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Fe/Cr- and Co/Cr-Mediated Catalytic Asymmetric 2-Haloallylations of Aldehydes

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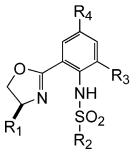
In connection with our efforts to develop a practical synthesis of the marine natural product halicondrin B and its analogues, we reported a synthesis of the C14−C26 segment by using Ni/Cr- and Co/Cr-mediated catalytic asymmetric coupling reactions (Scheme 1).[1] We have realized the possibility that the C14−C19 building block could be obtained through a catalytic asymmetric 2-haloallylation (see the reaction highlighted by a box in Scheme 1). Otera reported that 2-bromoallylation of aldehydes with 2,3-dibromopropene is effectively achieved by using Sn/HBr.[2] However, no method is known to synthesize 3-halohomoallylic alcohols in a catalytic asymmetric manner.[3] In this communication, we report Fe/Cr- and Co/Cr-mediated catalytic asymmetric 2-haloallylations of aldehydes.

We reported that sulfonamides such as **1a**,**b** are effective in Ni/Cr- and Co/Cr-mediated catalytic asymmetric vinylation and alkylation reactions in a catalytic asymmetric manner.[1] To achieve Cr-mediated asymmetric haloallylation reactions, we first screened the sulfonamide ligands for the coupling of heptanal (**3a**) with allyl bromide (**2a**) under the reaction conditions using (1) a Cr-ligand complex (10 mol %) generated from a sulfonamide and $CrCl_3$•3THF in the presence of Et_3N and Mn and (2) TMSCl as a chromium−alkoxide dissociating reagent.[4] Through this screening, it became evident that a sulfonamide with R_3 = H is far superior to the corresponding sulfonamide with R_3 = Me (cf, **1c** vs **1a**). We then optimized the ligand **1c**, from which three excellent sulfonamides **1d**−**f** emerged.[5] However, as **1d** can be synthesized in two steps from commercially available inexpensive 2-aminobenzonitrile, we used **1d** for further studies. Interestingly, an addition of 2,6-lutidine was found to improve asymmetric inductions significantly.[6] Under the optimized conditions, the allylation of **3a** with **2a** gave the corresponding homoallylic alcohol **4a** in 93% yield with 93% enantiomeric excess (ee) in the presence of 10 mol % of the catalyst (Entry 1 in Table 1). It is worthwhile noting that a satisfactory result was obtained even with 4 mol % of the catalyst (85% yield, 93% ee).[7]



1a : R_1=*i*-Pr, R_2=Me, R_3=Me, R_4=H
1b : R_1=*t*-Bu, R_2=2-naphthyl, R_3=Me, R_4=H

1c : R_1=*i*-Pr, R_2=Me, R_3=H, R_4=H
1d : R_1=*t*-Bu, R_2=Bn, R_3=H, R_4=H
1e : R_1=*t*-Bu, R_2=Bn, R_3=H, R_4=Me
1f : R_1=*t*-Bu, R_2=Bn, R_3=H, R_4=*n*-Bu

The optimized conditions were then applied to γ,γ-dimethylallyl bromide (**2b**) and methallyl bromide (X = Br in **2c**). The rate of catalytic allylation with γ-substituted allyl bromides was not noticeably different from that observed for allyl bromide.[8] On the contrary, the rate with β-substituted allyl bromides was significantly decreased compared to that of allyl bromide. For example, the catalytic allylation with methallyl bromide under the conditions developed for **2a** proceeded but sluggishly (ca. 30% conversion after 48 h). However, the coupling reaction was completed within 12 h using methallyl iodide (**2c**) (entry 4).

Scheme 1

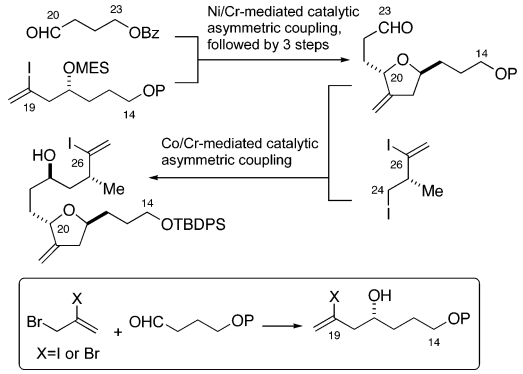
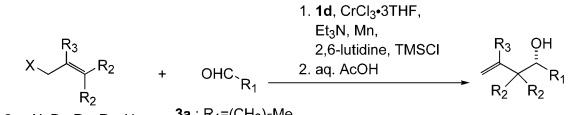


Table 1. Catalytic Asymmetric Allylations of Aldehydes[a]



2a : X=Br, R_2=R_3=H
2b : X=Br, R_2=Me, R_3=H
2c : X=I, R_2=H, R_3=Me

3a : R_1=$(CH_2)_5$Me
3b : R_1=$(CH_2)_3$O-TBDPS

4a : R_1=$(CH_2)_5$Me, R_2=R_3=H
4b : R_1=$(CH_2)_3$O-TBDPS, R_2=R_3=H
4c : R_1=$(CH_2)_3$O-TBDPS, R_2=Me, R_3=H
4d : R_1=$(CH_2)_3$O-TBDPS, R_2=H, R_3=Me

Entry	2a~c + 3a,b ⟶	4a~d	*ee* (%)[b]	yield (%)
1	**2a** **3a**	**4a**	93	93
2	**2a** **3b**	**4b**	92	90
3	**2b** **3b**	**4c**	94	94
4	**2c** **3b**	**4d**	93	91[c]

[a] All reactions were done with 10 mol% of the catalyst at 0 °C. [b] *Ee* of the products was established by ^{1}H-NMR analysis of its Mosher ester. [c] The reaction completed within 12 h.

We then investigated catalytic asymmetric 2-haloallylation. Disappointingly, under the optimized conditions given in Table 1, 2,3-dibromopropene (**5a**) did not give the desired products. The reactivity of **5a** against the reducing metals was electronically and sterically attenuated by the bromine at the β-position. To enhance the reactivity of the ligand **1d**−Cr complex, we attempted to replace $CrCl_3$ with $CrBr_3$.[9] However, due to its extremely poor solubility in THF, $CrBr_3$ remained unchanged in the presence of **1d**, Mn, and Et_3N even at 70 °C. Interestingly, in the presence of iron tris-(2,2,6,6-tetramethyl-3,5-heptanedione) ($Fe(TMHD)_3$),[10] $CrBr_3$ was reduced to a low-valent Cr species and formed a complex with the ligand **1d**.[11] Gratifyingly, 2-bromoallylation of **6a** with **5a** in the presence of 10 mol % of the complex (generated from **1d**, $Fe(TMHD)_3$, $CrBr_3$, Mn, and Et_3N (all in THF) and TMSCl and 2,6-lutidine) afforded, after selective TMS-desilylation, the desired product **7a** in 75% yield with 93% ee (entry 1 in Table 2). Even with 5 mol % of the catalyst, the 2-bromoallylation smoothly proceeded to give the desired product in 70% with 92% ee. The same reaction of a functionalized aldehyde **6b** gave an equally satisfactory result (entry 2). In demonstrating the applicability of

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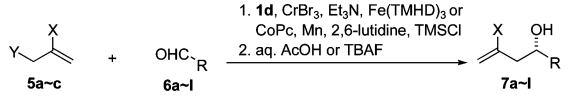
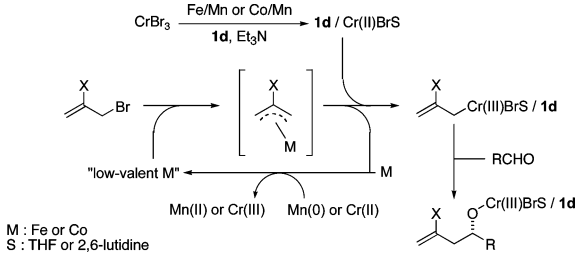
Table 2. Catalytic Asymmetric 2-Haloallylations[a]



Entry	5a~c	+	6a~l	→	7a~l	yield	ee[e]
1[b,f]	**5a**: X=Y=Br		**6a**: R=$(CH_2)_5Me$[i]		**7a**: X=Br, R=$(CH_2)_5Me$	75%	93%
2[b]	**5a**: X=Y=Br		**6b**: R=$(CH_2)_3O$-TBDPS[i]		**7b**: X=Br, R=$(CH_2)_3O$-TBDPS	75	92
3[b]	**5a**: X=Y=Br		**6c**: R=$(CH_2)_3O$-TBS		**7c**: X=Br, R=$(CH_2)_3O$-TBS	60	91
4[b]	**5a**: X=Y=Br		**6d**: R=$(CH_2)_2CH(SEt)_2$		**7d**: X=Br, R=$(CH_2)_2CH(SEt)_2$	70	90
5[b]	**5a**: X=Y=Br		**6e**: R=cyclohexyl		**7e**: X=Br, R=cyclohexyl	70	90
6[b]	**5a**: X=Y=Br		**6f**: R=CH=CH$(CH_2)_2Me$[g]		**7f**: X=Br, R=CH=CH$(CH_2)_2Me$	75	87
7[b]	**5a**: X=Y=Br		**6g**: R=CH=CHPh		**7g**:X=Br, R=CH=CHPh	75	83
8[b]	**5a**: X=Y=Br		**6h**: R=Ph		**7h**: X=Br, R=Ph	86	84
9[b,f]	**5b**: X=I, Y=Br		**6b**: R=$(CH_2)_3O$-TBDPS		**7i**: X=I, R=$(CH_2)_3O$-TBDPS	50	93
10[c]	**5b**: X=I, Y=Br		**6b**: R=$(CH_2)_3O$-TBDPS		**7j**: X=I, R=$(CH_2)_3O$-TBDPS	63	93
11[b]	**5c**: X=Cl, Y=Br		**6b**: R=$(CH_2)_3O$-TBDPS		**7k**: X=Cl, R=$(CH_2)_3O$-TBDPS	45[h]	90
12[d]	**5c**: X=Cl, Y=Br		**6b**: R=$(CH_2)_3O$-TBDPS		**7l**: X=Cl, R=$(CH_2)_3O$-TBDPS	90	90

[a] All reactions were done with 10 mol% of the catalyst at 0 °C. [b] $Fe(TMHD)_3$ was used. [c] Co(Pc) was used. [d] This reaction was done under the conditions specified in Table 1. [e] ee of the product was established by chiral HPLC analysis or by ^1H NMR analysis of its Mosher ester. [f] For determination of absolute chemistry, see Supporting Information. [g] Trans isomer. [h] The aldehyde was not completely consumed. [i] **6a** = **3a** (in Table 1), **6b** = **3b**.

Scheme 2. Proposed Mechanism for the Fe/Cr- or Co/Cr-Mediated Reactions



these reaction conditions for other functionalized aldehydes, we noticed that 2,6-lutidine not only improves the enatioselectivity (vide ante) but also acts as an acid scavenger. In the absence of 2,6-lutidine, 2-bromoallylation of the TBS-protected aldehyde **6c** gave the product accompanied with a significant amount of the diol, whereas in the presence of 2,6-lutidine the 2-bromoallylation reaction gave the expected product **7c** without contamination of the TBS-deprotected byproduct (entry 3). The applicability of these reactions was tested for several additional types of aldehydes. As summarized in Table 2, saturated and α-branched aldehydes gave 90% or better ee's (entries 1−5). However, α,β-unsaturated and aromatic aldehydes gave slightly lower ee (83−87%) (entries 6−8).

We then applied the conditions developed for 2-bromoallylation to 2-iodoallylation and were pleased to observe that 2-iodo-3-bromopropene (**5b**) gave the expected product with good enantioselectivity (entry 9). However, its chemical yield was only modest.[12] We wished to improve its overall efficiency. In this regard, we noticed that an active chromium−bromide complex can be formed via cobalt phthalocyanine (CoPc) and that the Co/Cr-mediated system enhanced the reaction rate.[13] Gratifyingly, the Co/Cr-mediated reaction was very effective in the 2-iodoallylation of **6b** with **5b** (entry 10). On the contrary, 2-chloroallylation is best achieved with 2-chloro-3-bromopropene (**5c**) under the $CrCl_3$·3THF conditions given in Table 1 (entry 12).

Mechanistically, the Fe/Cr- and Co/Cr-mediated 2-halo-allylations might involve sequences of steps depicted in Scheme 2. Both low-valent Co and Fe species are known to facilitate radical formation from alkyl halides.[13,14] The bromine or iodine at the β-position appears to play an important role in forming and/or stabilizing the allyl radical generated in the Fe/Cr/Mn- or Co/Cr/Mn-multimetallic system.[15] On the other hand, the **1d**/Cr(II) complex is formed from Fe(III) or Co(II)/$CrBr_3$/**1d**/Mn/Et_3N (vide ante). A transmetalation between the **1d**/Cr(II) complex and the metalloallyl species should result in the **1d**/allyl-Cr(III) complex which is identical (except for a difference in the allyl vs vinyl) to the complex suggested for the catalytic Ni/Cr-mediated couplings.[1] This complex would then undergo the addition to aldehydes through a six-centered transition state.[16]

In conclusion, we have developed a novel Fe/Cr- and Co/Cr-mediated 2-haloallylation that allows, for the first time, aldehydes and 2-haloallyl halides to couple in a catalytic asymmetric manner. The coupling reactions are operationally simple and scalable and furnish products with a synthetically useful level of enantiomeric excess. This method will provide direct and economical access to valuable synthetic intermediates.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. *J. Org. Chem.* **1984**, *49*, 172.

(3) For a stoichiometric enantioselective synthesis of bromohomoallylic alcohols with the chiral borane and 2-bromoallyltributyltin reagents, see: Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495.

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(5) The ligands **1e** and **1f** gave a slightly better asymmetric induction than **1d**, but the difference was insignificant.

(6) Other amines including pyridine, 2,6-di-*tert*-butylpyridine, quinoline, and acridine were found to be ineffective in improving ee. The exact role of 2,6-lutidine is not clear at this time.

(7) For Cr-mediated catalytic asymmetric allylations, see: (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Morganti, S,; Umani-Ronchi, A. *Org. Lett.* **2001**, *3*, 1153. (b) Bandini, M.; Cozzi, P. G.; Umani-Ronchi, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 2327. (c) Inoue, M.; Suzuki, T.; Nakada, M. *J. Am. Chem. Soc*. **2003**, *125*, 1140.

(8) Catalytic allylation completed within 12 h with crotyl bromide, prenyl bromide (entry 3 in Table 1), and 1,3-dibromopropene.

(9) We expected that $CrBr_3$ would exhibit higher reduction potential than $CrCl_3$. For a similar concept for Ti species, see: Mukaiyama, T.; Kagayama, A.; Igarashi, K. *Chem. Lett.* **2000**, 336. In addition, we expected that $CrBr_3$ and $CrCl_3$ might behave differently due to the difference in their Lewis acidity.

(10) $Fe(DBM)_3$ was also found to be equally effective.

(11) The progress of the complex formation could be monitored by a change of solution color that turned into dark green.

(12) The iodoallylation reactions between **6b** and **5b** (2.5 equiv) under the conditions of Otera[2] gave the expected product but in poor yield (~10%).

(13) Co/Cr-Mediated 2-bromoallylation of **6b** was significantly faster than the corresponding Fe/Cr-mediated 2-bromoallylation with a lower ee (89%).

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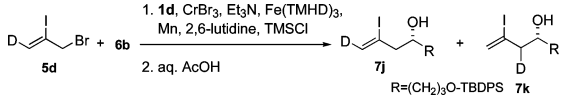
(15) The Fe/Cr mediated iodoallylation of **6b** with **5d** affored a 1:2.6 mixture of **7j** and **7k**, thereby indicating that a metallotropic rearragement takes place. However, the observed product ratio may suggest that this metallo allyl species is not completely symmetrized before the C−C bond-formation. Because Cr-mediated allylation reactions are known to go through a six-membered cyclic transition state,[16] this observation may suggest that Fe facilitates the oxidative addition of **5d**.



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