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Asymmetric Catalysis of Nozaki−Hiyama Allylation and Methallylation with A New Tridentate Bis(oxazolinyl)carbazole Ligand

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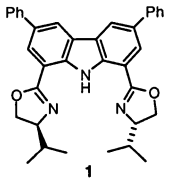
Cr(II)-mediated C−C bond-forming reactions originally developed by Nozaki and Hiyama et al.[1] have been studied extensively because of their potential utility.[2] These reactions have also been applied to numerous total syntheses of complex natural products due to their high chemoselectivity and excellent compatibility with various functional groups.[2]

Although a huge excess of toxic chromium salts had been required to complete these reactions in the early stage,[2] the catalytic redox system reported by Fürstner et al. reduced the quantity of chromium salts, making these reactions more valuable and environmentally benign.[3]

Asymmetric catalysis of Nozaki−Hiyama reactions would allow control over the enantioselectivity, thereby further enhancing the versatility of these powerful transformations. Surprisingly, however, limited studies on asymmetric catalysis of these reactions have been reported.[2] Cozzi and Umani-Ronchi reported enantioselective Nozaki−Hiyama reactions using the commercially available salen ligand, but the enantioselectivities and yields were not satisfactory.[4,5] In addition, the formation of a considerable amount of side product was also a problem. To overcome these difficulties a new chiral ligand for Nozaki−Hiyama reactions is required. In this work we report a new chiral ligand effective for the asymmetric catalysis of Nozaki−Hiyama allylation and methallylation.

We have designed and synthesized a C_2-symmetrical tridentate bis(oxazolinyl)carbazole ligand **1**,[6] in which the allyl-Cr(III)−ligand does not undergo significant dissociation due to the stabilization by three bonds: a σ-bond with the carbazole nitrogen and two coordination bonds with the oxazoline nitrogens. This leaves a vacant coordination site at which an aldehyde can bind.[7] Hence, the reaction of allyl-Cr(III)−ligand **1** complex with an aldehyde is expected to proceed enantioselectively.



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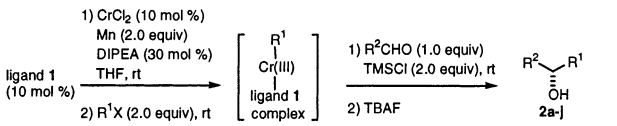
We adopted the Fürstner's condition[3] because metallic Mn, the co-reducing reagent, is suitable for the enantioselective allylation due to its low intrinsic reactivity toward organic halides.[3,8] Ligand **1**, $CrCl_2$, Mn, and DIPEA were mixed in THF under an atmosphere of Ar at room temperature.[9] The Cr(II)−ligand **1** complex prepared in situ was used for the enantioselective allylation.[10] Isolated crude products were treated with TBAF to afford alcohol **2a** in 93% yield (two steps, 90% ee, entry 1 in Table 1). The enantioselectivity increased to 93% ee (entry 2) when the reaction was carried out at 0 °C.[11]

Allyl chloride afforded almost the same result as that of allylbromide (entry 3), but allyliodide gave a low enantioselectivity (entry 4). One reason for the low selectivity is found in the formation of racemate by the reaction of the achiral allylmanganase reagent formed in situ.[12]

Table 1. Enantioselective Allylations of Aldehydes



entry	product	R^1	X	R^2	ee(%)[a,b]	yield(%)[c]	time(h)
1	**2a**	allyl	Br	Ph	90(*S*)[f]	93	12
2[d]	**2a**	allyl	Br	Ph	93(*S*)[f]	89	12
3	**2a**	allyl	Cl	Ph	89(*S*)[f]	95	16
4	**2a**	allyl	I	Ph	64(*S*)[f]	52	12
5	**2b**	allyl	Br	*p*-BrPh	92(*S*)[g]	87	12
6	**2c**	allyl	Br	PhCH=CH	95(*S*)[h]	87	12
7[d]	**2d**	allyl	Br	$PhCH_2CH_2$	86(*R*)[i]	91	12
8	**2e**	allyl	Br	*c*-C_6H_{11}	94(*S*)[f]	95	12
9	**2e**	allyl	Cl	*c*-C_6H_{11}	93(*S*)[f]	88	12
10	**2f**	allyl	Br	*n*-C_5H_{11}	92(*R*)[j]	83	12
11	**2g**	methallyl	Br	Ph	46(*S*)[k]	77	16
12	**2g**	methallyl	Cl	Ph	95(*S*)[k]	96	16
13	**2h**	methallyl	Cl	PhCH=CH	90(*S*)[l]	50	16
14	**2i**	methallyl	Br	*c*-C_6H_{11}	96(*S*)[m]	96	16
15	**2i**	methallyl	Cl	*c*-C_6H_{11}	95(*S*)[m]	98	16
16	**2j**	methallyl	Br	*n*-C_5H_{11}	79(*R*)[e,n]	65	16
17	**2j**	methallyl	Cl	*n*-C_5H_{11}	96(*R*)[e,n]	83	16

[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 ^{1}H 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.

As shown in Table 1, other aldehydes, including saturated and unsaturated aliphatic aldehydes, were all allylated with 86−95% ee in high yields. Furthermore, this enantioselective reaction was successfully extended to methallylation of aldehydes by the use of appropriate methallylhalide, with 90−96% ee (entry 11−17). Thus, the highly enantioselective reactions using ligand **1** proved to be applicable to a broad range of aldehydes.

It is noteworthy that the chiral aldehyde **3** was methallylated to give **4**, which is a key intermediate of calcitriol lactone synthesis,[13] with 97% de using *ent*-ligand **1** (Figure 1).[14] This diastereoselective reaction is apparently a chiral catalyst-controlled reaction because without *ent*-ligand **1** almost no diastereoselectivity was observed (−3% de) and high diastereoselectivity (−94% de) was also obtained with ligand **1**. Therefore, this catalytic asymmetric reaction has immense potential in natural product synthesis.

We anticipated that the Cr−ligand **1** complex would be recycled because of its predicted stability. As shown in Table 2, the Cr−ligand **1** complex, which had been recovered after the reaction, was successfully recycled twice.[15] It is worth noting that ee of the

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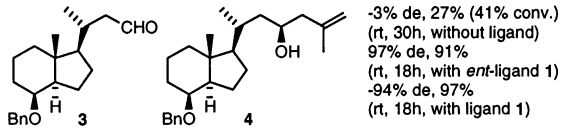
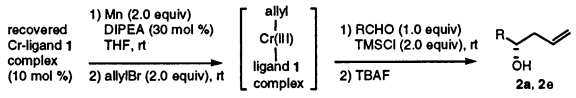


Figure 1. Application to the steroid side-chain synthesis.

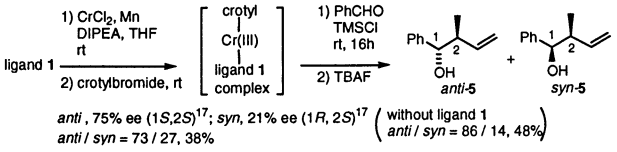
Table 2. Recycling the Recovered Cr−Ligand **1** Complex



entry	product	R	ee(%)[a,b]	yield(%)[c]	time(h)	recycling
1[d]	**2a**	Ph	92(*S*)[e]	86	24	first time
2[d]	**2a**	Ph	93(*S*)[e]	79	24	second time
3	**2e**	*c*-C_6H_{11}	95(*S*)[e]	84	16	first time
4	**2e**	*c*-C_6H_{11}	94(*S*)[e]	90	16	second time

[a−d] See the footnotes to Table 1. [e] See ref 19a.

Scheme 1. Enantioselective Crotylation of Benzaldehyde



products in the recycling experiments are almost unchanged from the values in entry 2 (93% ee) and entry 8 (94% ee) of Table 1, respectively.

The diastereoselectivity of the reaction of benzaldehyde with crotylbromide was somewhat lower than that observed in the absence of ligand **1** (Scheme 1).[16] The reaction was *anti*-selective and the enantioselectivities were 75% ee (*anti*-form) and 21% ee (*syn*-form).[17]

Configuration of the major enantiomer of *anti*-**5** was (1*S*,2*S*), showing that benzaldehyde preferentially reacted from its *si*-face.[18] This *si*-face selectivity can be seen in Table 1 where **2d**, **2f**, and **2j** have (*R*)-configuration, and others have (*S*)-configuration, revealing that all aldehydes reacted predominantly from their *si*-face.

The *anti*-selectivity noted above is not high enough to indicate the cyclic Zimmermann−Traxler-like transition state, which may account for the *si*-face selectivity. Thus, an acyclic transition state cannot be ruled out. Hence, we are currently investigating the reaction mechanism.[20]

In summary, a tridentate ligand **1** effective for the asymmetric catalysis of Nozaki−Hiyama allylation and methallylation has been developed. Ligand **1** is thought to form a chiral Cr complex with $CrCl_2$ in which ligand **1** is firmly bound to chromium. This complex possesses great potential as the asymmetric catalyst for other Cr-mediated reactions. Furthermore, there are numerous possibilities of developing other asymmetric catalysts using an alternative metal, because ligand **1** is able to incorporate other metal ions. Moreover, immobilization of the Cr−ligand **1** complex is interesting because the Cr−ligand **1** complex is water-tolerant and can be recycled.

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Supporting Information Available: Experimental details and characterization data for the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) *N*-ethylpiperidine, triethylamine, and tri-*n*-butylamine were also effective for this highly enantioselective reaction, but the yields were slightly lowered.
(10) For experimental procedure, see Supporting Information.
(11) Low temperature (0 °C) did not increase the enantioselectivity in other reactions except entry 7.
(12) (a) In the absence of $CrCl_2$ and ligand **1**, the allylated products were obtained in 8 and 14% yield under the conditions of entries 2 and 7, respectively. Aliphatic aldehydes are surmised to be rather inert to allylmanganase reagent. Cf. ref 3.
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(14) $CrCl_2$ (20 mol %), *ent*-ligand **1** (20 mol %), Mn (4.0 equiv), methallyl chloride (2.0 equiv), and DIPEA (1.0 equiv) were used. Without *ent*-ligand **1**, the reaction proceeded sluggishly. The details will be communicated.
(15) Characterization of the recovered Cr−ligand **1** complex is now under investigation.
(16) The same condition for the enantioselective allylation was used.
(17) *Anti*/*syn* ratio, ee, and absolute configuration of the major enantiomers were determined by 600 MHz ^{1}H NMR and HPLC of Mosher's ester of **7**; see ref 4e. Yields were the combined yield.
(18) (a) Enantioselectivity and yield of the crotylation of benzaldehyde increased to 77% ee (*anti*-form), 26% ee (*syn*-form), and 53% combined yield when the reaction was carried out at 0 °C.
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(20) An additional interesting feature of this reaction is that no pinacol product (cf. ref 4) was found in the all reactions reported here.

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