table 13. NHK allylation of benzaldehyde using ligands **34a–p**.



Entry	Ligand	Conversion (Yield [%])	*ee* [%] (Configuration)
1	**34a**	100 (93)	38 (*S*)
2	**34b**	100 (91)	32 (*R*)
3	**34e**	100 (91)	36 (*R*)
4	**34f**	100 (88)	57 (*S*)
5	**34g**	100 (87)	30 (*R*)
6	**33l**	95 (87)	44 (*R*)
7	**34p**	68 (54)	54 (*R*)



35

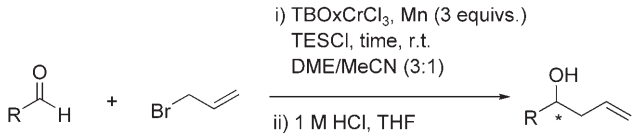
A series of other aromatic aldehydes were tested with 3 mol % catalyst loadings and allylations proceeded in high yield and with enantiomeric excesses in the range 95–97 % (entries 3–5). Aliphatic aldehydes were also successful substrates with cyclohexanecarboxaldehyde giving an enantiomeric excess of 98 % (*R*) with a yield of 90 % after 40 h at room temperature (entry 7). In addition, octanal and *tert*-butylaldehyde gave similarly high levels of enantiomeric excesses (97 %) (entries 8 and 10).

This chromium complex was tested in the addition of other allylic bromides to a series of aldehydes (Table 15). As examples, the crotylation of benzaldehyde afforded high diasteroeselectivities of 4.4:1 ratio favouring the *anti*-product in 84 % yields with 97 % *ee* for both diastereomers, (Table 15, entry 1). Crotylation of cyclohexanecarboxaldehyde gave an *anti:syn* ratio of 6.3:1 and enantioselectivities of 96 % and 97 %, respectively (entry 4). These results are the highest reported to date in the asymmetric crotylation of aldehydes using a Cr(II)-based system.

This (TBOx) chromium complex was further extended to the allenylation of benzaldehyde which was found to be most successful using one equivalent of TESCl as the silyl source, resulting in an enantioselectivity of 96 % (*R*), in a yield of 89 % after 48 h at room temperature (Table 16).[34]

Allenylation of a range of aldehydes under these optimum conditions led to excellent enantioselectivities in all cases, with furaldehyde being particularly successful, where an *ee* of 97 % and yield of 79 % was obtained.

Table 14. NHK allylation of aldehydes catalysed by chromium complex **35**.



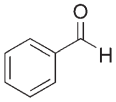
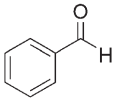
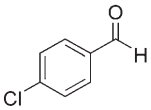
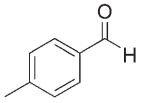
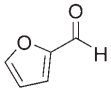
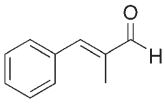
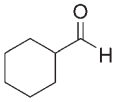
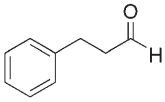
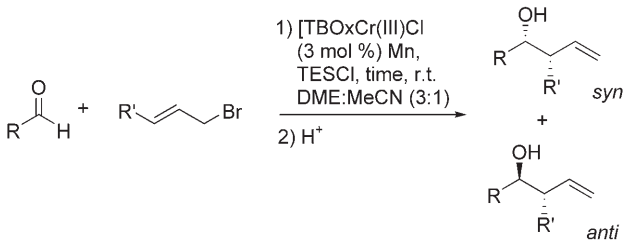
Entry	RCHO	Loading (mol %)	Time [h]	Yield [%]	*ee* [%] (Configuration)
1		3	18	93	98 (*R*)
2		10	8	95	99 (*R*)
3		3	18	93	95 (*R*)
4		3	24	91	96 (*R*)
5		3	18	86	97 (*R*)
6		3	18	89	96 (*R*)
7		3	40	90	98 (*R*)
8		3	40	89	97 (*S*)
9		3	18	81	97 (*S*)
10		3	40	68	97 (*S*)

Table 15. TBOxCr(III)Cl-catalysed addition of substituted allylic bromides to aldehydes.



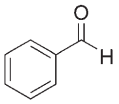
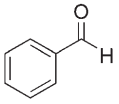
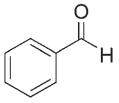
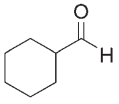
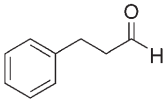
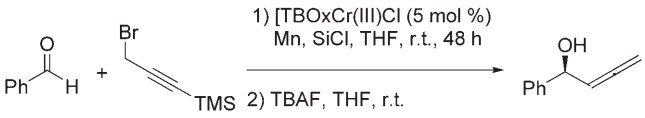
Entry	RCHO	R′	Time [h]	Yield [%]	*anti:syn*	*ee* [%] *anti/syn*
1		Me	36	84	4.4:1	97/97
2		Me	36	76	5.5:1	95/96
3		*n*-C_3H_7	48	71	8.4:1	91/91
4		Me	60	73	6.3:1	96/97
5		Me	36	88	4.2:1	94/94

Table 16. Asymmetric NHK allenylation of benzaldehyde.

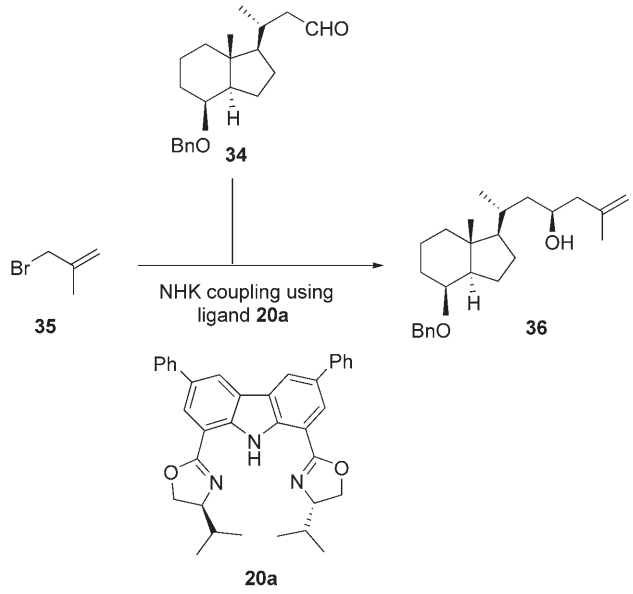


Entry	Alkyne	SiCl	Yield [%]	*ee* [%] (*R*)
1	1 equiv.	1 equiv. of TMSCl	77	17
2	1 equiv.	1 equiv. of TESCl	71	96
3	1 equiv.	1.2 equivs. of TESCl	74	95
4	1.25 equivs.	1 equiv. of TESCl	82	96
5	1.5 equivs.	1 equiv. of TESCl	91	96
6	1 equiv.	1 equiv of TESCl	89	96

8 Applications of Catalytic Nozaki–Hiyama–Kishi Reaction in Total Synthesis

As previously discussed, the Nozaki–Hiyama–Kishi reaction display a range of features which have led to its application in the synthesis of a range of natural products. The unique features previously outlined which Nozaki–Hiyama–Kishi reactions demonstrate, in particular, the pronounced chemoselectivity and remarkable compatability with an array of functional groups render the Nozaki–Hiyama–Kishi reaction well suited for application in the synthesis of natural products. Although the development of successful enantioselective NHK reactions is still ongoing, there have been already been some reports of its application in the synthesis of natural products.

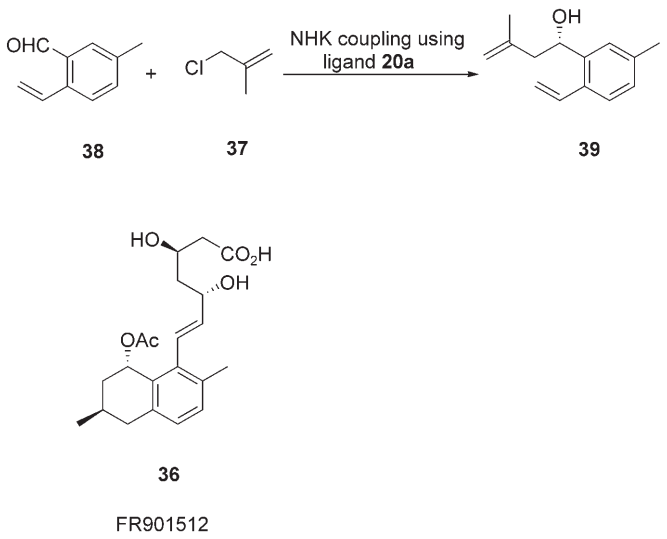
Nakada has applied bisisopropyl ligand **20a** in the methallylation of chiral aldehyde **34** to give **36** which is a key intermediate of calcitriol lactones. Ligand **20a** gave (−) 94% *de*, with its enantiomer giving 97% *de* (Scheme 14).[16]



Scheme 14.

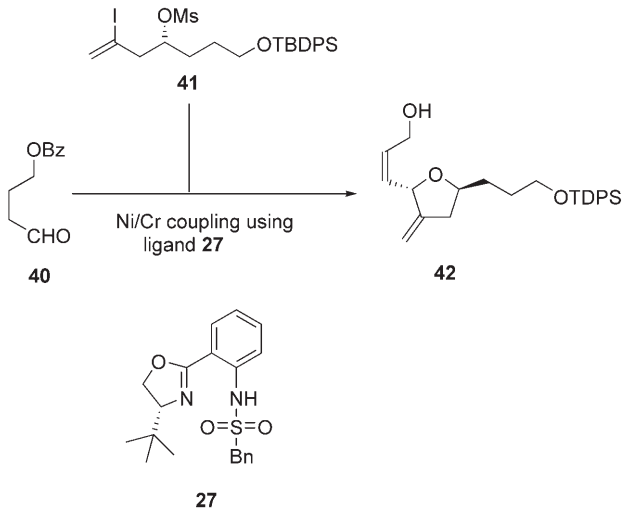
Ligand **20a** was recently applied by Nakada in the synthesis of the potent HMG-CoA reductase inhibitor FR901512 36 (Scheme 15). Methallyl chloride **37** was coupled with aldehyde **38** to afford product **39** in excellent yield (93%) and an enantioselectivity of 92%.[35]

Kishi has used a catalytic enantioselective NHK reaction in the synthesis of the C-14/C-26 segment of halichondrins (Figure 1). The first bond formation was achieved *via* a catalytic, asymmetric Ni/Cr-mediated coupling reaction between **40** and **41** in the pres-



Scheme 15.

ence of 10 mol% of ligand **27**. Following debenzoylation, product **42** was isolated in 80% overall yield with a 9:1 stereoselectivity (Scheme 16).[20]



Scheme 16.

9 Conclusion

In the last ten years since Fürstner developed the first Nozaki–Hiyama–Kishi reaction catalytic in chromium, the subsequent enantioselective variant has become a valuable tool in catalytic asymmetric synthesis. The salen- and oxazoline-derived ligands which have been applied have advanced the scope of this reaction in terms of reactivity and asymmetric induction. Yamamoto's recently developed TBOxCr(III)Cl complex has afforded the highest enantioselectivities in a series of allylation, crotylation and allenylation studies. However, a ligand which provides the maximum reactivity and selectivity in a range of NHK processes remains elusive. Nevertheless, the future of the enantioselective NHK reaction as an important synthetic transformation seems assured due to the high reactivity and impressive enantioselectivities obtained thus far.

Acknowledgements

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