Asymmetric Catalysis

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First Regio- and Enantioselective Chromium-Catalyzed Homoallenylation of Aldehydes**

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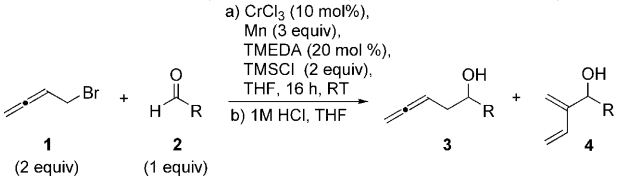
In memory of Jean-Pierre Finet

Metal-mediated allylation and allenylation are powerful transformations in organic synthesis.[1,2] In particular, the generation of enantiomerically enriched homoallylic and allenic alcohols is a thriving area because of the importance of these building blocks in the synthesis of biologically active natural products and pharmaceutical drugs.[3,4] Whereas many successful methods have been described for carbonyl allylation and allenylation, metal-catalyzed homoallenylation of carbonyl compounds has been scarcely reported despite the widespread utility of β-allenols as structural units.[5] Most of the non-asymmetric homoallenylations of carbonyl compounds reported to date require tedious preparation of the starting materials and suffer from drawbacks such as the lack of chemoselectivity or regioselectivity, which lowers the synthetic appeal of this reaction.[6] In addition, to the best of our knowledge, the regio- and enantioselective metal-catalyzed homoallenylation of aldehydes has not been reported. As part of our ongoing research into the development[7] and application[8] of chiral ligands to the enantioselective Nozaki–Hiyama–Kishi (NHK) reaction, we report herein the first regio- and enantioselective NHK homoallenylation of aldehydes.

The NHK reaction,[9] first reported in the late 1970s, has become an important and versatile carbon–carbon bond-forming process which has been widely applied in total synthesis.[10] Its unique and important features prompted us to consider the NHK reaction as a method to develop an efficient and regioselective homoallenylation of aldehydes. Hence, we surmised that the readily available homoallenyl bromide **1** would generate β-allenol **3** using chromium-mediated catalysis.[11] Because of the lack of a method allowing non-asymmetric homoallenylation of aldehydes, we first investigated the synthesis of racemic β-allenols through the addition of homoallenyl bromide **1** to aldehydes **2** using the $CrCl_3$ (10 mol%)/Mn (3 equiv) in the presence of TMSCl (Table 1). After screening of solvents, temperatures, and ligands, the best reaction conditions included THF as the solvent and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) as the ligand (20 mol%), leading to a mixture of alcohols **3**/**4** wherein **3** was the major product.[12] Under these optimized conditions, a range of aromatic and aliphatic aldehydes were successfully homoallenylated to give pure β-allenols **3** after careful purification by column chromatography (Table 1).

Table 1: Chromium-catalyzed homoallenylation of various aldehydes.



1 (2 equiv) **2** (1 equiv) **3** **4**

Entry	R	**3**/**4**[a]	Product	Yield [%][b]
1	C_6H_5	77:23	**3a**	45
2	1-naphthyl	75:25	**3b**	48
3	*p*-ClC_6H_4	85:15	**3c**	50
4	*m*-ClC_6H_4	86:14	**3d**	55
5	(*E*)-PhCH=CH	69:31	**3e**	25
6	$PhCH_2CH_2$	70:30	**3f**	32
7	*c*-C_6H_{11}	74:26	**3g**	20

[a] Ratio **3**/**4** was determined by ^{1}H NMR spectroscopy of the crude product after workup. [b] Yield of isolated β-allenol **3** after careful purification. TMS = trimethylsilyl.

Similar levels of regioselectivity were obtained regardless of the aldehyde (Table 1). β-Allenols **3** were obtained in moderate to good yields with aromatic aldehydes (Table 1, entries 1–4), and the use of *trans*-cinnamaldehyde or aliphatic aldehydes led to a decrease in product yields (Table 1, entries 5–7). The best result was obtained with *meta*-chlorobenzaldehyde leading to pure β-allenol **3d** in 55% yield with an 86:14 ratio of **3**/**4** (Table 1, entry 4). With a racemic method in hand, we decided to explore the asymmetric variant using a chiral ligand to access enantioenriched β-allenols.[13] For this purpose, the ligand has to fulfill certain criteria to allow an efficient asymmetric homoallenylation: the chromium(III)–ligand intermediate has to be reactive with a wide range of

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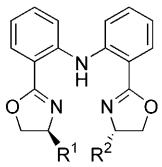
aldehydes (aromatic and aliphatic), and regioselectively and enantioselectively deliver the desired β-allenols **3**.

We recently reported the straightforward synthesis of tridentate C_2- and non-C_2-symmetric bis(oxazoline) ligands **5a–f** and their successful application to the enantioselective NHK allylation, crotylation, and methallylation of aldehydes (Figure 1).[7,8] Because of the high diastereo- and enantioselectivities induced by these tridentate ligands, we envisioned that **5a–f** could satisfy the above criteria.

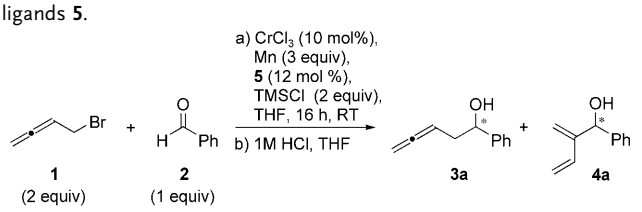


5a : $R^1 = R^2 = t$Bu
5b : R^1 = Ph, R^2 = Bn
5c : $R^1 = t$Bu, R^2 = Ph
5d : $R^1 = R^2 = i$Pr
5e : $R^1 = t$Bu, R^2 = Bn
5f : $R^1 = t$Bu, $R^2 = i$Pr
5g : $R^1 = R^2$ = H

Figure 1. Tridentate bis(oxazoline) ligands **5**.

By using the reaction conditions described previously with THF as the solvent,[8a] ligands **5** were investigated in the chromium-mediated homoallenylation of benzaldehyde with homoallenyl bromide **1** (Table 2). The results show a dramatic

Table 2: Chromium-catalyzed homoallenylation of benzaldehyde using ligands **5**.



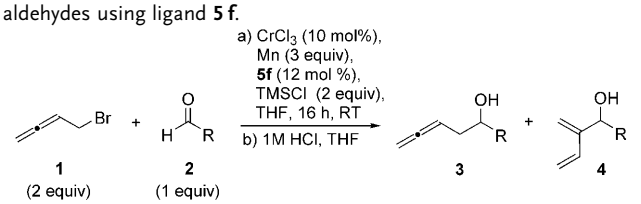
Entry	Ligand	**3a**/**4a**[a]	Conv. [%][b]	Yield **3a** [%][c]	*ee* [%] (Config.)[d]
1	**5a**	71:29	80	39	8 (*S*)
2	**5b**	74:26	93	33	11 (*R*)
3	**5c**	84:16	85	40	49 (*R*)
4	**5d**	100:0	35	16	84 (*R*)
5	**5e**	100:0	45	23	91 (*R*)
6	**5f**	100:0	87	51	96 (*R*)
7	**5g**	69:31	83	43	–

[a] Ratio **3a**/**4a** was determined by ^{1}H NMR spectroscopy of the crude product after workup. [b] Conversion of substrates into alcohols **3a** and **4a** was determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [c] Yield of isolated product after careful purification. [d] The *ee* value was determined by chiral HPLC methods and the absolute configuration of the alcohol was assigned by a modified Mosher's method (see the Supporting Information).

influence of the oxazoline substitution pattern upon the reactivity, regioselectivity, as well as the extent of asymmetric induction of this reaction. Homoallenylation using ligands **5a–c** proceeded in high conversions but with moderate regioselectivities and low *ee* values (Table 2, entries 1–3). At this point, we were pleased to observe that ligands **5d–f** allowed the formation of β-allenol **3a** as the only product with good to excellent enantioselectivities (Table 2, entries 4–6). The best result was obtained with the *tert*-butyl/isopropyl ligand **5f**, which afforded only the desired β-allenol **3a** in a 51% yield in favor of the *R* enantiomer in 96% *ee* (Table 2, entry 6). This is the same sense of induction as previously observed for the allylation, methallylation, and crotylation of benzaldehyde using **5f** as the ligand.[8] These results also represent one of the few examples in the literature where non-symmetric bis(oxazoline) ligands are used to induce high enantioselectivity in an asymmetric process.[8,14] Furthermore, the importance of the oxazoline substitution pattern is underlined by the homoallenylation of benzaldehyde using the unsubstituted ligand **5g** (Table 2, entry 7) which led to a mixture of alcohols **3a** and **4a** (**3a**/**4a** 69:31).

The chromium-catalyzed addition of homoallenyl bromide **1** using the optimal ligand **5f** was then used with other aldehydic substrates (Table 3). The yields (40–73%) and

Table 3: Asymmetric chromium-catalyzed homoallenylation of various aldehydes using ligand **5f**.

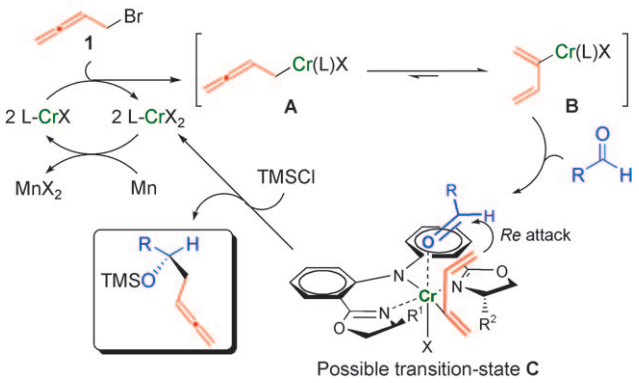


Entry	R	**3**/**4**[a]	Product	Yield [%][b]	*ee* [%] (Config.)[c]
1	C_6H_5	100:0	**3a**	51	96 (*R*)
2	1-naphthyl	97:3	**3b**	50[d]	92 (*R*)
3	*p*-ClC_6H_4	100:0	**3c**	53	91 (*R*)
4	*m*-ClC_6H_4	100:0	**3d**	63	98 (*R*)
5	*p*-$MeOC_6H_4$	100:0	**3h**	40	95 (*R*)
6	*p*-$MeSC_6H_4$	100:0	**3i**	50	93 (*R*)
7	3-furyl	100:0	**3j**	49	87 (*R*)
8	(*E*)-PhCH=CH	100:0	**3e**	58	96 (*R*)
9	$PhCH_2CH_2$	100:0	**3f**	50	95 (*S*)[e]
10	*c*-C_6H_{11}	100:0	**3g**	73	60 (*S*)[e]

[a] The ratio **3**/**4** was determined by ^{1}H NMR spectroscopy of the crude product after workup. [b] Yield of isolated product after purification. [c] The *ee* value was determined by chiral HPLC methods and the absolute configuration of the alcohol was assigned by a modified Mosher's method or by comparison of the specific rotation to literature values (see the Supporting Information). [d] Obtained as a 97:3 mixture of **3**/**4**. [e] Same sense of induction as entries 1–8.

regioselectivities obtained for both aromatic and aliphatic aldehydes were similar to those with benzaldehyde. In terms of enantiodiscrimination, the reaction of **1** with aromatic and heteroaromatic aldehydes gave rise to (*R*)-β-allenols **3** with excellent enantiomeric excesses regardless of the substitution on the aromatic ring in **2** (Table 3, entries 1–7).[15] As in the case of aromatic aldehydes, the homoallenylation of *trans*-cinnamaldehyde and 3-phenylpropanal furnished the desired β-allenols **3e** and **3f**, respectively, with excellent enantioselectivities (Table 3, entries 8 and 9), and the chiral β-allenol **3g** derived from cyclohexanecarboxaldehyde was obtained with good enantiocontrol (Table 3, entry 10).

On the basis of the above results, a plausible mechanism for the catalytic asymmetric homoallenylation of aldehydes using ligand **5 f** (L) is shown in Scheme 1. We propose that the homoallenyl bromide **1** reacts with two equivalents of the



Scheme 1. Possible mechanism for the chromium-mediated homoallenylation ($R^1 = i$Pr, $R^2 = t$Bu).

ligand–chromium complex (L–CrX) to form the organochromium(III) reagents **A** and **B** and one equivalent of L–CrX_2 complex, similar to the catalytic cycle outlined by Fürstner and Shi.[16] The regioselectivity of this addition may be explained by a rapid equilibration of the homoallenyl and 1,3-butadien-2-yl chromium(III) intermediates **A** and **B**. The 1,3-butadien-2-yl chromium(III) species **B** is more favored and is proposed to add to the aldehyde via transition state **C**. In this transition state, the 1,3-butadien-2-yl moiety would be bonded to chromium in the equatorial position while the aldehyde would coordinate at the apical position through an *anti* geometry to minimize the steric interactions between the R group and the oxazoline ring.[17] Therefore, *Re*-face attack should be favored through this transition state. Notably, a mechanism involving a dinuclear complex or proceeding through an intermolecular pathway cannot be ruled out at this stage.[18]

In summary, we have disclosed the first regio- and enantioselective homoallenylation of aldehydes using the chiral ligand **5 f**. A noteworthy feature of this reaction is the excellent level of regioselectivity for the addition of the chromium(III) intermediate to give only the desired β-allenol in most cases. In the future, this novel reaction should allow access to a wide range of chiral β-allenols of considerable synthetic interest. Applications as well as a detailed study of the mechanism are underway and will be reported in due course.

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[15] Notably, homoallenylation of 4-methoxybenzaldehyde, 4-methylthiobenzaldehyde, and 3-furaldehyde (Table 3, entries 5–7) using ligand **5f** gave rise to (*R*)-β-allenols **3** in 40–50% yields while the use of TMEDA as a ligand led to low conversions (<10%) of the same substrates into alcohols **3** and **4**.

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