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A Chiral Bipyridyl Alcohol for Catalytic Enantioselective Nozaki–Hiyama–Kishi Allylation of Aldehydes and Ketones

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Abstract: A class of bipyridyl alcohol ligands has been developed. A catalyst synthesized using a chromium(II)-ligand promotes the enantioselective Nozaki–Hiyama–Kishi (NHK) allylation of aldehydes and ketones with allylic halides. The allylation of various aromatic, α,β-unsaturated, and aliphatic aldehydes and ketones produces the desired homoallylic alcohols in satisfactory yields (up to 98%) and high enantioselectivities (up to 99% *ee*). The present method can be applied widely and affords an efficient means of obtaining chiral homoallylic alcohols.

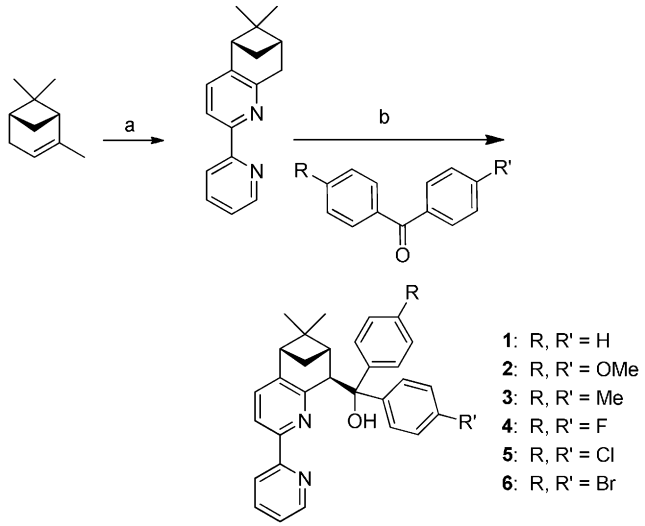
Keywords: asymmetric catalysis; bipyridyl alcohol; chromium catalysis; enantioselectivity; Nozaki–Hiyama–Kishi allylation

The enantioselective allylation of carbonyl functional groups for producing homoallylic alcohols has acquired considerable attention because of the versatility of the products (homoallylic alcohols), which are major building blocks for synthesizing many natural products and pharmaceuticals.[1] The development of asymmetric catalytic processes for obtaining secondary homoallylic alcohols from aldehydes has greatly enhanced the potential of synthesis. However, the catalytic asymmetric allylation of ketones for obtaining enantiopure tertiary homoallylic alcohols is more challenging because of the substantial difference in the reactivity between aldehydes and ketones. Therefore, intensive research has been conducted in this area in recent years, leading to the development of a large and diverse array of chiral catalysts for adding an allyl transfer reagent to carbonyl functional groups.

Cr(II)-mediated C–C bond forming reactions originally developed by Nozaki et al.[2] have been studied extensively because of their potential utility.[3] In addition, these reactions have been applied to synthesize several complex natural products because they exhibit high chemoselectivity and excellent compatibility with various functional groups.[3] Organochromium reagents are easily prepared *in situ* through the oxidative addition of Cr(II) species to allyl, propargyl, aryl, vinyl halides and triflates [requiring catalytic amounts of an Ni(II) salt for sp^2 carbon centers] and can be added to aldehydes to produce the corresponding alcohols in satisfactory yields.[3a,b,4] The major drawback of the original NHK allylation is the requirement for high stoichiometric amounts of Cr(II) salts for the formation of the organochromium nucleophile.[2,5] Fürstner and Shi[6] developed the original NHK allylation which requires only catalytic amounts of active Cr(II) species. Cheap and toxicologically benign Mn is used as the reducing agent and a trialkylchlorosilane affects the perpetuation of the catalytic cycle.

These preliminary improvements have motivated numerous efforts to improve the enantioselectivity of this reaction. Several structurally dissimilar chiral ligands have been used as enantioselective catalysts for the allylation of aldehydes, and this has resulted in various degrees of asymmetric induction.[7] Lately, carbonyl allylation has been extended to ketones.[8] After 2009,[8c] to the best of our knowledge, there has been no report about NHK allylation of ketones. Developing new and effective chiral ligands for the NHK allylation of ketones is extremely complicated and requires a wide screening of chiral ligands.

Our study on chiral bipyridine ligands obtained from enantioenriched pinene revealed satisfactory enantioselectivities in several asymmetric transformations.[9] The successful application of these ligand systems motivated us to screen the NHK allylation of aldehydes and ketones. We posited that manipulating a pineno-bipyridyl alcohol framework plays a crucial role in further improving the catalytic properties, and thus, may afford a promising stereochemical outcome.



Scheme 1. Ligand synthesis: a) ref.[9]; b) LDA, benzophenone, THF, −50 °C.

Pineno-bipyridyl alcohols are readily obtainable from (+)-α-pinene in six steps, which include the stereoselective alkylation of chiral bipyridine with ketones (Scheme 1). X-ray crystallographic analysis of (+)-**1** (Figure 1) verified the general structure of these tridentate N_2O ligands.

Initial evaluation of non-symmetrical bipyridyl alcohol ligands (**1**–**6**) in the Cr(II)-catalyzed addition of allyl bromide to benzaldehyde revealed that the bipyridyl alcohol ligand **1** afforded a satisfactory yield (83%) and excellent enantioselectivity (90%)

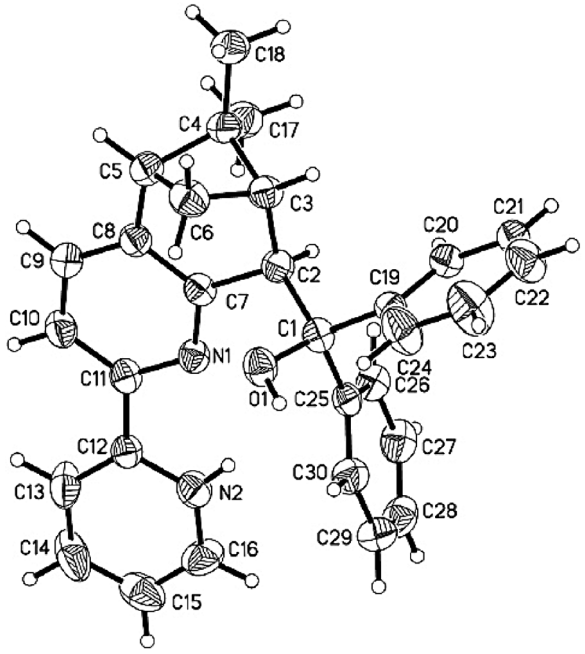
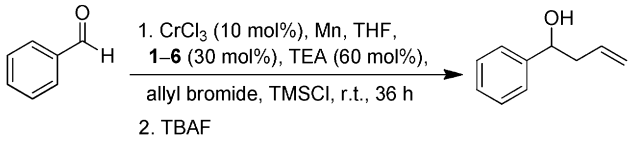


Figure 1. X-ray crystallographic structures of bipyridyl alcohol **1** (CCDC 995407).[10]

Table 1. Optimization of chiral bipyridyl alcohol ligands for the chromium-catalyzed addition of allyl bromide to PhCHO.



Entry	Ligand	Yield [%][a]	*ee* [%][b]	Configuration
1	**1**	83	90	*R*
2	**2**	88	89	*R*
3	**3**	80	85	*R*
4	**4**	87	76	*R*
5	**5**	70	72	*R*
6	**6**	80	74	*R*

[a] Isolated yield.
[b] The *ee* % was determined on a Chiracel OD-H HPLC column.

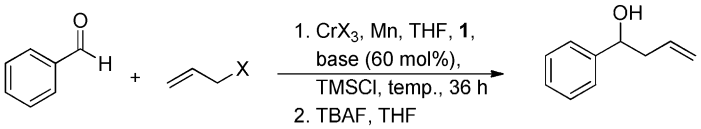
(Table 1, entry 1). Ligands **2** and **3**, bearing an electron-donating group, gave slightly lower enantioselectivities than did their parent ligand **1**. However, ligands **4**–**6**, which contained halogen substituents on the *para*-phenyl group, exhibited satisfactory yields and lower enantioselectivities. The electronic and steric characters of a substituent on the phenyl ring of the ligand had little influence on the enantioselectivity of the reaction (Table 1, entries 2–6).

The allylation of benzaldehyde in the presence of a Cr-**1** catalyst was further optimized with respect to the nature of the solvents at various reaction temperatures and bases, catalyst loadings, and allyl counterparts. Table 2 shows the optimization results. Of all the solvents used, tetrahydrofuran (THF) was the most favorable because it afforded superior yields and enantiomeric excesses (*ee*) (Table 2, entries 1–5). The reaction of benzaldehyde at lower temperatures in the presence of triethylamine (TEA), or after replacing TEA with the Hünig's base or K_2CO_3 did not furnish any beneficial results (Table 2, entries 6–9).

In addition, the amounts of catalyst and $CrCl_3$ were studied to improve the enantioselectivity of the NHK allylation. Reducing the catalyst loading slightly affected the enantioselectivity of the reaction; however, the yields of the allylation were 31% and 80% by using 10 mol% and 20 mol% catalyst, respectively (entries 10 and 11). When $CrCl_3$ and the catalyst loading were reduced to 5 mol% and 10 mol%, respectively, the selectivity and yield of the reaction decreased (entry 12). Conversely, an increase in the amount of the Cr-**1** catalyst to 40 mol% did not increase the enantioselectivity (entry 13).

The active role of different allyl halides in the enantioselective NHK allylation has been investigated. However, the observed enantioselectivity yielded by allyl chloride (83%) was not as high as that yielded

Table 2. Optimization of reaction conditions for Nozaki–Hiyama–Kishi allylation of benzaldehyde.



Entry	Metal	Allyl halide	Solvent	*T* [°C]	Base	Metal [mol%]	Ligand [mol%]	Yield [%][a]	*ee* [%][b]
1	$CrCl_3$	allyl bromide	THF	r.t.	TEA	10	30	83	90
2	$CrCl_3$	allyl bromide	CH_2Cl_2	r.t.	TEA	10	30	27	60
3	$CrCl_3$	allyl bromide	DMF	r.t.	TEA	10	30	20	84
4	$CrCl_3$	allyl bromide	toluene	r.t.	TEA	10	30	NR	–
5	$CrCl_3$	allyl bromide	ether	r.t.	TEA	10	30	NR	–
6	$CrCl_3$	allyl bromide	THF	0	TEA	10	30	76	84
7	$CrCl_3$	allyl bromide	THF	−20	TEA	10	30	83	84
8	$CrCl_3$	allyl bromide	THF	r.t.	DIPA	10	30	84	88
9	$CrCl_3$	allyl bromide	THF	r.t.	K_2CO_3	10	30	73	89
10	$CrCl_3$	allyl bromide	THF	r.t.	TEA	10	10	31	86
11	$CrCl_3$	allyl bromide	THF	r.t.	TEA	10	20	80	88
12	$CrCl_3$	allyl bromide	THF	r.t.	TEA	5	10	43	86
13	$CrCl_3$	allyl bromide	THF	r.t.	TEA	10	40	77	85
14	$CrCl_3$	allyl chloride	THF	r.t.	TEA	10	30	78	83
15	$CrBr_3$	allyl bromide	THF	r.t.	TEA	10	30	74	80
16	$CrBr_3$	allyl chloride	THF	r.t.	TEA	10	30	80	87

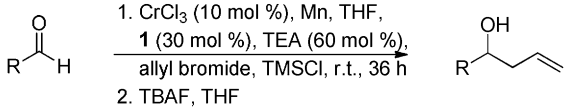
[a] Isolated yield.
[b] Enantiomeric ratio determined by HPLC equipped with a chiral stationary phase.

by allyl bromide (entry 14). We considered that the Cr source may play a significant role in the NHK allylation. The reactions were induced using allyl bromide and allyl chloride in the presence of $CrBr_3$; they yielded an appreciable amount of products with an 80% *ee* and 87% *ee*, respectively (entries 15 and 16).

Considering the optimized reaction conditions, we investigated the generality of the NHK allylation by using various aldehydes. All of the reactions were completed within 36 h, producing adducts with good to excellent yields (51–95%) and enantioselectivities (48–99% *ee*). The position and electronic property of a substituent on the aromatic ring exerted a limited influence on the stereoselectivity of the reaction; (Table 3, entries 2–12), 4-cyanobenzaldehyde was an unsuitable substrate for the transformation (entry 12). Substrates with electron-withdrawing (entries 2–7), electron-donating (entries 8–12), and neutral (entries 1, 13 and 14) in various substitution patterns (*para*, *meta* and *ortho*) participated in this reaction efficiently. Aromatic groups and heteroaromatic groups, such as furyl and thienyl, could be effectively used to afford the respective homoallyl alcohol derivatives with excellent enantioselectivities (entries 15 and 16). Products with excellent enantioselectivities were obtained when aliphatic aldehydes were used; the allylation of cyclohexanecarboxaldehyde afforded the corresponding homoallyl alcohol with a 51% yield and >99% *ee* (entry 18).

After optimizing the reaction parameters for the allylation, we extended the catalytic enantioselective

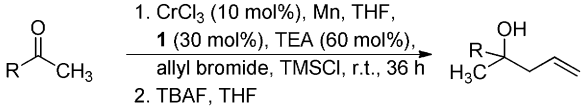
Table 3. Nozaki–Hiyama–Kishi allylation reactions of aldehydes catalyzed by Cr(II)-**1** complexes.



Entry	R	Product	Yield [%][a]	*ee* [%][b]	Configuration[c]
1	Ph	**7**	83	90	*R*
2	2-$CH_3OC_6H_4$	**8**	92	82	*R*
3	3-$CH_3OC_6H_4$	**9**	80	84	*R*
4	4-$CH_3OC_6H_4$	**10**	95	90	*R*
5	2-$CH_3C_6H_4$	**11**	53	92	*R*
6	3-$CH_3C_6H_4$	**12**	78	82	*R*
7	4-$CH_3C_6H_4$	**13**	67	85	*R*
8	2-ClC_6H_4	**14**	94	69	*R*
9	3-ClC_6H_4	**15**	86	83	–
10	4-ClC_6H_4	**16**	79	73	*R*
11	3-CNC_6H_4	**17**	90	76	–
12	4-CNC_6H_4	**18**	55	48	–
13	1-naphthyl	**19**	84	85	*R*
14	2-naphthyl	**20**	95	80	*R*
15	2-furyl	**21**	90	86	*R*
16	2-thienyl	**22**	95	85	*R*
17	*n*-pentyl	**23**	56	90	*R*
18	cyclohexyl	**24**	51	>99[d]	*R*

[a] Isolated yields.
[b] Enantiomeric ratio determined by HPLC equipped with a chiral stationary phase.
[c] Assigned by comparison of the sign of optical rotation with reported value.[7y]
[d] Enantiomeric ratio determined by ^{1}H NMR of Mosher's ester.

Table 4. Nozaki–Hiyama–Kishi allylation reactions of ketones catalyzed by Cr(II)-**1** complexes.



Entry	R	Product	Yield [%][a]	*ee* [%][b]	Configuration[c]
1	Ph	**25**	82	88	*R*
2	3-$CH_3OC_6H_4$	**26**	96	91	–
3	3-$CH_3C_6H_4$	**27**	81	90	*R*
4	3-BrC_6H_4	**28**	98	97	*R*
5	3-CNC_6H_4	**29**	81	91	–
6	3-$CF_3OC_6H_4$	**30**	77	85	*R*
7	2-naphthyl	**31**	88	91	*R*
8	PhCH=CH	**32**	92	67	*R*
9	*n*-butyl	**33**	58	51	*R*

[a] Isolated yields.
[b] Enantiomeric ratio determined by HPLC equipped with a chiral stationary phase.
[c] Assigned by comparison of the sign of optical rotation with reported value.[8c,j]

addition of allylchromium to a selection of ketones. Table 4 shows the results. In all cases, homoallylic alcohols with satisfactory enantioselectivities (up to 97% *ee*) were obtained with aromatic, aliphatic, and aromatic ketones. Aryl ketones were excellent substrates for the transformation; allylation of 1-(2-bromophenyl)ethanone (Table 4, entry 4) afforded the corresponding homoallyl alcohol with a 98% yield and 97% *ee*. Exceptional functional group tolerance was observed when halide-containing compounds were used. The nature of the substituent on the aryl ring weakly affected the enantioselectivity of the reaction (entries 2–6). Moreover, the allylation of 2′-acetonaphthone afforded the corresponding homoallyl alcohol with an 88% yield and 91% *ee*. The allylation of a representative conjugated enone exclusively produced a 1,2-allylation product with a high yield with decreased enantioselectivity (entry 8). The allylation of 2-hexanone, an aliphatic ketone, afforded the corresponding homoallylic alcohol with a moderate yield and 51% *ee* (entry 9).

In conclusion, we demonstrated the high catalytic enantioselective allylation of aldehydes and ketones by using a chiral Cr(II) complex prepared with bipyridine alcohol and $CrCl_3$. Various aldehydes and ketones, including aromatic, heteroaromatic, and aliphatic aldehydes and ketones, afforded homoallylic alcohols with satisfactory yields and excellent enantioselectivities (up to 99% *ee*) for the NHK allylation.

Experimental Section

Ligand Synthesis: (10,10-Dimethyl-5-pyridin-2-yl-6-azatricyclo[7.1.1.$0^{2,7}$]-undeca-2(7),3,5-trien-8-yl)-diphenylmethanol (1)

n-BuLi (3 mL, 4.8 mmol, 1.6 M in hexane) was added to a solution of diisopropylamine (728 μL, 5.2 mmol) in THF (8 mL) at −78 °C, and the solution was stirred for 30 min to produce lithium diisopropylamide (LDA). A solution of bipyridine (1.00 g, 4.0 mmol) in THF (8 mL) was added to the LDA solution and stirred for 2 h to generate a dark blue solution. A solution of benzophenone (800 mg, 4.4 mmol) in THF (8 mL) was added to this dark blue solution and the temperature was slowly raised to room temperature and maintained there for 8 h. The reaction was quenched by adding NH_4Cl solution and the mixture was then extracted with EtOAc. The combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was purified using flash column chromatography involving silica gel as the stationary phase and ethyl acetate-hexane (1:9) as the mobile phase; this procedure produced **1**; yield: 1.20 g (2.77 mmol, 70%). $[\alpha]_D^{20}$: −388° (*c* 1.03, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.86$ (s, 1H), 8.69–8.68 (d, $J = 4.0$ Hz, 1H), 8.27–8.20 (m, 2H), 7.80–7.75 (td, $J_1 = 16.0$ Hz, $J_2 = 1.3$ Hz, 1H), 7.46–7.29 (m, 7H), 7.10 (s, 5H), 4.48 (s, 1H), 2.63–2.57 (m, 2H), 2.11–2.05 (m, 1H), 1.41 (s, 3H), 0.89 (s, 3H), −0.08 to −0.11 (d, $J = 12.0$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 156.8$, 155.3, 151.5, 149.3, 146.9, 145.8, 144.3, 137.2, 135.0, 128.2, 127.9, 127.1, 127.1, 126.5, 123.7, 120.7, 118.8, 81.9, 47.9, 45.8, 43.0, 28.8, 26.4, 21.2; IR (KBr): $\nu = 3861$, 3846, 3831, 3743, 3679, 3655, 3622, 3568, 3153, 3057, 2975, 3947, 2872, 2362, 2355, 1558, 1493, 1465, 1435, 1393, 1337, 1292, 1252, 1218, 1184, 1116, 1087, 1024, 993, 965, 940, 904, 860, 788, 762, 742, 699, 630 cm^{-1}.

General Procedure for the Nozaki–Hiyama–Kishi Reaction

A mixture of $CrCl_3$ (8.0 mg, 0.05 mmol) and Mn (83.0 mg, 1.5 mmol) in THF (1.00 mL) was stirred at room temperature for 1 h, and ligand **1** (64.8 mg, 0.15 mmol) and TEA (42.0 μL, 0.30 mmol) were then added to the solution. After 1 h of stirring at room temperature, allyl bromide (65 μL, 0.75 mmol) was added and the solution was stirred for another 1 h. Aldehydes or ketones (0.5 mmol) and trimethylsilyl chloride (95 μL, 0.75 mmol) were then added and the solution was stirred at room temperature for 36 h. The reaction was quenched by adding a saturated $NaHCO_3$ solution (5 mL), and the solid residue was removed by filtration through a plug of celite. The filtrate was extracted with EtOAc (3×10 mL), and the combined extracts were dried over $MgSO_4$. After the filtration and concentration of the organic phase, the residue was dissolved in THF (2 mL). Tetra-*n*-butylammonium fluoride (2.0 mL, 2.0 mmol, 1 M in THF) was added slowly, and the solution was stirred for 15 min. The reaction was quenched by adding water (3 mL), and the aqueous phase was extracted with EtOAc (3× 5 mL). The combined extracts were dried over $MgSO_4$. After the filtration and concentration of the organic phase, the residue was purified through flash column chromatography by using silica gel as the stationary phase and ethyl ace-

tate-hexane (1:19) as the mobile phase to obtain the corresponding homoallyl alcohols (**7**–**33**). The enantiomeric excess was determined using high-performance liquid chromatography with a chiral column (Chiralcel OD-H or OJ column, flow rate: 0.25 mL/min).

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[10] CCDC 995407 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

A Chiral Bipyridyl Alcohol for Catalytic Enantioselective Nozaki–Hiyama–Kishi Allylation of Aldehydes and Ketones

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