Enantioselective Allylation of Aldehydes with (Dialkoxyallyl)chromium(III) Complexes

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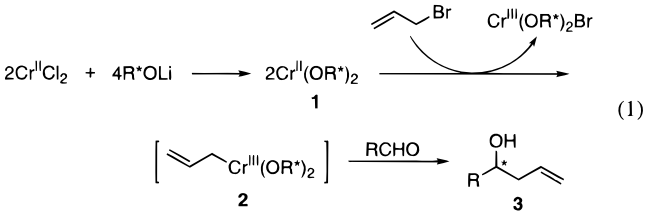
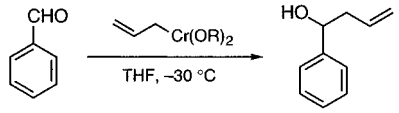
The chromium(II) chloride-mediated addition of allylic bromides to aldehydes referred to as the Nozaki−Hiyama reaction[1] has proved to be a valuable tool for C−C bond formation in virtue of its high chemo- and stereoselectivity and ease of the reaction under mild conditions. Despite its synthetic utility,[2] as far as we are aware, only one example of earlier work aimed at asymmetric addition of allylchromium reagents to aldehydes has been reported;[3] in chromium(II) chloride-mediated allylation of pentanal, the best asymmetric induction was observed when lithium ephedrinate was used as a chiral ligand, but the enantiomeric excess of the resulting homoallylic alcohol was only 29% with poor yield (18%). Quite recently, Kishi et al.[4] first reported the Nozaki−Hiyama-type coupling between benzaldehyde and allyl bromide using a dipyridyl chiral ligand with a significant level of asymmetric induction in 74% ee with 51% yield. These observations indicate that the use of allylic chromium reagents, in which the metal is ligated by such chiral modifiers, can lead to asymmetric allyl coupling, but with less satisfactory results. In our investigations aimed at developing the asymmetric induction for chromium-based allylation,[5] we envisioned that the allylic chromium dialkoxide reagents, in which the metal is covalently bound with chiral hydroxy compounds, can be successfully employed to induce high stereoselectivity. Many chromium alkoxides have been prepared by alcoholysis of $[Cr[N(SiMe_3)_2](THF)_2]$ or from chromocene,[6] but an earlier report[7] suggested that a convenient practical approach might be applicable for the formation of divalent transition metal alkoxides by using lithium alcoholates and anhydrous transition metal halides. We thus speculated as summarized in eq 1 that the chiral chromium(II) dialkoxide **1** would be in situ prepared from $CrCl_2$ and the optically active lithium alcoholates, and subsequent oxidative addition of allyl bromide to **1** would rapidly occur to generate the chirally modified allylchromium(III) reagent **2**, which would be allowed to react with the coexisting prochiral aldehyde to yield the homoallylic alcohol **3** with asymmetric induction. In this paper, we report a new type of highly enantioselective allyl coupling with aldehydes according to eq 1, which involves the chirality-inducing process utilizing the allylchromium(III) reagents with covalently bound chiral alkoxy or aryloxy auxiliaries.



(1)

According to the above mechanistic speculation outlined in eq 1, we first attempted asymmetric addition to benzaldehyde by employing the chiral dialkoxychromium(III) reagents modified by the chiral alcohols **4**−**6** as illustrated by type A in Figure 1. Thus, treatment of $CrCl_2$ and the lithium salts of the chiral alcohols in THF at −30 °C resulted in in situ formation of the chiral chromium(II) dialkoxides (**1** in eq 1), which were then allowed to react with allyl bromide, providing the allylchromium(III) reagents (**2** in eq 1). Subsequent coupling of these type-A allylic chromium(III) reagents with benzaldehyde at −30 °C afforded 1-phenyl-3-butenol (**17**) (Table 1, entries 1−3). As seen in Table 1, however, these reactions showed low chemical yields and their enantioselectivities were only 10−20% ee.

Table 1. Asymmetric Allylation of Benzaldehyde Using (Dialkoxyallyl)- or [Bis(aryloxy)allyl]chromium(III) Compounds



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entry	type of allylchromium(III)	hydroxy compd	yield[a] of **17** (%)	% ee[b] (config)[c]
1	A	**4**	27	20 (*R*)
2	A	**5**	53	14 (*S*)
3	A	**6**	52	10 (*S*)
4	B	**7**	49	11 (*R*)
5	B	**8**	56	46 (*S*)
6	C	**9**	47	37 (*R*)
7	C	**10**	34	21 (*R*)
8	C	**11**	64	42 (*R*)
9	C	**12**	40	65 (*S*)
10	C	**13**	32	39 (*R*)
11	C	**14**	77	44 (*R*)
12	C	**15**	72	30 (*R*)
13	C	**16**	62	82 (*R*)

[a] Isolated yield after chromatographic purification. [b] Determined by HPLC analysis (Chiralcel OB column, Daicel Chemical Industries, Ltd.). [c] Assigned by comparison of the sign of optical rotation with reported value.[9]

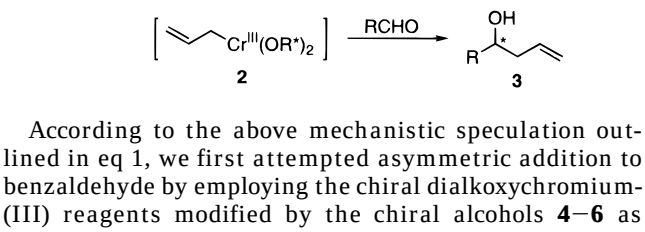

Figure 1. Type-A (dialkyloxyallyl)chromium(III) reagents.

We next employed the chiral dihydroxy compounds **7** and **8** to form type-B cyclic bis(aryloxy)- and dialkoxychromium(III) reagents (Figure 2), and the asymmetric

(1) (a) Okude, Y.; Hirano, S.; Hiyama, T.; Nozaki, H. *J. Am. Chem. Soc.* **1977**, *99*, 3179. (b) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685.

(2) For recent reviews on the use of organochromium compounds in carbon−carbon bond-forming reactions, see: (a) Cintas, P. *Synthesis* **1992**, 248. (b) Saccomamo, N. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2, pp 173−209. (c) Hodgson, D. M. *J. Organomet. Chem.* **1994**, *476*, 1.

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(5) For asymmetric allylation by other metals, see: Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723 and references cited therein.

(6) O'Brien, P. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol. 3, p 737.

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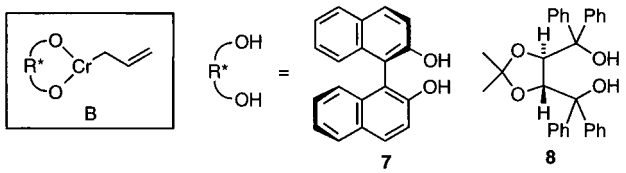


Figure 2. Type-B (dialkoxyallyl)- and bis(aryloxy)allyl]chromium(III) reagents.

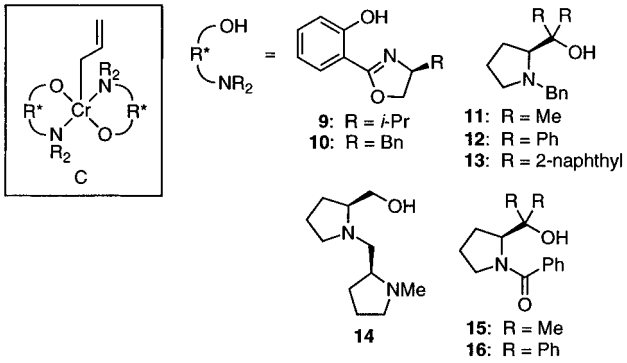


Figure 3. Type-C (dialkoxyallyl)- and [bis(aryloxy)allyl]-chromium(III) reagents.

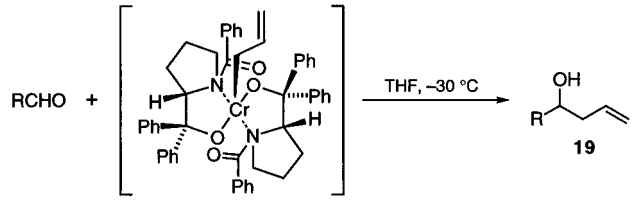
addition to benzaldehyde leading to the homoallylic alcohol **17** was conducted following the same procedure as described above for the type-A reagents. As summarized in Table 1, while the use of the (*R*)-1,1′-bi-2-naphthoxychromium(III) reagent resulted in only low enantioselectivity (10% ee, Table 1, entry 4), in the case where the chromium(III) reagent installing the chiral diol **8** was used (Table 1, entry 5), the enantioselectivity was found to be appreciably improved; however, it still remains at a low level of 46% ee.

We next attempted to employ the chiral monohydroxy compounds with nitrogen functions, i.e., **9**−**16**, for generation of the chiral allylic chromium(III) complexes represented by type C (Figure 3), which would be in a chelated trans planar structure rigidifying the array of atoms and serve to differentiate the enantiotopic faces during the coupling. Thus, allyl coupling with benzaldehyde was carried out using these allyl chromic reagents, and the results are listed in Table 1. Among these chiral allylchromium(III) compounds of type C, the reagent prepared from the *N*-benzoyl-L-prolinol derivative **16** proved to be the most efficacious in chiral induction, affording (*R*)-**17** with the highest enantiomeric excess of 82% (Table 1, entry 13). In this case, the intermediary chromium(II) dialkoxide complex is considered to constitute preferential coordination between chromium and the nitrogen atom rather than the oxygen atom of the amide group to form the five-membered chelate ring, although chromium coordination can occur with both the nitrogen and oxygen atoms.[9] Thereby, bidentate coordination by the two ligands should have constructed efficient chiral circumstance around the metal center.

It should be noted that using the imino phenols **9** and **10** as chiral ligands (Table 1, entries 6 and 7) leads to much shorter reaction time (1−2 h), albeit with unsatisfactory asymmetric induction, compared with the reaction time in the allylation reactions using a series of the L-prolinol ligands **11**−**16**, which require 4−12 h (Tables 1, entries 8−13). From these observations, it is expected that type-C (diphenoxyallyl)chromium(III) complexes, through their structural modifications, serve as potential chiral inductors for asymmetric allylation.

(9) (a) Palenik, G. J.; Wester, D. W.; Rychlewska, U.; Palenik, R. C. *Inorg. Chem.* **1976**, *15*, 1814. (b) Collins, T. J.; Santarsiero, B. D.; Spies, G. H. *J. Chem. Soc., Chem. Commun.* **1983**, 681.

Table 2. Asymmetric Allylation of Aldehydes Using (Dialkoxyallyl)chromium(III) Complex 18



entry	aldehyde (R)	yield[a] of **19** (%)	$[\alpha]^{28}_D$ (benzene)	% ee[b] (confign)[c]
1	4-$MeOC_6H_4$	84	+30.5 (*c* 0.45)	49 (*R*)
2	4-ClC_6H_4	72	+23.5 (*c* 0.53)	88 (*R*)
3[d]	4-ClC_6H_4	47	+26.4 (*c* 0.38)	98 (*R*)
4	1-naphthyl	43	+64.3 (*c* 0.19)	80 (*R*)
5	$Ph(CH_2)_2$	60	+10.7 (*c* 0.48)	61 (*S*)

[a] Isolated yield after chromatographic purification. [b] Determined by HPLC analysis (Chiralcel OB or OD column, Daicel Chemical Industries, Ltd.). [c] Assigned by comparison of the sign of optical rotation with reported value.[8] [d] Preparation of the chromium(II) dialkoxide using **16** was carried out at room temperature.

The low chemical yield (32%), observed when the L-prolinol derivative **13** was employed (Table 1, entry 10), may be accounted for by the bulky naphthyl groups extruding to above and below the plane of the chromium(II) complex that sterically block further oxidative addition of allyl bromide, thus preventing the formation of the type-C allylic chromium(III) reagent.

Encouraged by the above result with the type-C (dialkoxyallyl)chromium(III) reagent incorporated with the *N*-benzoyl-L-prolinol **16**, i.e., **18**, we further explored the asymmetric coupling with aldehydes utilizing **18**. As summarized in Table 2, these reactions were found to proceed to form the corresponding homoallylic alcohols **19** with moderate to excellent enantioselectivities.[10] For the allyl coupling with *p*-chlorobenzaldehyde, when the chromium(II) dialkoxide species was formed from $CrCl_2$ and the chiral ligand **16** at room temperature (Table 2, entry 3) instead of −30 °C (Table 2, entry 2), the selectivity was enhanced from 88% ee up to 98% ee. In this case, a lowering of the chemical yield (47%) observed indicates that the chromium(II) dialkoxide intermediates have a tendency to undergo decomposition at room temperature.

In summary, we have demonstrated that the (dialkoxyallyl)chromium(III) complex **18** chirally modified by the *N*-benzoyl-L-prolinol derivative **16**, being suggested to constitute a rigid chelated trans plannar structure, leads to high induction in asymmetric preparation of homoallylic alcohols by allyl coupling with aldehydes.

Supporting Information Available: Experimental procedures and characterization data are provided for compounds **10**, **13**, **15**, and **16** (4 pages).

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(10) General procedure for the asymmetric allylation: To a stirred solution of $CrCl_2$ (2.0 mmol) in THF (5 mL) at −30 °C under an argon atmosphere was cannulated a solution of the lithium alkoxide, prepared by the addition of a 1.57 M (1.46 mL) solution of BuLi (2.3 mmol) in hexane to a solution of the hydroxy compound (4.0 mmol, 2 mmol for **7** and **8**) in THF (7 mL) at 0 °C. The mixture was stirred for 1 h at −30 °C, and allyl bromide (1.0 mmol) followed by the aldehyde (0.5 mmol) were added. After being stirred for 1−12 h at −30 °C, the reaction was quenched by addition of water. The insoluble material was removed by filtration through a Celite pad, and the filtrate was extracted with ether. The extracts were washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by column chromatography on silica gel to give the homoallylic alcohol with the chemical and optical yields reported in Tables 1 and 2.