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Studies on Catalytic Asymmetric Nozaki–Hiyama Propargylation

Masahiro Inoue and Masahisa Nakada*

Department of Chemistry, School of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

mnakada@waseda.jp

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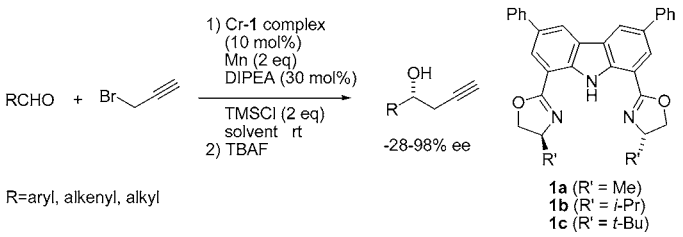
ABSTRACT



Catalytic asymmetric Nozaki–Hiyama propargylation with ligand 1c proceeds with good to excellent enantioselectivity. Tuning of ligand 1 dramatically changes the enantioselectivity, and we propose models A and B to explain the change and outcome of the enantioselectivity.

Recent progress in organic synthesis suggests that chiral homopropargyl alcohols are important intermediates because they can be used for Pd-mediated coupling reactions,[1] ene-yne metathesis,[2] heterocyclic compound formations,[3] silyl-formylation−allylsilylations,[4] and so on.

The methods for preparing chiral homopropargyl alcohols mostly depend on asymmetric synthesis, that is, methods of using chiral allenyl compounds[5] and enantioselective methods have been reported.[6−8] Among them, catalytic asymmetric propargylation[7,8] is important in terms of efficiency. However, the asymmetric catalysis of propargylation reported so far mostly rely on the chiral Lewis acid-mediated addition reaction of allenyltin compounds to aldehydes.

Propargylations using low-valent metal and propargyl halide are superior to the Lewis acid-mediated reaction of allenyltin compounds because both reagents are readily available.[6c,8] The propargylation using Cr(II) and propargyl halide is particularly useful due to its high chemoselectivity and excellent compatibility with various functional groups; hence, this method has been developed by some research groups.[9]

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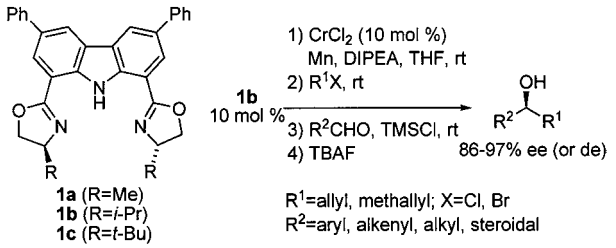
Recently, Cozzi and Umani-Ronchi et al. reported enantioselective propargylation using commercially available salen ligand and $CrCl_2$, but the enantioselectivities and yields were not satisfactory.[8] In addition, this reaction is limited to aromatic aldehyde, and the formation of a considerable amount of the side-product derived from a pinacol coupling was also a problem.

We have reported the highly enantioselective Nozaki−Hiyama allylation utilizing a newly developed carbazole tridentate ligand and have shown its wide applicability (Scheme 1).[10] Thence, we have investigated the asymmetric

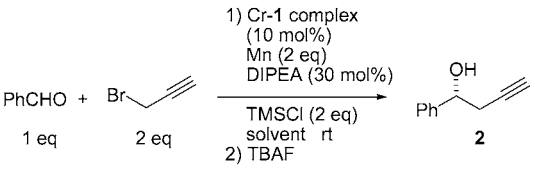
Scheme 1. Asymmetric Catalysis of Nozaki−Hiyama Allylation[10]



catalysis of Nozaki−Hiyama propargylation, and herein we report the successful results and dramatic change in enantioselectivity achievable by tuning the chiral ligand.

First, ligand **1b**, $CrCl_2$, Mn, and DIPEA were mixed in THF under an atmosphere of Ar at room temperature to form the Cr(II)−ligand **1b** complex. Then, the Cr(II)−ligand **1b** complex thus prepared was used without isolation for the enantioselective propargylation of benzaldehyde. As shown in Table 1, the reaction was complete after 18 h, and after treatment of the crude product with TBAF to remove TMS ether, the propargylated (*S*)-product was obtained (80%, 28% ee, entry 3).

Table 1. Asymmetric Catalysis of Nozaki−Hiyama Propargylation with Ligands **1a**−**c**



entry	ligand	time (h)	yield (%)	ee (%)[a,b]
1	**1a**	16	94	−26 (*S*)
2	**1a**[c]	16	78	−24 (*S*)
3	**1b**	18	80	−28 (*S*)
4	**1b**[c]	24	74	−24 (*S*)
5	**1c**[c]	60	75	71 (*R*)

[a] Ee determined by HPLC. [b] Absolute configuration determined by comparison of the optical rotation to the literature value. [c] Cr−ligand **1** complex was prepared using the method described in Supporting Information.

Next, the effect of the substituent of the ligands on the enantioselectivity was surveyed. The propargylation with the Cr(II)−ligand **1a** complex, prepared by the same method for the Cr(II)−ligand **1b** complex, afforded the (*S*)-product (94%, 26% ee, entry 1). Since formation of the Cr−ligand **1c** complex was slow and a considerable amount of $CrCl_2$ remained, the Cr−ligand **1c** complex was prepared by a different method.[11] The reaction with the Cr−ligand **1c** complex required longer reaction time (60 h) to afford (*R*)-product (75%, 71% ee, entry 5).

We suspected that the structure of the Cr−ligand **1c** complex would be different from the structure of the Cr(II)−ligand **1a** or **1b** complexes prepared in situ. To clarify this point, the Cr−ligand **1a** and **1b** complexes were prepared by the same method for the Cr−ligand **1c** complex and the propargylation was carried out; however, almost the same results as in entries 1 and 3 were obtained (entries 2 and 4, respectively).

The result with the Cr−ligand **1c** complex (entry 5) surprised us because not only was the ee increased but also the enantioselectivity was reversed, in contrast to the previously reported enantioselective allylation, which generally produced (*R*)-products (Scheme 1).[12]

To date, we have no evidence that the Cr−ligand **1c** complex, prepared by the different method, has a structure similar to the Cr(II)−ligand **1a** and **1b** complexes; however, the results in Table 1 suggest that the preparation method of the Cr−ligand **1** complex is not a major factor in the change in enantioselectivity.

It should be noted that no allenyl alcohol was obtained in the reactions in Table 1 because a mixture of the homopropargyl alcohol and the allenyl alcohol usually forms in the Nozaki−Hiyama propargylation.[9]

As shown in Table 2, the conditions for this catalytic asymmetric propargylation were optimized. The propargylation was fast, and the yield was high in acetonitrile or propionitrile (entries 2 and 3); however, the ee decreased. In DMF, not only was the reaction slow but also the yield and ee were low (entry 4). Moreover, a small amount of the allenyl alcohol formed in DMF (propargyl alcohol/allenyl alcohol = 14/1). In the case of 1,4-dioxane or diglyme, the ee was comparable to the ee obtained in THF (entries 5 and 6). Finally, DME was found to be the best solvent for this propargylation because DME was superior to other solvents in all respects, that is, reaction time, yield, and ee (entries 1−7 and 10−12). Interestingly, no product was obtained at 0 °C in DME (entry 8), and propargyl chloride did not react with benzaldehyde in DME even after 120 h (entry 9).

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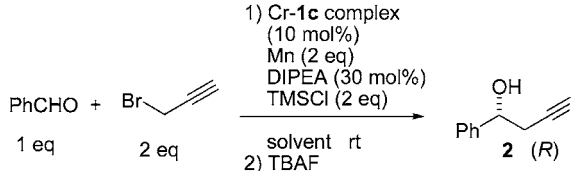
(11) For experimental details, see Supporting Information. The prepared Cr−ligand **1c** complex would be a Cr(III) complex because the isolation was carried out in open air. The stability of this complex had been confirmed; see ref 10a.

Table 2. Solvent Effect on Asymmetric Catalysis of Nozaki−Hiyama Propargylation with Ligand **1c**

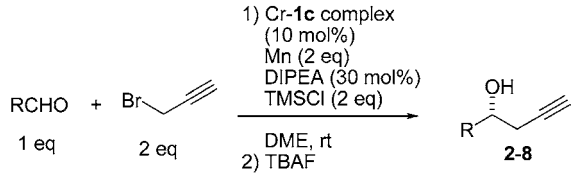


entry	solvent	time (h)	yield (%)	ee (%)[a]
1	THF	60	75	71
2	CH_3CN	18	93	56
3	C_2H_5CN	12	92	28
4	DMF	96	20[b]	17[c]
5	1,4-dioxane	36	33	71
6	diglyme	16	62	71
7	DME	12	93	78
8[d]	DME	48	NR	
9[e]	DME	120	trace	
10	CH_2Cl_2	48	55	62
11	$(CH_2Cl)_2$	48	trace[f]	
12	toluene	48	trace[f]	

[a] Ee determined by HPLC. [b] Combined yield of the homopropargyl alcohol and the allenyl alcohol (14:1). [c] Ee of homopropargyl alcohol. [d] Reaction was carried out at 0 °C. [e] Propargyl chloride was used instead of propargyl bromide. [f] No silylated product was observed.

Various aldehydes were successfully propargylated under the optimized conditions (Table 3). The reactions of 2-naphthaldehyde (entry 2) and (*E*)-cinnamaldehyde (entry 3) with ligand **1c** afforded the (*R*)-products (95%, 74% ee; 91%, 73% ee, respectively). The (*R*)-product preferentially formed in the reactions of hydrocinnamaldehyde (entry 4) and *n*-pentylaldehyde (entry 5), too. However, the yield and ee were somewhat low (20%, 51% ee; 55%, 58% ee, respectively). On the other hand, the reactions of rather bulky aliphatic aldehydes showed high ee; thus, cyclohexylaldehyde (entry 6) was propargylated in 86% yield (82% ee). In the case of pivalaldehyde, the most bulky aldehyde in Table 3, the ee of the product increased to 98% ee.

Table 3. Asymmetric Catalysis of Nozaki−Hiyama Propargylation of Aldehydes with Ligand **1c**



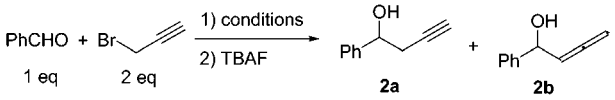
entry	R (product no.)	time (h)	yield (%)	ee (%)[a]
1	Ph (**2**)	12	93	78 (*R*)[b]
2	2-naphthyl (**3**)	20	95	74 (*R*)[b]
3	(*E*)-PhCH=CH (**4**)	16	91	73 (*R*)[b]
4	$PhCH_2CH_2$ (**5**)	16	20	51 (*S*)[b]
5	$CH_3(CH_2)_4$ (**6**)	16	55	58 (*S*)[b]
6	cyclohexyl (**7**)	16	86	82 (*R*)[b]
7	*t*-Bu (**8**)	16	41	98 (*R*)[c]

[a] Absolute configuration determined by comparison of the optical rotation to the literature value. [b] Ee determined by HPLC. [c] Ee determined by ^1H NMR of the corresponding MTPA ester.

It has been shown that the allenylchromium(III) intermediate is in equilibrium with the propargylchromium(III) intermediate and their ratio depends on their structure and/or the used additives.[13] Consequently, these intermediates usually afford a mixture of the homopropargyl alcohol and the allenyl alcohol as the product.

As described above, however, formation of allenyl alcohol was not observed in the propargylation with ligand **1** except entry 4 of Table 2. We also carried out the propargylation without ligand **1** (Table 4) and found that the allenyl alcohol formed as a minor product (entry 1). The exclusive formation of the propargylated alcohol with ligand **1** cannot be explained clearly now, but ligand **1** could stabilize the allenylchromium intermediate or accelerate its preferential formation to make the propargylation favorable.[14]

Table 4. Propargylation of Benzldehyde without Chiral Ligand **1**



entry[a]	solvent	$CrCl_2$ (mol %)	DIPEA (mol %)	time (h)	yield[b] (%; **2a**/**2b**)
1	DME	10	30	12	93; 15/1
2	DME	0	30	12	0
3	DME	0	0	16	0
4	DMF	0	0	96	6; 3.5/1

[a] TMSCl (2 equiv) and Mn (2 equiv) were used in all reactions. [b] Combined yield of **2a** and **2b**.

The reactions without $CrCl_2$ and ligand **1** in the presence of DIPEA (entry 2) in DME and in the absence of DIPEA (entry 3) in DME were also carried out, but no reaction occurred. These results suggest that the homopropargylic alcohol does not derive from the allenylmanganese intermediate in DME.

As noted above, a small amount of the allenyl alcohol was generated in DMF (entry 4, Table 2), and we also observed formation of the allenyl alcohol when the reaction was carried out without $CrCl_2$ and ligand **1** in DMF (entry 4, Table 4). Hence, it is surmised that the propargylmanganese intermediate would form in DMF and competitively react in part with benzaldehyde to give the allenyl alcohol.

The enantioselectivity of this catalytic asymmetric reaction could be explained as follows: *si*-face selectivity of the

(12) We did not prepare ligands with phenyl or benzyl oxazolines, but we will test these ligands accordingly.

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(14) Same result has been observed in the reaction using HMPA as an additive or diphenylchromium as a reagent.[9e]

aldehyde in this propargylation dominates when the substituent of ligand **1** is small, and *re*-face selectivity of the aldehyde emerges when the substituent of ligand **1** becomes large (Table 1). In addition, the results in Table 3 indicate that *re*-face selectivity increases when the aldehyde becomes bulky. These relationships, that is, the reversal of the enantioselectivity by changing the substituent of ligand **1** and the increase in *re*-face selectivity with increasing bulkiness of aldehyde, could be rationally explained by proposed models A and B in Figure 1.

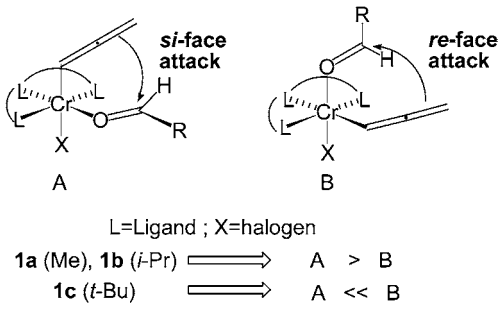

Figure 1. Proposed models A and B.

That is, when the substituent of ligand **1** is small, aldehyde would tend to coordinate at the equatorial position (model A, Figure 1), favoring the *si*-face reaction under the influence of the asymmetric circumstance. On the other hand, when the substituent of ligand **1** is bulky, steric strain between aldehyde and the oxazoline substituents would be large; therefore, aldehyde would coordinate at the apical position (model B), favoring the *re*-face reaction under the influence of the asymmetric circumstance (Figure 1).

However, several other explanations for the change in enantioselectivity are possible. For example, possibilities that the reaction proceeds intermolecularly and that the Cr−ligand **1** complex is a dinuclear complex[15] cannot be ruled out. Furthermore, the stereochemical outcome of this propargylation reaction could derive from the different chromium complexes. Hence, further studies on the structure of the Cr−ligand **1** complex and the mechanism of this reaction are in progress.

In summary, we have found that the Nozaki−Hiyama propargylation with ligand **1c** proceeds with good to excellent enantioselectivity. The enantioselectivity of this Nozaki−Hiyama propargylation was changed dramatically by tuning of ligand **1**, and we proposed models A and B to explain the change and outcome of the enantioselectivity. We are now developing asymmetric catalysis of other Nozaki−Hiyama reactions.

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Supporting Information Available: Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For example, see: Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882−2883.