Asymmetric Catalysis

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Studies into Asymmetric Catalysis of the Nozaki–Hiyama Allenylation**

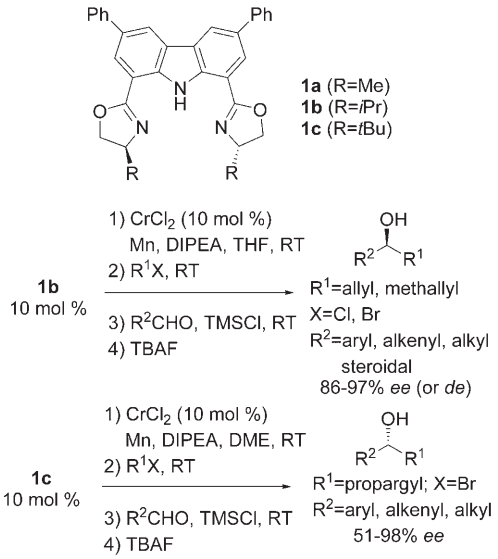
*Masahiro Inoue and Masahisa Nakada**

The allene moiety represents a versatile and useful functional group in organic synthesis because of its unique reactivity.[1] Recent developments in the chemistry of allenes suggest that allenic alcohols are important synthetic intermediates because they can be stereoselectively converted into compounds with other functional groups, for example, the amino alcohols[2] and 2,5-dihydrofurans,[1a,3] and they can also be used as substrates for Pauson–Khand reactions[1a,4] and Pd-mediated reactions.[1a,5]

Allenic alcohols are generally prepared by allenylation of carbonyl compounds,[1b,e,6] and chiral ones have been elaborated by asymmetric synthesis.[1a,7,8] Among the enantioselective methods, catalytic asymmetric synthesis[1a,9] is important in terms of efficiency; however, most of the asymmetric catalysis of allenylation reported so far requires preparation of propargyltin or propargylsilane compounds in advance, thereby rendering the asymmetric catalysis of allenylation inconvenient.

On the other hand, allenylations with low-valent metals and propargyl halides are advantageous with regard to their ease of manipulation; thus, the required operation is just mixing the commercially available reagents.[6a] The allenylation with Cr^{II} and a propargyl halide is particularly useful due to its easy operation, high chemoselectivity, and excellent compatibility with various functional groups; hence, this method has been developed by some research groups.[10]

We have reported highly enantioselective Nozaki–Hiyama allylations[11] and propargylations[12a] by utilizing a new carbazole tridentate ligand and have shown the wide applicability of this ligand (Scheme 1). Since no enantioselective allenylation with a low-valent metal and propargyl halide has been reported, we have examined the asymmetric catalysis of the Nozaki–Hiyama allenylation, and we report herein the first successful results.



Scheme 1. Asymmetric catalysis of the Nozaki–Hiyama allylation, methallylation, and propargylation. DIPEA = diisopropylethylamine, TMS = trimethylsilyl, TBAF = tetrabutylammonium fluoride, DME = 1,2-dimethoxyethane.

It has been shown that an equilibrium between the allenylchromium(III) and propargylchromium(III) intermediates exists in the reaction with Cr^{II} and a propargylic halide and that the ratio of these intermediates depends on their structure and/or additives.[10b,12–14] Consequently, these intermediates deliver the homopropargylic alcohol and the allenic alcohol, respectively.

Allenylations of carbonyl compounds with Cr^{II} and the terminally substituted propargyl halides afford allenic alcohols as the major products;[10b,12–14] hence, we surmised that the terminally silylated propargyl halide would generate the 2-silylated secondary allenic alcohol,[15] which can be easily desilylated[8c] and can also be used as the allenylsilane.

[*] M. Inoue, Prof. M. Nakada
Department of Chemistry
Faculty of Science and Engineering
Waseda University
3-4-1, Ohkubo, Shinjuku, Tokyo 169-8555 (Japan)
Fax: (+81) 3-5286-3240
E-mail: mnakada@waseda.jp

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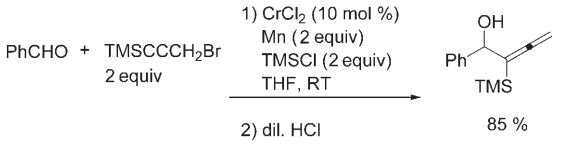
Therefore, we focused our attention on the study of the asymmetric catalysis of the Nozaki–Hiyama allenylation with terminally silylated propargyl halides.

First, a Cr^{II}-mediated reaction of commercially available 1-trimethylsilyl-3-bromopropyne[16] with benzaldehyde in the absence of the chiral ligand under catalytic conditions[11,13a] was carried out (Scheme 2). The reaction was complete after 4 h and afforded the allenic alcohol as the sole product in 85% yield.



Scheme 2. The catalytic Nozaki–Hiyama allenylation without ligand.

Consequently, a Cr^{II}/chiral-ligand-mediated reaction of 1-trimethylsilyl-3-bromopropyne with benzaldehyde was carried out. This catalytic asymmetric allenylation followed the same procedure as that used for the catalytic asymmetric allylation and propargylation.[11]

The reaction with ligand **1a** was complete after 6 h and generated the *R* product in 90% yield with 64% *ee* (Table 1, entry 1).[17] The reaction with **1b** took 8 h to finish and generated the *R* product in 92% yield with 52% *ee* (entry 2). Interestingly, the enantioselectivity in the reaction with **1c** was reversed to afford the *S* product in 92% yield with 29% *ee* after 12 h.[18] It is noteworthy that the least bulky ligand **1a** gave the best result and only allenic alcohols were generated in all the reactions described in entries 1–3. The reaction with the propargyl chloride and **1a** did not improve the result (entry 4; 85%, 47% *ee*).

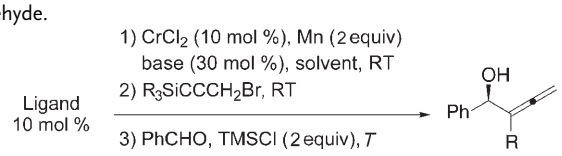
Next, the reaction was carried out in various solvents by using the most effective ligand, that is, **1a**, and propargyl bromide. The reactions in DME (entry 5) and acetonitrile (entry 6) required 12 h for completion and the *ee* values were slightly decreased. Although the reaction time was not shortened, propionitrile increased the *ee* value to 71% (entry 7). Other solvents gave fruitless results; for example, the reaction in CH_2Cl_2 required much more time and both the yield and the *ee* value were decreased (entry 8; 24 h, 49%, 57% *ee*). DMF generated the allenic alcohol (36%, 74% *ee*) along with the propargylic alcohol (20%, 4% *ee*).

The reaction at 0°C delayed the reaction time (16 h); however, the *ee* value was increased to 76% (entry 10). Hence, all the reactions were carried out at 0°C after this. Use of molecular sieves did not affect the *ee* value and merely prolonged the reaction time (entry 11).

The base used to prepare the chiral catalyst was also surveyed.[11b] Potassium carbonate (entry 12) and bulky γ-collidine (entry 13), which would not coordinate to chromium, gave results comparable with those obtained by the use of DIPEA; however, pyridine (entry 12) gave diminished results in all respects (reaction time, yield, and *ee* value), probably due to its strongly coordinating nature.

We found that the silyl group of the propargyl halide affected the enantioselectivity; that is, while silyl groups bulkier than the TMS group (TES, TIPS, DMPS, and MDPS) did not improve the enantioselectivity (entries 15–18), the smaller DMS group (entry 19) afforded the best result (81%, 80% *ee*).

Table 1: Asymmetric catalysis of the Nozaki–Hiyama allenylation of benzaldehyde.



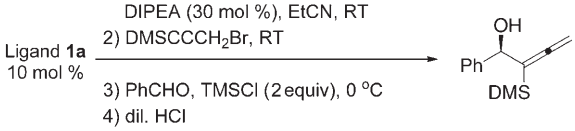
Entry	Ligand	Solvent	*T* [°C]	Base[a]	R_3Si[b]	*t* [h]	Yield [%]	*ee* [%][c]
1	**1a**	THF	RT	DIPEA	TMS	6	90	64
2	**1b**	THF	RT	DIPEA	TMS	8	92	52
3	**1c**	THF	RT	DIPEA	TMS	12	92	−29[d]
4[e]	**1a**	THF	RT	DIPEA	TMS	8	85	47
5	**1a**	DME	RT	DIPEA	TMS	12	72	61
6	**1a**	CH_3CN	RT	DIPEA	TMS	12	74	60
7	**1a**	EtCN	RT	DIPEA	TMS	12	83	71
8	**1a**	CH_2Cl_2	RT	DIPEA	TMS	24	49	57
9	**1a**	DMF	RT	DIPEA	TMS	48	56[f]	74[g]
10	**1a**	EtCN	0	DIPEA	TMS	16	80	76
11[h]	**1a**	EtCN	0	DIPEA	TMS	20	81	76
12	**1a**	EtCN	0	K_2CO_3	TMS	16	72	76
13	**1a**	EtCN	0	γ-collidine	TMS	16	65	76
14	**1a**	EtCN	0	pyridine	TMS	30	64	65
15	**1a**	EtCN	0	DIPEA	TES	24	81	74
16	**1a**	EtCN	0	DIPEA	TIPS	30	49	66
17	**1a**	EtCN	0	DIPEA	DMPS	24	66	73
18	**1a**	EtCN	0	DIPEA	MDPS	30	79	73
19	**1a**	EtCN	0	DIPEA	DMS	16	81	80

[a] 30 mol% was used. [b] TES = triethylsilyl, TIPS = triisopropylsilyl, DMPS = dimethylphenylsilyl, MDPS = methyldiphenylsilyl. [c] The *ee* value as determined by HPLC. [d] The minus sign indicates that the enantioselectivity of the reaction was reversed in this case to afford the *S* product. [e] 1-trimethylsilyl-3-chloropropyne was used instead of 1-trimethylsilyl-3-bromopropyne. [f] A mixture of allenic alcohol and homopropargylic alcohol (1.8:1) was obtained and the combined yield is given. [g] The *ee* value of the allenic alcohol as determined from the corresponding α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) ester. The *ee* value of the homopropargylic alcohol was 4%. [h] 4 Å molecular sieves (200 wt%) were added.

As noted above, when DMF was the solvent (Table 1, entry 9), the *ee* value of the allenic alcohol was high (74% *ee*). Consequently, the reaction in the presence of an additive possessing a polar functional group was examined. The additives possessing an oxygen–phosphine bond (Table 2, entries 1–4) or oxygen–sulfur bond (entry 5) had no effect on the enantioselectivity; however, some ureas improved the *ee* value. Thus, the reaction in the presence of DMPU afforded the product in 91% yield with 82% *ee* (entry 6), and the reaction in the presence of DMI gave the best enantioselectivity (entry 7; 97%, 83% *ee*). Other ureas (entries 8–11) did not improve upon the result given in entry 7.

Under the optimized conditions (Table 2, entry 7), various aldehydes were successfully allenylated with high enantioselectivity. *p*-Methoxybenzaldehyde and *p*-chlorobenzaldehyde were allenylated in 90% yield with 80% *ee* (Table 3, entry 1) and in 91% yield with 82% *ee* (entry 2), respectively. Hydrocinnamaldehyde (entry 3; 99%, 72% *ee*), cyclohexyl-

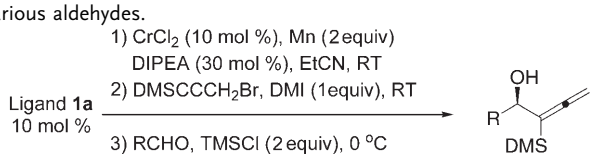
Table 2: Effect of additive on the catalytic asymmetric Nozaki–Hiyama allenylation of benzaldehyde.



Entry	Additive[a] (1 equiv)	*t* [h]	Yield [%]	*ee*[b] [%]
1	HMPA	24	75	76
2	$Ph_3P(O)$	24	69	80
3	$nBu_3P(O)$	36	23	77
4	$(PhO)_3P(O)$	48	20	55
5	DMSO	30	73	79
6	DMPU	24	91	82
7	DMI	24	97	83
8	DMI[c]	36	17[d]	73
9	TMU	48	21[e]	67
10	DEDPU	36	71	75
11	DTBI	16	73	81

[a] HMPA = hexamethyl phosphoramide, DMSO = dimethylsulfoxide, DMPU = *N*,*N*′-dimethylpropylene urea, DMI = 1,3-dimethyl-2-imidazolidinone, TMU = *N*,*N*,*N*′,*N*′-tetramethylurea, DEDPU = *N*,*N*′-diethyl-*N*,*N*′-diphenylurea, DTBI = 1,3-di-*tert*-butyl-2-imidazolidinone. [b] The *ee* value as determined by HPLC. [c] 10 equivalents of DMI were used. [d] A large amount of pinacol coupling product was formed (52% yield). [e] Homopropargylic alcohol was identified by ^{1}H NMR spectroscopy; the ratio of products was allenic alcohol:homopropargylic alcohol = 50:1.

Table 3: Asymmetric catalysis of the Nozaki–Hiyama allenylation of various aldehydes.



Entry	R	*t* [h]	Yield [%]	*ee*[a] [%]
1	*p*-MeOPh	36	90	80
2	*p*-ClPh	24	91	82
3	$PhCH_2CH_2$	24	99	72
4	*c*-C_6H_{11}	24	95	74
5	*n*-C_5H_{11}	24	81	75

[a] The *ee* value as determined by HPLC.

aldehyde (entry 4; 95%, 74% *ee*), and pentanal (entry 5; 81%, 75% *ee*) were also allenylated with good enantioselectivity, thereby revealing the generality of this catalytic asymmetric allenylation.

The absolute configurations of the products were determined by comparing the sign of the specific rotation with known compounds;[19] this disclosed that all the aldehydes showed the same enantioface selectivity. Thus, all the aldehydes were allenylated predominantly at the *si* face.

Compared with the previously reported catalytic asymmetric propargylation,[12a] in which the aldehydes showed *re*-face selectivity (Scheme 1), the enantioface selectivity in the allenylation is reversed. This reversal is well explained, as shown in Figure 1. Thus, since the terminally silylated propargyl group was positioned at the less-hindered apical

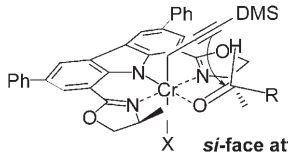
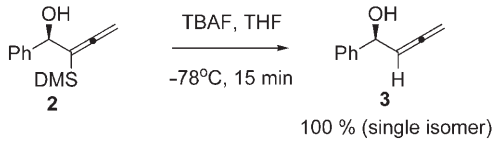


Figure 1. Proposed model for the catalytic asymmetric Nozaki–Hiyama allenylation. DMS = dimethylsilyl.

position of the asymmetric catalyst, the aldehyde coordinated at the equatorial position and was allenylated from the *si* face under the influence of the asymmetric circumstances.

However, several other explanations for the enantioselectivity are possible. For example, the possibilities of the reaction proceeding intermolecularly or the Cr–**1** complex being a dinuclear complex[20] cannot be ruled out. Furthermore, the stereochemical outcome of this allenylation reaction could derive from different chromium complexes. Hence, further studies on the structure of the Cr–**1a** complex and the mechanism of this reaction are in progress.

The product obtained through this asymmetric catalysis would be a good synthetic intermediate because the silyl group can be easily desilylated.[8c] For example, as shown in Scheme 3, the allenylated product **2** was easily desilylated to afford **3** in 100% yield without diminishing the *ee* value.



Scheme 3. Desilylation of the products.

In summary, ligand **1a** was found to realize the catalytic asymmetric allenylation of various aldehydes with high enantioselectivity. To the best of our knowledge, this is the first successful example of the asymmetric catalysis of the Nozaki–Hiyama allenylation. The product obtained from this reaction would be a useful synthetic intermediate because the 2-silylated secondary allenic alcohol can be easily desilylated or can be used as the allenylsilane; hence, we will investigate the utility of this allenic alcohol for the total synthesis of natural products.

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[17] The allenylation of benzaldehyde with 1-bromo-2-butyne was examined under the same conditions as those described in entry 1 of Table 1; however, a mixture of the allenic alcohol and the homopropargylic alcohol was obtained in a ratio of 2.7:1 in 90% combined yield, and the *ee* values were 22 and 14%, respectively.

[18] This change of enantioselectivity has also been observed in the catalytic asymmetric propargylation. For the results and the proposed explanation, see reference [12a].

[19] (*S*)-1-phenyl-2,3-butadien-1-ol: $[\alpha]_D^{26} = +28.7$ ($c = 0.72$, $CHCl_3$) (*R* form:[19a] $[\alpha]_D^{20} = -55.4$ ($c = 0.82$, $CHCl_3$)); (*R*)-1-phenyl-2,3-hexadien-1-ol: $[\alpha]_D^{26} = +3.04$ ($c = 0.77$, $CHCl_3$) (*S* form:[19b] $[\alpha]_D^{23} = -2.4$ ($c = 1.41$, $CHCl_3$)); (*R*)-1,2-nonadien-4-ol: $[\alpha]_D^{26} = -5.00$ ($c = 0.73$, $CHCl_3$) (*S* form:[19c] $[\alpha]_D^{23} = +4.5$ ($c = 0.2$, $CHCl_3$)); (*R*)-1-cyclohexyl-2,3-butadien-1-ol: $[\alpha]_D^{26} = -7.7$ ($c =$ 0.40, benzene) (*S* form:[19b] $[\alpha]_D^{24} = +10.5$ ($c = 1.02$, benzene)); a) C.-M. Yu, C. Kim, J.-H. Kweon, *Chem. Commun.* **2004**, 2494 – 2495; b) K. Iseki, Y. Kuroki, Y. Kobayashi, *Tetrahedron: Asymmetry* **1998**, *9*, 2889 – 2894; c) E. J. Corey, G. B. Jones, *Tetrahedron Lett.* **1991**, *32*, 5713 – 5716. With regard to the products of *p*-methoxybenzaldehyde and *p*-chlorobenzaldehyde, the absolute configurations were determined by analogy because these products showed the same sign (minus) as that of the product of benzaldehyde.

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