The application of bis(oxazoline) ligands in the catalytic enantioselective methallylation of aldehydes

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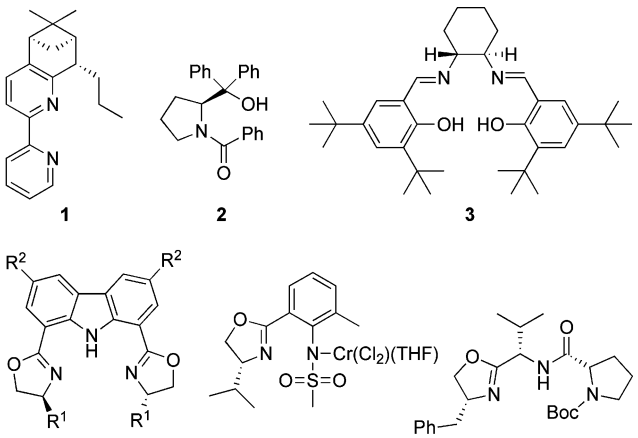
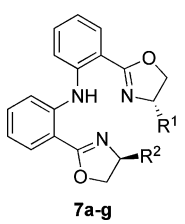
A series of symmetric and non-symmetric bis(oxazoline) ligands were applied in the Nozaki–Hiyama–Kishi methallylation of a range of aromatic and aliphatic aldehydes. A non-symmetrical ligand with *tert*-butyl/benzyl-substituted oxazolines provided the highest enantioselectivity of 99.5% for the methallylation of benzaldehyde.

The Nozaki–Hiyama–Kishi reaction was first reported in the late 1970's and has proven to be a highly versatile procedure for the formation of C–C bonds involving the nucleophilic addition to carbonyl compounds of intermediate organochromium(III) reagents, which are generated *in situ* from the insertion of chromium(II) species into allyl, alkenyl, alkynyl, propargyl and aryl halides or sulfonates.[1] A number of unique and important features including pronounced chemoselectivity for reactions with aldehydes in the presence of ketones and an unprecedented compatibility with numerous functional groups in both reaction partners have led to the reaction being utilised in the synthesis of many complex natural products, two examples being the total synthesis of palytoxin and halichondrin B which both involved extensive use of chromium additions.[2] The development of a catalytic redox process by Fürstner in 1996 significantly enhanced the synthetic utility of the reaction.[3] However, the presence of relatively few examples in the literature of successful enantioselective Nozaki–Hiyama–Kishi reactions highlights the significant difficulties encountered due to poor ligand coordination and specificity, in addition to the tendency of chromium(II) to form dimers or clusters with polydentate ligands. The most successful enantioselective reactions relied on over stoichiometric amounts (up to 400%) of chiral ligands. Examples of these ligands include bipyridine ligand **1**, which afforded 28–74% ee for the allylation and alkenylation of benzaldehyde,[4] and the *N*-benzoylprolinol ligand **2**, which gave up to 98% ee for the reaction of allyl bromide with a range of aldehydes.[5]

In 1999 Cozzi and co-workers developed the first catalytic enantioselective Nozaki–Hiyama–Kishi (NHK) reaction using chromium(II) complexes of chiral salen **3**.[6] High levels of enantioselectivity were obtained for the allylation (77–90% ee) and crotylation (78–90% ee) of a range of aldehydes.[7] There have since been numerous applications of a range of ligands, particularly those containing a chiral oxazoline ring in the catalytic asymmetric NHK reaction. Nakada's bis(oxazolinyl)carbazole ligand **4a** provided enantioselectivities of up to 73% ee in the asymmetric allylation of benzaldehyde,[8] whilst Kishi's ligand **5** afforded enantioselectivities of up to 94%.[9] Sigman recently reported the development of proline-oxazoline ligand **6**, which achieved 94% ee in the allylation of benzaldehyde.[10] The reaction scope has recently been extended by Nakada to include allenylation and methallylation of benzaldehyde employing ligand class **4**, with optimum enantioselectivities of 95% and 83% respectively.[8,11] We recently reported the synthesis[12] and application[13] of bis(oxazoline) ligands **7** in the catalytic asymmetric chromium-catalysed allylation and crotylation of a variety of aromatic and aliphatic aldehydes. The convergent synthesis, which utilises a Buchwald–Hartwig aryl amination as the key step, allowed for the preparation of both the symmetric **7a–c** and non-symmetric **7d–g** series of ligands. There are few other examples of the application of C_1-symmetric bis(oxazoline) ligands in asymmetric catalysis apart from the groups of Nishiyama[14] and Bolm.[15] We now report the application of a range of these ligands in the catalytic asymmetric methallylation of aldehydes. This is an important asymmetric transformation as, in addition to creating a secondary alcohol chiral centre, the 2,2-disubstituted olefin is a useful functional handle for further manipulation. Such potential has previously been realised in the synthesis of a key intermediate of calcitriol lactones.[16]





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

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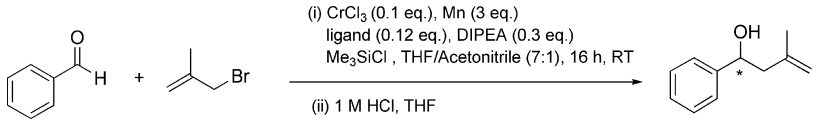
Ligands **7a–g** were initially investigated in the chromium(II)-mediated reaction of benzaldehyde **8a** with methallyl bromide **9** (Table 1).† Our previous studies have shown that the optimal reaction conditions for allylation and crotylation employ THF–acetonitrile (7 : 1) as the solvent and *N*,*N*-diisopropylethylamine as the base. The methallylations proceeded cleanly using these conditions, with high conversions after 16 hours at room temperature. The best symmetrical ligand was the bis(isopropyl)-substituted

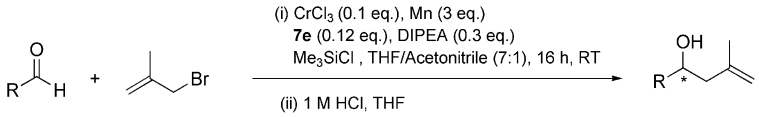
Table 1 Catalytic asymmetric methallylation of benzaldehyde using ligands **7a–g**

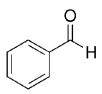
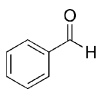
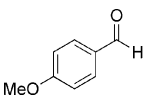
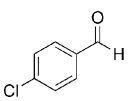
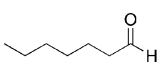
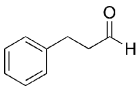


Entry	Ligand	R^1	R^2	Conv.[a] (%)	Yield[b] (%)	ee[c] (%) (conf.)
1	**7a**	Bn	Bn	80	70	7 (*R*)
2	**7b**	*i*-Pr	*i*-Pr	90	75	58 (*S*)
3	**7c**	*t*-Bu	*t*-Bu	70	58	5 (*S*)
4	**7d**	Ph	Bn	78	65	19 (*R*)
5	**7e**	*t*-Bu	Bn	86	64	95 (*R*)
6	**7f**	*t*-Bu	*i*-Pr	75	60	35 (*R*)
7	**7g**	*i*-Pr	Bn	78	60	16 (*S*)

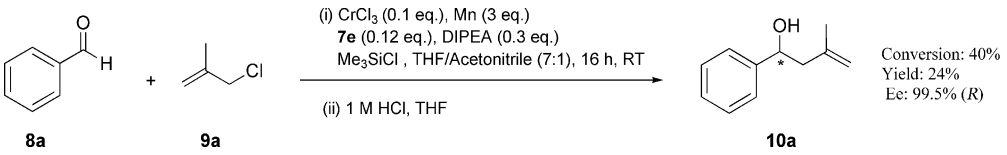
[a] Determined from the 300 MHz ^{1}H NMR spectrum of the crude silylated product. [b] Isolated yields of the allylic alcohol **10a**. [c] Determined by chiral HPLC analysis of the alcohol product **10a** using a Daicel Chiralcel OD column (see general procedure†). [d] Determined by comparison of the chiral HPLC retention times with literature values.[17]

Table 2 Catalytic asymmetric Nozaki–Hiyama–Kishi methallylation of aldehydes using ligand **7e**



Entry	Aldehyde		Conv.[a] (%)	Yield[b] (%)	ee[c] (%) (conf.[d])
1		8a	86	64	95 (*R*)
2[e]		8a	100	92	50 (*R*)
3		8b	50	41	59 (*R*)
4[f]		8c	90	78	65 (*R*)
5[g]		8d	58	48	33 (*R*)
6[f,g]		8e	70	57	89 (*S*)
7		8f	75	60	55 (*S*)

[a] Determined from the 300 MHz ^{1}H NMR spectrum of the crude silylated product (except entry 2). [b] Isolated yields of the homallylic alcohol **10a–f**. [c] Determined by chiral HPLC analysis on a Daicel Chiralcel OD or AD column (see general procedure†). [d] Determined by comparison of the chiral HPLC retention times with literature values.[16,17] [e] $ZrCp_2Cl_2$ used in place of TMSCl.[18] [f] Enantiomeric excess determined by HPLC analysis of the 3,5-dinitrobenzoate ester. [g] Configuration determined by analogy with alcohol **10e**.



Scheme 1 Catalytic asymmetric Nozaki–Hiyama–Kishi methallylation of benzaldehyde using methallyl chloride.

ligand **7b**, which afforded alcohol **10a** with a moderate enantioselectivity of 58% (*S*) (Table 1, entry 2). Both the bis(benzyl) ligand **7a** and the bis(*tert*-butyl) ligand **7c** afforded poor enantioselectivities of 7% (*R*) and 5% (*S*), respectively. Of the unsymmetrical ligands, the *tert*-butyl/isopropyl ligand **7f** provided a disappointing enantioselectivity of 35% (*R*). The optimal enantioselectivity of 95% (*R*) was obtained using the *tert*-butyl/benzyl-substituted ligand **7e** (Table 1, entry 5). A small change in ligand structure to the isopropyl/benzyl-substituted oxazoline ligand **7g** led to a reversal and lowering of enantioselectivity to 16% (*S*). These are similar trends to those we observed in the allylation and crotylation of benzaldehyde using ligands **7a–g**, with ligand **7e** again affording the best enantioselectivity.

We then proceeded to examine the enantiodiscriminating ability of ligand **7e** in the reaction of methallyl bromide **9** with a range of aromatic and aliphatic aldehydes **8a–f** (Table 2).

In an effort to increase the yield of homoallylic alcohol **10a**, we changed our dissociating agent from TMSCl to $ZrCp_2Cl_2$ (Table 2, entry 2).[18] While we observed complete conversion after 16 hours at room temperature and a yield of 92%, there was a significant decrease in enantioselectivity to 50% (*R*). We also wished to examine the effect of having electron-donating and electron-withdrawing groups on the aromatic aldehyde, and thus studied *para*-methoxybenzaldehyde **8b** and *para*-chlorobenzaldehyde **8c** as substrates. The enantioselectivities obtained were moderate, 59% (*R*) and 65% (*R*) respectively, with the yield obtained for **8b** (41%) being significantly lower than that obtained with **8c** (78%) (Table 2, entries 3 and 4). Asymmetric nucleophilic addition to aliphatic aldehydes is a less developed process, and we were pleased to find that aldehydes **8d–f** were successful substrates, and, in the case of heptaldehyde **8e**, an ee of 89% (*S*) was obtained.

Replacing methallyl bromide **9a** with the less reactive methallyl chloride **9b** (Scheme 1) gave both low conversion (40%) and yield (24%) with an excellent enantioselectivity of 99.5% (*R*). To the best of our knowledge, this is the best enantioselectivity achieved to date for the methallylation of benzaldehyde. As a comparison with literature values, ligand **4c**[16] afforded enantiomeric excesses of up to 95% whereas ligand **6** gave an ee of 91%.[10]

In summary, we have applied both symmetric (**7a–c**) and non-symmetric (**7d–g**) bis(oxazoline) ligands in the asymmetric methallylation of a range of aromatic and aliphatic aldehydes. The best ligand was found to be the *tert*-butyl/benzyl-substituted ligand **7e**, which provided enantioselectivities of 95% and 99.5% in the reaction of benzaldehyde with methallyl bromide and methallyl chloride, respectively. Our results again highlight the significant effect the substituents on the oxazoline rings have on both the magnitude and sense of asymmetric induction. Efforts are ongoing to elucidate the structures of the chromium–ligand complexes to determine the mechanism of the reaction and explain these effects. The results of such investigations will form the basis of future publications from these laboratories.

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Notes and references

† **General procedure**: A flame-dried Schlenk tube was charged with dry THF (1 mL) and dry acetonitrile (150 μL). Anhydrous chromium(III) chloride (4.0 mg, 25.3 μmol) and manganese (41.7 mg, 0.76 mmol) were added simultaneously to the solvent mixture. The resulting suspension was allowed to stand at room temperature for approximately 30 min until the characteristic purple colour of the chromium(III) salt disappeared. The mixture was stirred vigorously under an atmosphere of nitrogen for 1 h, resulting in a green reaction mixture. DIPEA (13 μL, 75.9 μmol) was added followed by the bis(oxazoline) ligand **7** (30.4 μmol), immediately resulting in a deep green catalyst mixture. This was stirred at room temperature for 1 h prior to the addition of the halide (0.51 mmol), with the resulting chromium(III) allyl solution being stirred for a further 1 h. The reaction was initiated by the addition of aldehyde (0.25 mmol) and chlorotrimethylsilane (64 μL, 0.51 mmol), and stirred under an atmosphere of nitrogen at room temperature for 16 h. The resulting green–brown suspension was quenched with saturated aqueous $NaHCO_3$ (1 mL) and extracted with Et_2O (3 × 1 mL). The combined organic layers were concentrated *in vacuo* to give a green residue. This was flushed through a small silica gel column (1.5 × 5 cm, pentane–AcOEt, 9 : 1) to remove the catalyst, and after evaporation of the solvent, the reaction products were isolated as a yellow oil. The percentage conversion of the reaction was determined at this stage from the ^{1}H NMR spectrum of the crude product (generally a mixture of silylated and free alcohol) by measuring the ratio of aldehyde to product and assuming that all aldehyde consumed was converted to product. The yellow oil was dissolved in THF (1 mL), a few drops of aqueous 1 M HCl were added, and the resulting solution was stirred for 10 min, at which point TLC (9 : 1 pentane–AcOEt) showed complete desilylation. The solvent was removed *in vacuo* and the resulting aqueous phase was extracted with Et_2O (3 × 2 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. This was purified by flash column chromatography on silica gel (1 × 15 cm) using 5 : 1 cyclohexane–AcOEt as the eluent to give the required product as a pale yellow oil. Enantioselectivity was determined by HPLC as follows: **10a**: Chiralcel OD, hexane–isopropanol, 98 : 2, flow rate 1.0 mL min^{-1}): (*R*) = 14.1 min, (*S*) = 16.9 min; **10b**: Chiralcel, OD, hexane–isopropanol, 99 : 1 to 90 : 10 over 30 min, flow rate 0.5 mL min^{-1}): (*R*) = 22.7 min, (*S*) = 23.9 min; **10c** (3,5-dinitrobenzoate ester): Chiralcel AD, hexane–isopropanol, 99 : 1 to 90 : 10 over 20 min, flow rate 0.5 mL min^{-1}): (*S*) = 22.8 min, (*R*) = 28.2 min; **10d** (3,5-dinitrobenzoate ester): Chiralcel OD, hexane–isopropanol, 95 : 5, flow rate 0.2 mL min^{-1}: (*R*) = 35.5 min, (*S*) = 37.9 min; **10e** (3,5-dinitrobenzoate ester): Chiralcel OD, hexane–isopropanol, 99 : 1, flow rate 0.2 mL min^{-1}: (*R*) = 29.5 min, (*S*) = 34.4 min; **10f**: Chiralcel OD, hexane–isopropanol, 90 : 10, flow rate 0.2 mL min^{-1}: (*R*) = 26.5 min, (*S*) = 32.9 min.

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