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Catalytic Enantioselective Nozaki−Hiyama Allylation Reaction with Tethered Bis(8-quinolinolato) (TBOx) Chromium Complex

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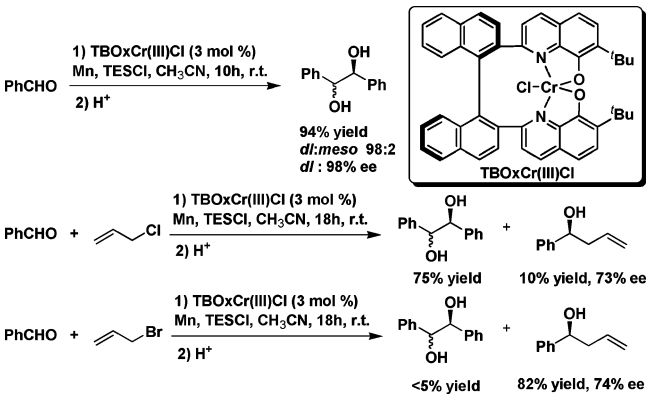
The addition of organochromium compounds to aldehydes, known as the Nozaki−Hiyama (NH) reaction,[1] has proven to be a powerful C−C bond formation method by virtue of its high chemo- and stereoselectivity and ease of the reaction under mild conditions.[2] Catalytic asymmetric NH methodologies have been recognized as important and effective methods and environmentally friendly processes for the synthesis of chiral homoallylic alcohols. Although there have been a limited number of reports on asymmetric catalysis of these reactions,[3] the enantioselectivities, yields, and the scope of the substrates were not satisfactory.[3,4] Herein, we report this catalytic, highly enantioselective NH allylation reaction.

We earlier developed and synthesized a new chiral tethered bis-(8-quinolinolato) (TBOx) chromium catalyst and applied it to the highly enantio- and diastereoselective pinacol coupling reaction of aldehydes.[5] This successful catalytic redox system was then applied to the NH allylation reaction between benzaldehyde and allylchloride. Competitive reactions between the pinacol coupling reaction and the NH allylation reaction were observed. The desired homoallylic alcohol was obtained as minor product with 10% yield and 73% ee. Fortunately, once the more reactive allylbromide was applied to the reaction with benzaldehyde, the homoallylic alcohol from the NH allylation reaction turned out to be the major product with 82% yield and 74% ee (Scheme 1).

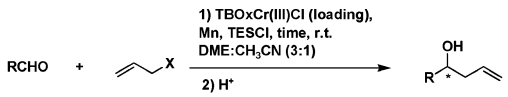
Scheme 1

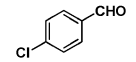
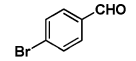
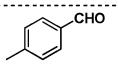
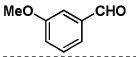
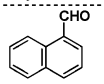
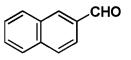
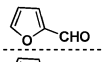
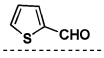
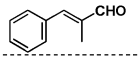
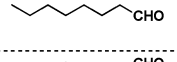
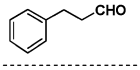
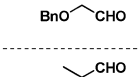


After carefully optimizing the experimental parameters, the following general reaction procedure was established. First, TBOxCr-(III)Cl (3 mol %) and Mn were mixed in CH_3CN:DME (1:3) under an atmosphere of Ar at room temperature. After 10 min, to the reaction mixture was added allylbromide, and the mixture was stirred for 30 min. Then, benzaldehyde and TESCl were added successively and slowly.[6] After the indicated reaction time, the isolated crude product was treated with 1 N HCl to afford the homoallylic alcohol with 93% yield and 98% ee (entry 3, Table 1).

As shown in Table 1, the catalyst loading could be decreased to 1 mol % while maintaining good yields and enantioselectivities (entries 2 and 15). Even when 0.5 mol % catalyst was used for the reaction between benzaldehyde and allylbromide, (*R*)-1-phenylbut-3-en-1-ol in 75% yield with 86% ee was afforded (entry 1). By using 10 mol % catalyst, 99% ee for benzaldehyde (entry 4) and 98% ee for cyclohexanecarboxaldehyde (entry 18) with good yields

Table 1. Nozaki−Hiyama Allylation Reactions of Aldehydes Catalyzed by TBOxCr(III)Cl



entry	RCHO	X	loading (mol %)	time (h)	yield[a] (%)	ee[b] (%) (config.)[c]
1		Br	0.5	48	75	86 (*R*)
2		Br	1	24	91	96 (*R*)
3		Br	3	18	93	98 (*R*)
4		Br	10	8	95	99 (*R*)
5		Br	3	18	93	95 (*R*)
6		Br	3	18	93	95 (*R*)
7[d]		Br	3	24	91	96 (*R*)
8[d]		Br	3	24	83	93 (*R*)
9		Br	3	24	81	97 (*R*)
10		Br	3	24	81	93 (*R*)
11		Br	3	24	88	95 (*R*)
12[e]		Br	3	18	86	97 (*R*)
13[e]		Br	3	18	87	95 (*R*)
14[e]		Br	3	18	89	96 (*R*)
15		Br	1	40	79	96 (*R*)
16		Br	3	40	90	98 (*R*)
17		Cl	3	40	68	98 (*R*)
18		Br	10	24	88	98 (*R*)
19		Br	3	40	89	97 (*S*)
20		Cl	3	40	76	98 (*S*)
21		Br	3	18	81	97 (*S*)
22		Cl	3	24	79	97 (*S*)
23		Br	3	24	81	94 (*R*)
24		Cl	3	40	77	95 (*R*)
25[e]		Br	3	40	68	97[f] (*R*)
26[e]		Cl	3	60	54	98[f] (*R*)

[a] Isolated yield after chromatographic purification. [b] Enantiomeric excess was determined by chiral HPLC analysis. [c] Assigned by comparison of the sign of optical rotation with reported value. [d] CH_3CN:toluene (1:1) was used as solvent. [e] Crude products were treated with TBAF in THF. [f] Enantiomeric excess was determined by ^{19}F NMR of the corresponding MTPA ester.

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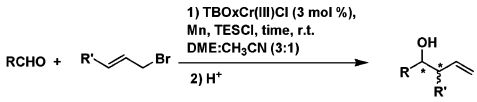
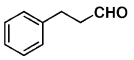
Table 2. TBOxCr(III)Cl-Catalyzed Addition of Other Allylic Bromides to Aldehydes



entry	RCHO	R'	time (h)	yield[a] (%)	*anti*:*syn*[b]	ee(%)[c] *anti* / *syn*
1[e]		CH_3	36	84	4.4:1	97 / 97
2[d,e]		CH_3	36	76	5.5:1	95 / 96
3[d]		n-C_3H_7	48	71	8.4:1	91 / 91
4[d]		n-C_5H_{11}	60	65	10.3:1	90 / 87
5		CH_3	60	73	6.3:1	96 / 97
6[f]		CH_3	36	88	4.2:1	94 / 94

[a] Isolated yield of a mixture of *anti* and *syn* product after chromatographic purification. [b] Determined by ^{1}H NMR of crude product. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] $EtOCH_2CH_2OEt$ was used as solvent instead of DME. [e] The absolute configuration of the major *anti* isomer was determined to be *R*,*R*.[7] [f] The absolute configuration of the major *anti* isomer was determined to be *S*,*R*.[8]

were obtained. Because aliphatic aldehydes are not as reactive as aromatic aldehydes, the pinacol coupling reactions of aliphatic aldehydes are slower. Due to this, not only allylbromide (entries 16, 19, 21, 23, and 25) but also allylchloride (entries 17, 20, 22, 24, and 26) could be applied to the NH allylation reaction of different aliphatic aldehydes to afford homoallylic alcohols in good yields and good enantioselectivities, albeit with longer reaction time. The present catalyst system proved to be quite tolerable to changes in steric effect (entries 8 and 10 in comparison to 3, entries 25 and 26 in comparison to 16) and in electron density effect (entries 5 and 6 for electron-withdrawing groups, entries 7−9 for electron-donating groups in comparison to 3). We achieved good yields and over 95% ee with other aryl aldehydes as well (entries 11−13). Additionally, an α,β-unsaturated aldehyde also proved to be a good substrate (entry 14).

To further explore the substrate scope, more allylic bromides were used in the NH allylation of aldehydes. Surprisingly, the observed diastereoselectivity of the crotylation of benzaldehyde was high with a 4.4:1 ratio favoring *anti*-product in 84% yield with 97% ee for both *anti* and *syn* forms (entry 1, Table 2). The crotylation of cyclohexanecarboxaldehyde gave out the homoallylic alcohols with a 6.3:1 ratio of *anti* to *syn* in 73% yield with 96% ee (*anti* form) and 97% ee (*syn* form) (entry 5). When the size of R was decreased, lower diastereoselectivities were observed with higher yield and similar enantioselectivities (entry 6 in comparison to 5). More interestingly, when the size of R′ was increased, higher diastereoselectivities were observed with only a slight decrease of yields and enantioselectivities (entries 3 and 4 in comparison to 2). To the best of our knowledge, the observed diastereoselectivities and the enantiomeric excesses for each diastereomer of those aldehydes are the highest to date in an asymmetric crotylation using a Cr(II)-based system.[3g,m]

In summary, TBOxCr(III)Cl was shown to efficiently catalyze the asymmetric NH allylation reaction of both aromatic and aliphatic aldehydes. (1) Excellent enantioselectivities (up to 99% ee) for the NH allylation reaction of aldehydes were obtained.[9] (2) The lowest catalyst/substrate ratio (0.5 mol %) for an asymmetric catalytic NH allylation reaction was achieved.[10] (3) Crotylation of benzaldehyde led to a 5.5:1 ratio of *anti* to *syn* and >95% ee for both diastereomers.[11] Studies are currently underway to elucidate the mechanism.[12] Furthermore, the applications of TBOx in other asymmetric catalysis will be reported in due course.

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Supporting Information Available: Experimental procedures, 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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(6) By replacing TESCl with TMSCl or $PhMe_2SiCl$, homoallylic alcohol with lower yield and lower enantiomeric excesses was obtained.

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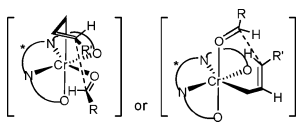
(9) For example, refs 3g and 3m (90 and 94% ee for PhCHO, respectively) in comparison to entry 4 in Table 1 (99% ee for PhCHO); refs 3g and 3m (93 and 89% ee for c-$C_6H_{11}CHO$, respectively) in comparison to entry 18 in Table 1 (98% ee for c-$C_6H_{11}CHO$).

(10) For example, ref 3g (10 mol % $CrCl_3$ and 30 mol % chiral ligand) and ref 3m (5 mol % $CrCl_3$ and 10 mol % chiral ligand) in comparison to entry 1 in Table 1 (0.5 mol % TBOxCr(III)Cl).

(11) For example, ref 3m (2.3:1 ratio favoring *anti*-product with 91% ee for the *anti* form and 95% ee for the *syn* form) in comparison to entries 1 and 2 in Table 2.

(12) The reaction proceeds through *cis*-β chromium complex via the possible transition structures shown below.



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