THE NOZAKI-HIYAMA-KISHI REACTION

Reported by Jeffrey M. Kallemeyn December 4, 2002

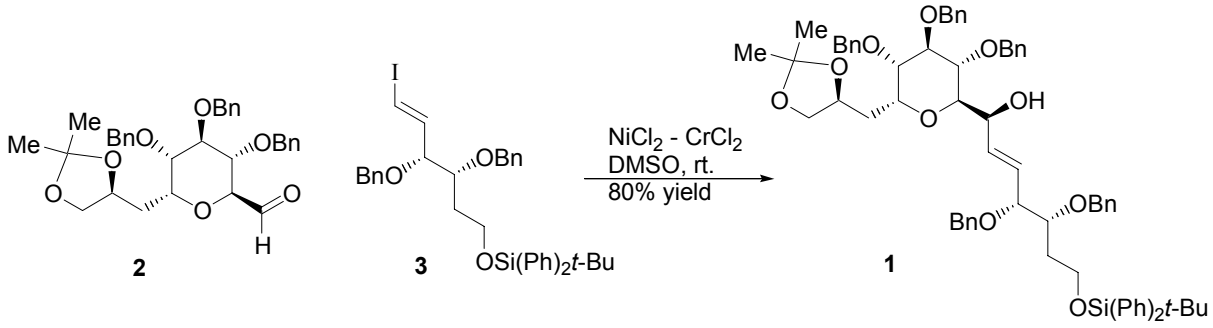
INTRODUCTION

The formation of carbon-carbon bonds is one of the most widely studied areas in organic synthesis. One class of carbon-carbon bond forming reactions involves the nucleophilic addition of vinyl or allyl organometallics to aldehydes, yielding allylic or homoallylic alcohols. A number of strong nucleophiles, such as lithium, magnesium, and copper organometallics, as well as weaker nucleophiles, such as silicon and boron organometallics, have been used for these bond formations.[1,2,3] The poor chemoselectivity and stereochemical predictability of these allyl and vinyl organometallics often limit their use in natural products synthesis, restricting their role to early synthetic steps where functionality is typically limited. It would be desirable to have a reliably predictable and highly chemoselective method for the formation of allyic and homoallylic alcohols that could be used in late synthetic steps.

Herein, organochromium-mediated allyl and vinyl additions to aldehydes are described. These transformations, commonly known as the Nozaki-Hiyama-Kishi (NHK) reaction, are very mild, give predictable stereochemical outcomes and show exceptional chemoselectivity. The NHK reaction is tolerant of functional group diversity on both the organochromium species as well as on the aldehyde, resulting in its wide utility in complex natural product synthesis. One example that highlights these attributes is the synthesis of palytoxin (Equation 1).[4,5]

During the synthesis of the marine natural product palytoxin, Kishi and coworkers envisioned the formation of the *trans*-allylic benzoate **1** as a key intermediate. Attempts to synthesize **1** from aldehyde **2** via Wittig and aldol reactions were unsuccessful. Cuprate couplings showed promise in model studies, but the required cuprate reagent could not be formed from the *trans*-iodoolefin **3**. Reaction of components **2** and **3** via a vinyl organochromium addition allowed for the synthesis of **1** in 80% yield with a 1.3:1 diastereomeric ratio (Equation 1). Compatibility of the organochromium reagent with ketals, ethers and silyl ethers is evident in this synthesis.

Equation 1.



KEY FEATURES OF THE NHK REACTION

Studies on Vinylation

The first vinyl organochromium additions to aldehydes were shown by Nozaki and Hiyama in 1983.[6] Various substitution patterns on the alkene gave minimal changes in reactivity. Esters, amides, nitriles, ketones, acyls, acetals, ketals, ethers, silyl ethers, alcohols and olefins were found to be stable under these conditions, making this reaction chemoselective for aldehydes. Vinyl organochromium reagents could also be formed in the presence of aldehydes from vinyl iodides, bromides and triflates, thus enabling the reaction to be used in an intramolecular sense.[7] Alkynyl halides could also be used to give propargyl alcohols.[8]

In early studies, a strong dependence on the source of chromium was noted, with different batches giving either good conversion or no conversion. Concurrently, both Kishi[4] and Nozaki[7] determined this batch dependence to be a result of trace amounts of nickel (II) present in commercially available chromium. Doping the chromium source with catalytic nickel (II) gave reproducible results in all cases. At least two equivalents of chromium (II) are required to reduce nickel (II) to the active nickel (0) species (Figure 1) which is believed to undergo an oxidative addition to the vinyl halide. Subsiquent transmetallation of the vinyl nickel (II) leads to the vinyl chromium (III) species. It is important to control the amount of nickel in the reaction to minimize formation of homocoupling products between vinyl organonickel species.[4] Addition of 4-*t*-butyl pyridine was found to minimize homocoupling, allowing the use of higher nickel loadings that result in faster reactions.[9] Formation of the thermodynamically stable chromium (III) alkoxide is believed to drive the reaction to completion.[7]

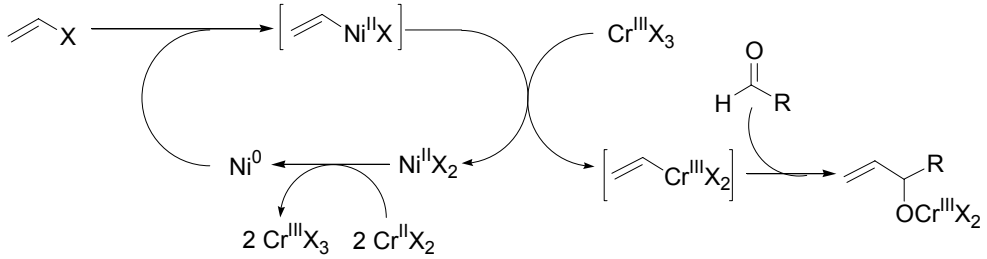


Figure 1. Proposed Catalytic Cycle for Nickel.

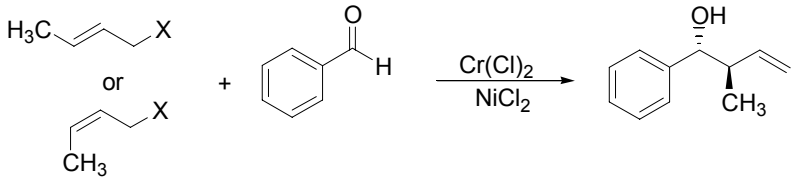
Reactions using di-substituted alkenes give stereochemical retention about the double bond, whereas tri-substituted alkenes give only the trans-products, regardless of the initial alkene geometry.[6] In contrast to cuprate and Grignard additions, vinyl organochromium reagents do not add to aldehydes under chelation control but add to the opposite face of the aldehyde, as predicted by a Felkin-Ahn model.

Studies on Allyllation

Allylic halides are also used in the NHK reaction producing homoallylic alcohols. Crotyl organochromium reagents surprisingly give anti addition products in a stereoconvergent manner.[10] For

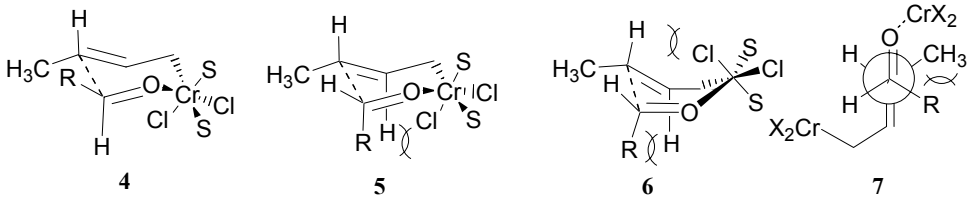
example, both (*E*) and (*Z*)-crotyl organochromium reagents add to benzaldehyde to give only the anti product (Equation 2). Due to the lability of the halogen bond, allylic halides undergo a facile oxidative insertion to chromium (II), yielding the allyl organochromium (III) reagent via disportionation. Thus, nickel is not required for this reaction. A mechanism proceeding through an acyl radical has also been proposed.[2]

Equation 2.



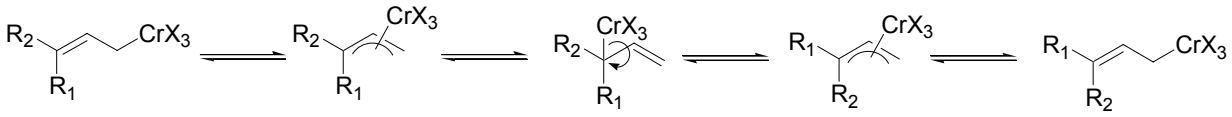
Formation of anti products through γ-addition is rationalized by the Zimmerman-Traxler transition state,[11] with coordination of the aldehyde to the chromium (III).[12] Possible transitions states are shown in Chart 1. Chair conformation **4**, which leads to the anti products, is preferred over the chair conformation **5** due to steric interations between the R group and ligands on the chromium. Analysis of the possible boat conformation **6** and open conformation **7** leading to anti products show that these transition states are not operating due to severe steric interactions.

Chart 1. Possible Transition States.



The stereoconvergence results from isomerization of the allyl organochromium reagent through a π-allyl complex, followed by bond rotation (Scheme 1). When γ,γ-disubsituted allyl halides are used, the reaction is stereodivergent presumably because isomerization is slowed by the increased steric hindrance involved in the rotation of the terminal alkene.[13]

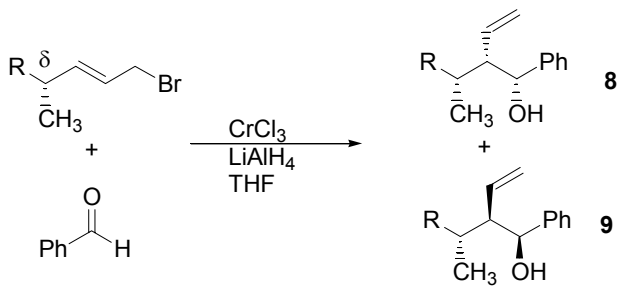
Scheme 1.



The effect of incorporating stereocenters in crotyl halides has been well studied by Mulzer and coworkers.[14,15] The δ stereocenter has a strong directing influence on the diastereoselectivity (Scheme 2, Entry 1), whereas the ε and ζ stereocenters magnify the effect of the δ stereocenter (Entries 2 and 3), leading to a preference for the formation of the syn product **8** over the anti product **9**. The observed products arise from a Felkin-Ahn transition state. The increased diastereoselectivity arises from

increased steric bulk from ε and ζ stereocenters. Studies have also shown the effect of stereocenters adjacent to the β-allyic carbon, resulting in 1,4 stereocontrol.

Scheme 2.



Entry	R	8: 9
1	BnO	82: 18
2	BnO, OBn, ε	91: 9
3	O, O, OBn, ζ, ε	96: 4

Double stereodifferentiation experiments were studied in which stereocenters are present on both crotyl halide and aldehyde. If only a δ stereocenter is present, high diastereomeric ratios were observed for the "matched" case, whereas the "mismatched" cases gave very poor diastereoselctivites. For crotyl halides with δ and ε stereocenters, high diastereomeric ratios were observed for both "matched" and "mismatched" cases. This shows that the crotyl δ-sterecenter inducts the stereochemical information through the reaction and that in cases where additional stereocenters are present, the stereochemistry of the aldehyde can be overridden.

Reaction of propargyl organochromium reagents with aldehydes gives a mixture of allenic alcohols and homopropargyl alcohols, depending on the reaction conditions.[16] Knochel and coworkers[17] have developed conditions that favor the formation of allenic alcohols, with regioselectivities greater than 96:4. Alkyl chlorides, nitriles and esters were shown to be compatible with organochromium reagents, but not with other organometallic species.

CATALYTIC METHODS

Development of a process that is catalytic in chromium would reduce the amount of potentially toxic chromium waste. Several obstacles needed to be overcome before a catalytic cycle could be realized. The chromium (III) needs to be released from the product and then reduced to chromium (II) in order to complete the catalytic cycle.

The first NHK reaction catalytic in chromium was described by Fürstner and Shi.[18] The release of the chromium (III) from the product was facilitated by the use of trimethylsilyl halide (Figure 2). This silicon reagent is more oxophilic than the chromium and thus provides the silyl ether product. However, a competition between chromium and silicon for the product was still observed at low chromium loadings, requiring that 7-15 mol% of chromium be used. The chromium (III) could then be

reduced to chromium (II) by addition of a co-reductant; manganese (0) was suitable for reducing the chromium without effecting the reaction (Figure 2).

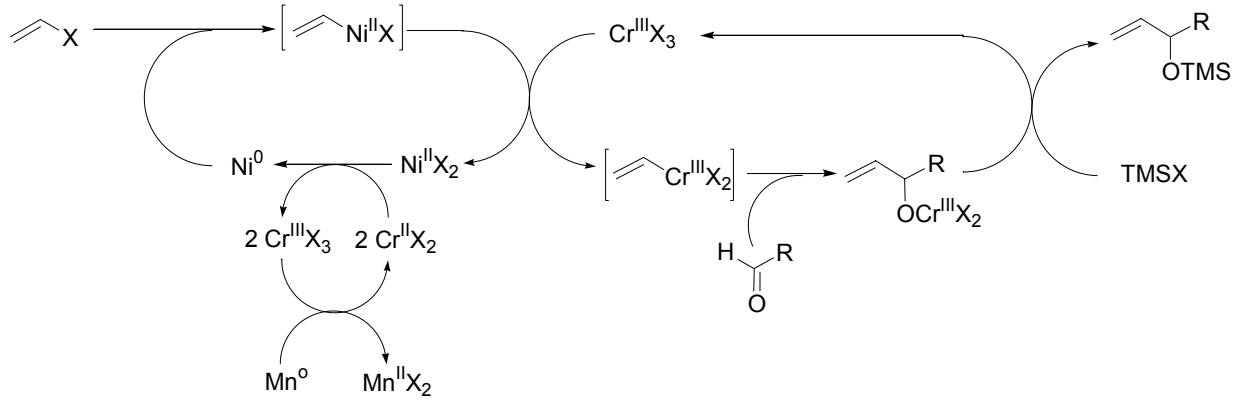


Figure 2. Chromium Catalytic Cycle.

The catalytic system gives allylations and vinylations in comparable yields and selectivities to the stoichiometric conditions. The ability to start with either chromium (II) or chromium (III) is a validation of the catalytic cycle. Cyclopentadienyl chromium species can be used in loadings as low as 1 mol%, most likely due to an increased turnover in the presence of trimethylsilyl chloride; however, decreased diastereoselectivities are observed.

ENANTIOSELECTIVE METHODS

The previous methods for the stereoselective addition of the organochromium reagent to aldehydes have all depended on substrate control. To provide selectivity in systems that do not have resident stereocenters or other control elements, it would be desirable to develop a reagent-controlled addition process. One major obstacle to this objective is that in the presence of strongly donating ligands, such as phosphines, the chromium has been shown to switch from σ-bound to π-bound form, a transformation which is believed to erode any stereoinduction by the ligands

Early approaches to enantioselective NHK reactions were developed using stoichiometric chromium. Several equivalents of the ligand are required to coordinate to the 2 equivalents of chromium. The use of a chiral bipyrdine ligand **10** gave a moderate increase in enatioselctivity.[19] For achiral aldehydes, enantiomeric ratios of 3.1:1 for vinyl additions and 6.7:1 for allyl additions were observed. The chiral ligands were found to be successful in increasing the diastereoselectivity of chrial electrophiles. In the synthesis of halichondrin, the influence of an α-stereocenter on the aldehyde increased the diastereomeric ratio from 1.3:1 without the chiral ligand, to 10:1 with the chiral ligand.

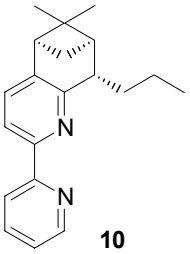
Another approach relies upon the use of chiral alcohols.[20] The optimum ligand in this class was found to be a proline derivative **11**, two equivalents of which are thought to bind to the chromium.

Reaction of this species with aromatic aldehydes and allyl halides gave enantiomeric ratios between 7-99:1, with yields of 43-84%. Unfortunately, no crotyl halides were used, so syn:anti ratios, which would give information about the nature of the transition state, are not available.

The most recent enantioselective NHK reactions build upon Fürstner's catalytic method and have the distinct advantage of using only a catalytic amount of chiral ligand. The first report of this type was by Cozzi and coworkers,[21] who used a chromium-salen catalyst **12** to obtain enantiomeric ratio between 71:29 and 92:8 for allyl chlorides and bromides. Interestingly, crotyl bromide addition results in the syn diastereomer, most likely arising from an open transition state.

Kishi has recently described the use of an oxazoline ligand **13** for enantioselective vinyl addition, in both stoichoimetric and catalytic systems.[22,23,24] X-ray crystallography showed that the ligand chelates to the chromium as a tridentate ligand. This gives a chromium (III) species that is almost a perfect octrahedron. The reaction is believed to proceed on two adjacent coordination sites, and possibly through a closed transition state that would give the desired anti selectivity for crotyl halides. However, no examples using a crotyl halide were used.

Chart 2. Chiral ligands



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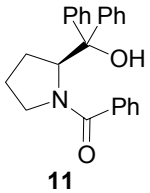

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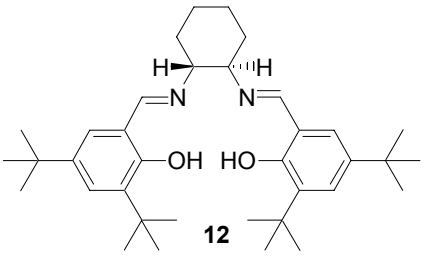

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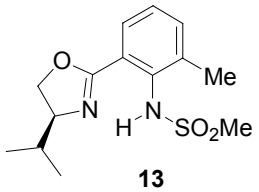


13

To date, only a limited number of enantioselective methods have been developed, each of which suffers from moderate yields and enantiomeric ratios. The development of new enantioselective methods based on catalytic systems is needed to increase the practicality of the NHK reaction. Currently, substrate control based on the propagation of existing stereocenters is the only effective method for stereoselective NHK reactions.

APPLICATIONS IN TOTAL SYNTHESIS

The NHK reaction has been applied many times in total synthesis. It has found particular use in late stage synthesis where chemoselectivity is particularly valued. In order to highlight the NHK reaction, Kishi used vinyl chromium additions five times in the synthesis of halichondrin B.[22,25] Each of these disconnections are shown in Figure 3.

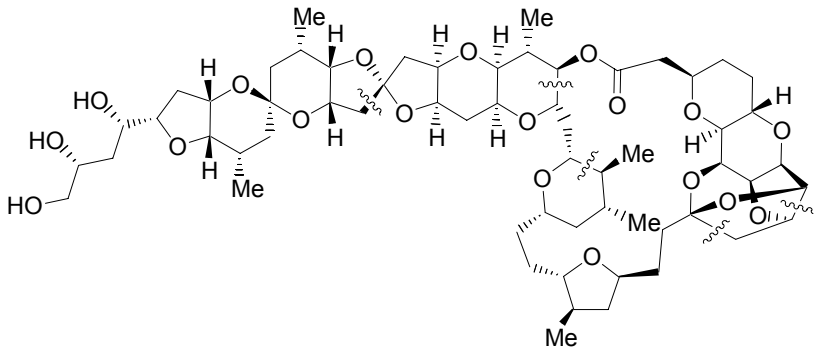
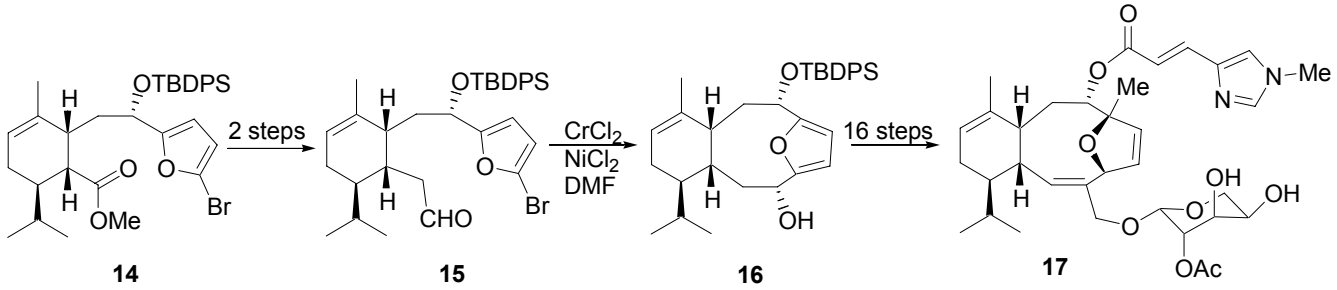


Figure 3. Halichondrin B.

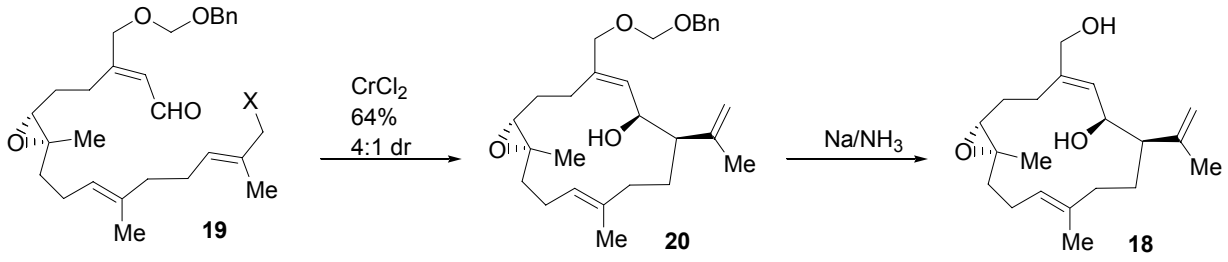
Natural product synthesis has also relied upon the NHK reaction to effect the desired transformation where related approaches fail. In the total synthesis of eleutherobin by Danishefsky and co-workers[26] (Scheme 3), several attempts to form the macrocyclic alkene in **17** via Wittig couplings failed. Free radical cyclization, lithiation induced cyclization or samarium diiodide reductive cyclization of aldehyde **15** also failed. By contrast, the intramolecular NHK reaction was used to give alcohol **16** in 74% yield and in a 15:1 diastereomeric ratio favoring the desired alcohol. Further manipulation of **16** gave eleutherobin (**17)**.

Scheme 3.



The synthesis of asperdiol **18**, a cembrandoid antitumor agent, by Still and coworkers highlights the NHK allylation (Scheme 4).[27] Cyclization of an advanced intermediate **19** using allylsilanes (X= SiR_3), allylstannanes (X= SnR_3) or reactive organometallics (X= Br) failed to give macrocycle **20**. NHK cyclization of allyl halide **19** gave the homoallylic alcohol **20** in 64% yield as a 4:1 mixture of anti-diastereomers. Conformational modeling gave no evidence as to why **20** is the favored diastereomer, but it is believed to be formed through a less strained conformation. Apserdiol (**18)** was obtained by deprotection of **20**.

Scheme 4.



CONCLUSION

As highlighted in the previous examples, the NHK reaction is a very mild and highly chemoselective method for forming carbon-carbon bonds, which makes it attractive for use in late stages of the synthesis of complex, multifunctionalized molecules. Functional group compatibility has been demonstrated with esters, amides, nitriles, ketones, acyls, acetals, ketals, ethers, silyl ethers, alcohols and olefins. An additional advantage to this method is that the vinyl or allyl halide can be activated in the presence of the aldehyde, allowing for this method to be used for intramolecular cyclizations. Although catalytic methods have been described, no practical catalytic enantioselective methods are available to date. This should be a focus of research in the coming years. Nevertheless, as shown by the many applications of this method, the NHK reaction, even it its present form, is very useful in total synthesis.

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