

# Selective Activation/Coupling of Polyhalogenated Nucleophiles in Ni/Cr-Mediated Reactions: Synthesis of C1–C19 Building Block of Halichondrin Bs

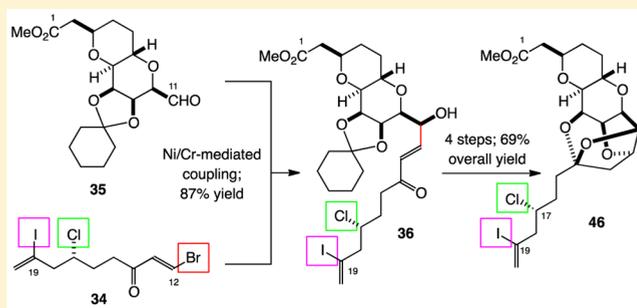
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**S** Supporting Information

**ABSTRACT:** The C1–C19 building block **46** of halichondrin Bs was synthesized via a selective activation/coupling of  $\beta$ -bromoeneone **34** with aldehyde **35** in a Ni/Cr-mediated reaction. The first phase of study was a method development to effect a coupling of a “naked” vinylogous anion with an aldehyde. The study with the coupling of **9** + **10**  $\rightarrow$  **11** revealed: (1)  $\beta$ -bromoeneone **9b** is a better nucleophile than the corresponding  $\beta$ -iodo- and  $\beta$ -chloroeneones **9a,c**; (2)  $(\text{Me})_2\text{Phen}(\text{OMe})_2\cdot\text{NiCl}_2$  **13b** is a better Ni-catalyst than  $(\text{Me})_2\text{Phen}(\text{H})_2\cdot\text{NiCl}_2$  **13a**; and (3) a low Ni-catalyst loading, for example, 0.05–0.1 mol % Ni-catalyst against 10 mol % Cr-catalyst, is crucial for an effective coupling. The second phase

of study was a method development to realize a selective activation/coupling of polyhalogenated nucleophiles such as **34**. The competition experiment of **10** + **9b** over **10** + **31a–c** revealed: (1)  $(\text{Me})_2\text{Phen}(\text{OMe})_2\cdot\text{NiCl}_2$  **13b** is more effective than  $(\text{Me})_2\text{Phen}(\text{H})_2\cdot\text{NiCl}_2$  **13a** for the required selective activation/coupling; (2) a low Ni-catalyst loading, for example, 0.05–0.1 mol % Ni-catalyst against 10 mol % Cr-catalyst, is crucial for discriminating  $\beta$ -bromoeneone **9b** from the three types of vinyl iodides **31a–c**. The third phase of study was an application of the developed method to execute the proposed coupling of **34** + **35**  $\rightarrow$  **36**. For this application, a polyether-type Ni-catalyst **37c**, readily soluble in the reaction medium, was introduced to achieve the selective activation/coupling with higher efficiency. With use of ion-exchange resin-based device, the coupling product **36** was transformed to the C1–C19 building block **46** of halichondrin Bs without purification/separation of the intermediates.



## INTRODUCTION

In conjunction with the ongoing research aimed at a unified total synthesis of the halichondrin class of marine natural products, we have been interested in a possibility of synthesizing the C1–C19 building block of halichondrin Bs via a coupling of **A** with **B**, because of its high degree of convergence (Scheme 1).<sup>1–4</sup> To execute this plan, we have realized that it is necessary to overcome two major obstacles: (1) how to achieve a selective activation of the  $\beta$ -haloeneone over the vinyl iodide, as well as the saturated chloride, present in the nucleophile and (2) how to realize an effective carbonyl addition of a “naked” vinylogous acyl anion to an aldehyde, see the structure in the bracket in Scheme 1. Based on the considerations given in the following sections, we have felt that a Ni/Cr-mediated coupling reaction could achieve this crucial C–C bond formation. In this paper, we report that, through extensive method-development efforts, it has become possible to achieve the proposed C–C bond formation at a synthetically useful level, thereby allowing us to achieve a convergent and practical synthesis of the C1–C19 building block of halichondrin Bs.

## RESULTS AND DISCUSSION

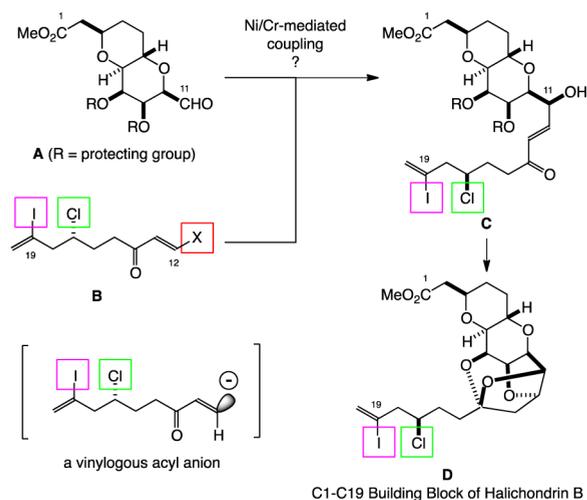
### General Notes on Cr-Mediated Coupling Reactions.

Cr-mediated couplings of organic halides/triflates with aldehydes belong to a class of 1,2-carbonyl addition reactions. In this process, the active nucleophiles  $\text{RCrX}_2$  are generated from halides/triflates *in situ*. Depending on the modes of activation, Cr-mediated couplings are divided into three subgroups: (1) Ni/Cr-mediated alkenylation, alkynylation and arylation; (2) Co or Fe/Cr-mediated alkylation, 2-haloallylation and (propargylation); and (3) Cr-mediated allylation and propargylation.<sup>5</sup>

Ni/Cr-mediated couplings of alkenyl halides/triflates with aldehydes were originally reported by Takai, Hiyama, Nozaki, and co-workers in 1983.<sup>6</sup> Since then, it was shown that the coupling was initiated by a catalytic amount of  $\text{NiCl}_2$  contaminated in  $\text{CrCl}_2$ .<sup>7</sup> It is now generally accepted that this coupling involves: (1) oxidative addition of Ni(0), formed from  $\text{NiCl}_2$  via reduction with  $\text{CrCl}_2$  *in situ*, to an alkenyl halide/triflate to form an alkenyl Ni(II)-species; (2) transmetalation of the resultant Ni(II)-species to Cr(II) $\text{Cl}_2$  to form alkenyl

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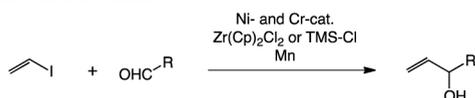
### Scheme 1. New Approach To Synthesize the C1–C19 Building Block in Halichondrin B



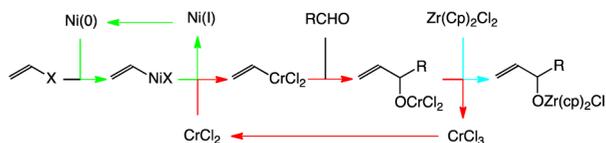
Cr(III)-species; and (3) carbonyl addition of the resultant Cr(III)-species to an aldehyde to form the product Cr(III)-alkoxide (Scheme 2). The chemistry has been developed to achieve this coupling in a catalytic, asymmetric manner.<sup>8</sup>

### Scheme 2. Catalytic Ni/Cr-Mediated Coupling Reactions: (A) Overall Transformation and (B) Ni- and Cr-Catalytic Cycles<sup>a</sup>

#### A: Overall Transformation



#### B: Ni- and Cr-Catalytic Cycles



<sup>a</sup>Zr(Cp)<sub>2</sub>Cl<sub>2</sub> or TMS-Cl is used to dissociate the product from Cr-species, to regenerate the Cr-catalyst.

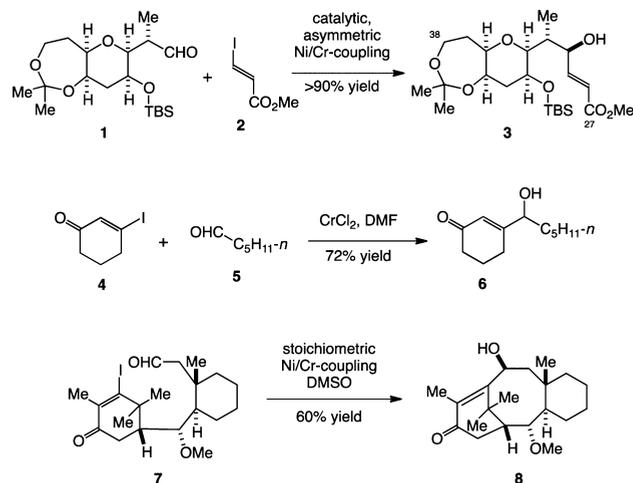
As mentioned, this bond-forming process is a Grignard-type carbonyl addition reaction. However, it is noteworthy that this reaction displays a remarkable selectivity toward aldehydes over other carbonyl compounds. Activation of halides/triflates in the presence of aldehydes provides not only an experimental convenience but also an opportunity to achieve chemical transformations in an unconventional manner, i.e., cyclization. Undoubtedly, the most valuable feature of this coupling is its exceptional compatibility with a wide range of functional groups. This unique potential is appreciated most when applied to polyfunctional molecules. Indeed, there are numerous examples in which this bond-forming process has been used at a late-stage in a multistep synthesis.

#### Coupling Efficiency of $\beta$ -Haloenones with Aldehydes.

The success of the proposed synthesis of C1–C19 building block **D** relies on a C–C bond formation between aldehyde **A** with a vinyllogous acyl anion generated from  $\beta$ -haloenone **B**. There are several methods reported for C–C bond formation between “masked” vinyllogous acyl anions and aldehydes.<sup>9,10</sup> To

the contrary, a literature search has revealed that only a handful of examples are known for C–C bond formation between “naked” vinyllogous acyl anions and aldehydes. Scheme 3 gives

### Scheme 3. Three Examples Relevant to the Proposed Coupling

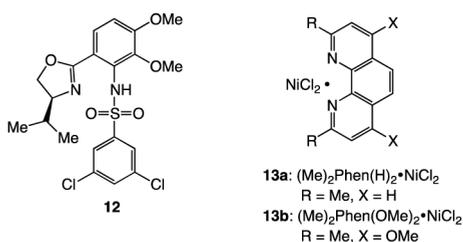
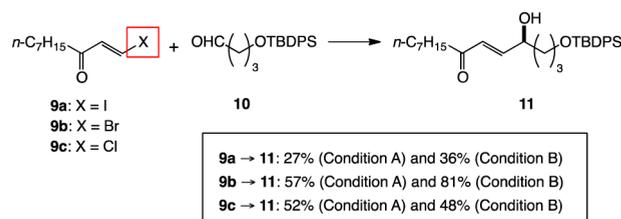


three relevant examples. In 1992, we reported a coupling reaction between methyl  $\beta$ -iodoacrylate **2** and aldehyde **1**, which allowed us effectively to form the C29–C30 bond of halichondrin. Since then, we improved the original stoichiometric, nonasymmetric reaction to the catalytic, asymmetric version.<sup>11</sup> Knochel and Rao disclosed a coupling of  $\beta$ -iodocyclohexenone **4** with aldehydes in the presence of CrCl<sub>2</sub> in DMF.<sup>12</sup> In connection with the synthetic efforts on the taxane class of natural products, we used the Ni/Cr-mediated coupling reaction to construct the taxane ring system, cf. **7**  $\rightarrow$  **8**.<sup>13,14</sup> Notably, these successful examples relied on Cr-organometallics. Based on this observation, we have focused on the Ni/Cr-mediated coupling, to realize the proposed coupling **A** + **B**  $\rightarrow$  **C**.

The first phase of our study was to assess the coupling efficiency of  $\beta$ -iodoenones with aldehydes, with use of model substrates (Scheme 4). We tested the coupling efficiency between  $\beta$ -iodoenone **9a** and aldehyde **10** with 10 mol % Cr-catalyst, prepared from (*S*)-sulfonamide **12**, and 1 mol % (Me)<sub>2</sub>Phen(H)<sub>2</sub>NiCl<sub>2</sub> **13a** in MeCN (Scheme 4).<sup>15,16</sup> This attempt demonstrated that expected coupling was indeed possible. However, its efficiency (27% isolated yield) was far below the synthetically useful level.<sup>17</sup>

We speculated that the activation of  $\beta$ -iodoenone **9a** with Ni-catalyst might be too fast, relative to the Cr-catalytic cycle, and some of the resultant alkenyl Ni(II)-species might be wasted, thereby causing a poor overall coupling efficiency. Based on this speculation, we conducted two experiments. First, we compared  $\beta$ -iodoenone **9a** with  $\beta$ -bromo- and  $\beta$ -chloroenones **9b,c**. We anticipated that, because of electronic effects, **9b,c** might be less reactive than **9a** and, therefore, might have a better reactivity-balance between the Ni- and Cr-catalytic cycles. Indeed, this experiment showed that (1) **9b,c** gave a better coupling efficiency than **9a** and (2) **9b** gave a slightly better coupling efficiency than **9c**.

With  $\beta$ -bromoeneone **9b**, we conducted the second experiment. Namely, we tested the overall coupling efficiency with less reactive Ni-catalyst and then with a lesser amount of the Ni-catalyst. Based on the previous studies, we were aware that

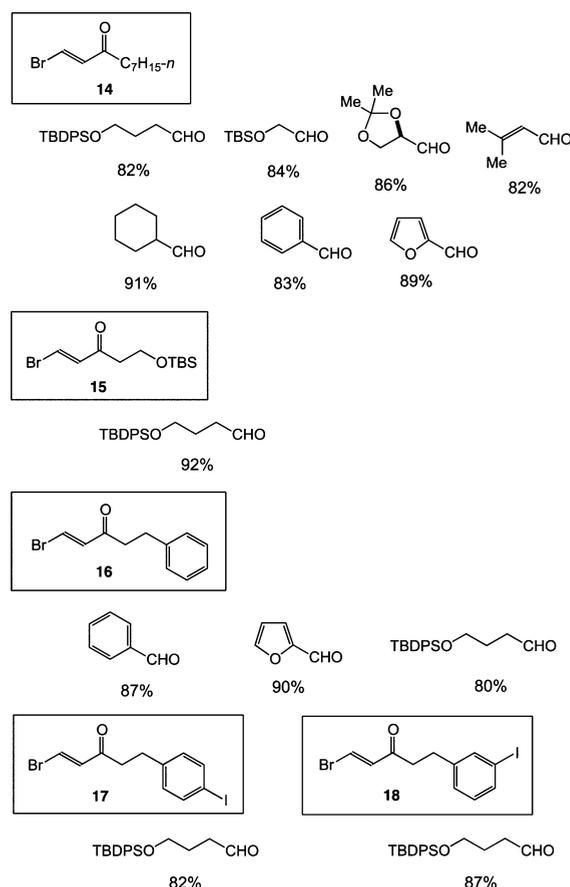
Scheme 4. Model Coupling Reactions Used to Assess the Coupling Efficiency<sup>a</sup>

<sup>a</sup>Coupling conditions: (A) 10 mol % Cr-complex prepared from sulfonamide **12** and 1 mol % nickel complex **13a** (B) 10 mol % Cr-complex prepared from sulfonamide **12** and 0.05 mol % nickel complex **13b**. The molar ratio of the substrates used was **9**:**10** = 1.5:1, and **11** was isolated by silica gel chromatography and indicated yields are based on aldehyde **10**.

$(\text{Me})_2\text{Phen}(\text{OMe})_2\cdot\text{NiCl}_2$  **13b** is a slower activator of vinyl iodides than  $(\text{Me})_2\text{Phen}(\text{H})_2\cdot\text{NiCl}_2$  **13a**.<sup>18</sup> Indeed, on replacing **13a** with **13b**, the coupling efficiency was noticeably improved. We then optimized the ratio of Ni- over Cr-catalysts; with 10 mol % Cr-catalyst fixed, 1, 0.5, 0.1, 0.05, and 0.01 mol % Ni-catalyst loadings were tested, thereby revealing that (1) the coupling efficiency improved with lowering the Ni-catalyst loading and (2) the coupling efficiency reached the plateau at the 0.05–0.1 mol % Ni-catalyst loading. It is worthwhile noting that the coupling reaction did not proceed without Ni-catalysts.

We used the coupling condition of “10 mol % Cr-catalyst, prepared from sulfonamide **12**, 0.05 mol % Ni-complex **13b**,  $\text{Zr}(\text{Cp})_2\text{Cl}_2$  (1.5 equiv), LiCl (2 equiv), and Mn (2 equiv) in MeCN ([C] 0.4 M) at room temperature” for a study of coupling efficiency. Table 1 summarizes the coupling efficiency for disubstituted *trans*- $\beta$ -bromo enones with aldehydes. All the cases studied gave expected products in good yields. We should note that the products thus obtained were stable enough to isolate and characterize. However, on standing in benzene, methylene chloride, and other solvents, at room temperature, they gradually decomposed, to yield the corresponding furans. With acid treatment (*p*-TSA or CSA/MeCN/RT), they gave the furans almost instantaneously. On acylation, however, the coupling products became stable even in the presence of acids (aq. TFA,  $\text{CH}_2\text{Cl}_2$ , RT).

Table 2 summarizes our attempts to expand this coupling reaction to other types of  $\beta$ -bromo enones. The first case studied was *cis*- $\beta$ -bromo enone **19**; the attempted coupling did not give the expected coupling product, but rather a ~9:1 mixture of coupling product **11**, identical to the coupling product obtained from *trans*- $\beta$ -bromo enone **9b** and furan **20**. The problem encountered was two-fold. First, the geometrical configuration of **19** was not retained in the coupling; we would attribute it to a facile *cis* → *trans* isomerization of the alkenyl Ni(II)-species formed from *cis*- $\beta$ -bromo enone **19**, thereby giving a mixture of *trans*- and *cis*-coupling products.<sup>17,19</sup>

Table 1. Examples Tested for the Coupling of Di-Substituted *trans*- $\beta$ -Bromo enones with Aldehydes<sup>a</sup>

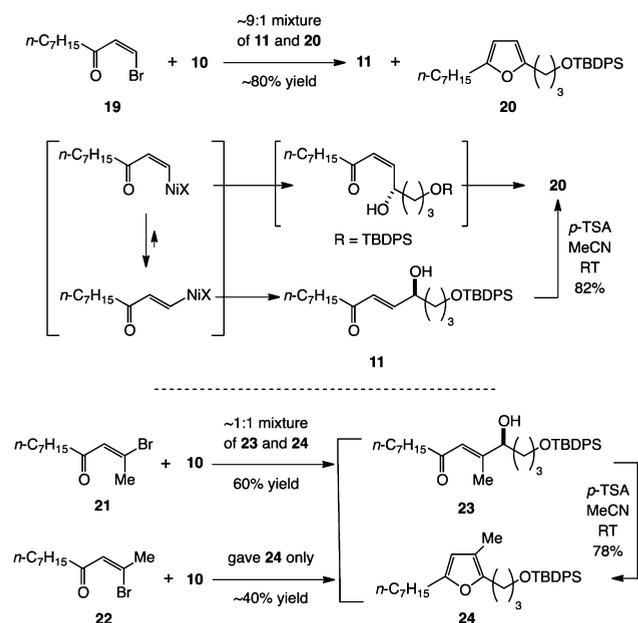
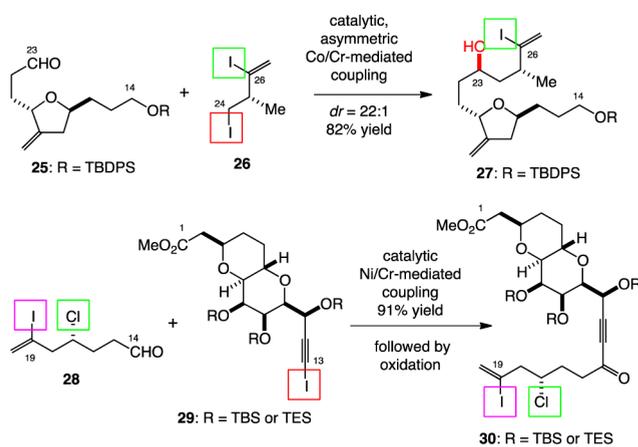
<sup>a</sup>Coupling condition: 10 mol % Cr-catalyst, prepared from sulfonamide **12**, 0.05 mol % Ni-complex **13b**,  $\text{Zr}(\text{Cp})_2\text{Cl}_2$  (1.5 equiv), LiCl (2 equiv), and Mn (2 equiv) in MeCN ([C] 0.4 M) at room temperature for 3 h. The molar ratio of aldehyde and nucleophile was 1:1.5; product was isolated by silica gel chromatography; and indicated yields are based on aldehyde.

Second, the resultant *cis*-coupling product appeared not to survive under the coupling condition employed, to form furan **20**.

*Trans*-trisubstituted  $\beta$ -bromo enone **21** gave a 1:1 mixture of coupling product **23** and furan **24**, whereas *cis*-trisubstituted  $\beta$ -bromo enone **22** gave only furan **24**. The observed results could be rationalized in the same term as given for the disubstituted *cis*- $\beta$ -bromo enone **19**.

Overall, the disclosed coupling reaction between an aldehyde and a “naked” vinylogous acyl anion is synthetically useful at least for disubstituted *trans*- $\beta$ -bromo enones. Interestingly, the developed method meets our need to achieve the proposed coupling reaction  $\text{A} + \text{B} \rightarrow \text{C}$  (Scheme 1).

**Selective Activation of  $\beta$ -Bromo enone over Vinyl Iodide and Saturated Chloride.** To the best of our knowledge, there is no literature precedent to support directly the proposed selective activation/coupling of a polyhalogenated nucleophile in the Ni/Cr-mediated coupling reactions. Perhaps, two examples shown in Scheme 5 are relevant, although remotely, to the proposed plan. The first example shows that a selective activation/coupling is possible with the use of selective activator in the Cr-mediated couplings, namely, cobalt- and iron-salts are known to activate saturated halides, but not vinyl

**Table 2. Attempted Coupling with Other Types of  $\beta$ -Bromo-enones<sup>a</sup>****Scheme 5. Two Examples Remotely Relevant to the Proposed Synthetic Plan**

halides.<sup>20,21</sup> The second example shows that a selective activation of iodoacetylene in the Ni/Cr-mediated reaction is possible without disturbing the vinyl iodide present in the electrophile.<sup>3c</sup>

In this work, we propose to activate selectively a  $\beta$ -bromo-enone over a vinyl iodide as well as a saturated chloride. As long as the Ni/Cr-mediated coupling is employed, the selective activation of a  $\beta$ -bromo-enone over a saturated chloride should not be an issue. Thus, the central question is the feasibility of activating selectively a  $\beta$ -bromo-enone over a vinyl iodide. We assume that, because of an electronic effect, a  $\beta$ -bromo-enone is more reactive toward Ni(0) than a vinyl iodide, thus giving a hope for realizing the proposed selective activation/coupling. The experimental results discussed in the previous section are very encouraging, because the activation/coupling of  $\beta$ -bromo-enones can be achieved with a trace amount of Ni-catalyst. However, it does not necessarily ensure

that a selective activation/coupling of a  $\beta$ -bromo-enone is possible without disturbing the vinyl iodide present in 34.

In order to test the feasibility of the proposed selective activation/coupling, we conducted competition experiments. Namely, aldehyde 10 was coupled with a 1:1 mixture of  $\beta$ -bromo-enone 9b and vinyl iodide 31a, b, or c in the presence of a different amount of Ni-catalysts 13a,b, followed by ratio-analysis of the two expected products 11 and 32 (<sup>1</sup>H NMR) (Table 3). The competition experiments demonstrated that (1)

**Table 3. Competition Experiment of *trans*- $\beta$ -Bromo-enone 9b over Vinyl Iodides 31a–c<sup>a</sup>**

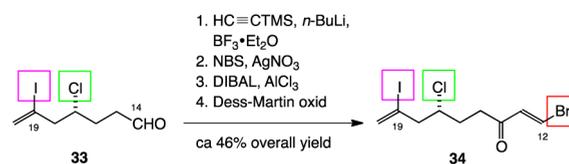
Ni-catalyst	13a		13b		13a		13b	
	11 : 32	11 : 32	11 : b*	11 : b*	11 : c*	11 : c*		
0.05 mol %	>100 : 1	>100 : 1	~38 : 1	~71 : 1	>100 : 1	>100 : 1		
0.1 mol %	>100 : 1	>100 : 1	30 : 1	~36 : 1	~42 : 1	>100 : 1		
0.5 mol %	~38 : 1	~66 : 1	1 : 1.1	12 : 1	16 : 1	~46 : 1		
1.0 mol %	22 : 1	26 : 1	1 : 2.3	1.5 : 1	4.6 : 1	5.2 : 1		

<sup>a</sup>Coupling conditions: nucleophile: a 1:1 mixture of 9b and 31a, b, or c. Reagents: 10 mol % Cr-catalyst, prepared from sulfonamide 12, 0.05 mol % Ni-complex 13a or 13b, Zr(Cp)<sub>2</sub>Cl<sub>2</sub> (1.5 equiv), LiCl (2 equiv), and Mn (2 equiv) in MeCN ([C] 0.4 M) at room temperature for 3 h. The product ratio was estimated from <sup>1</sup>H NMR analysis of crude coupling products. b\* and c\* are the coupling products derived from 31b and 31c, respectively.

0.05 and 0.1 mol % Ni-catalyst loadings, against 10 mol % Cr-catalyst loading, allow selectively to activate/couple  $\beta$ -bromo-enone 9b over all the three types of vinyl iodides 31a–c and (2) Ni-catalyst 13b gives a better discrimination of  $\beta$ -bromo-enone 9b over vinyl iodides 31a–c than Ni-catalyst 13a. Interestingly, 0.05 and 0.1 mol % Ni-catalyst loadings coincided with the Ni-catalyst amount ideal for  $\beta$ -bromo-enone couplings (see the previous section).

Encouraged by the results of competition experiments, we began the coupling study of 34 and 35 (Scheme 7). Requisite nucleophile 34 was readily prepared from the previously reported, optically pure aldehyde 33 (Scheme 6).<sup>22</sup> With respect to the electrophile, we tested several possible protecting groups at C8 and C9, thereby showing that the cyclohexylidene is the best option.<sup>23</sup>

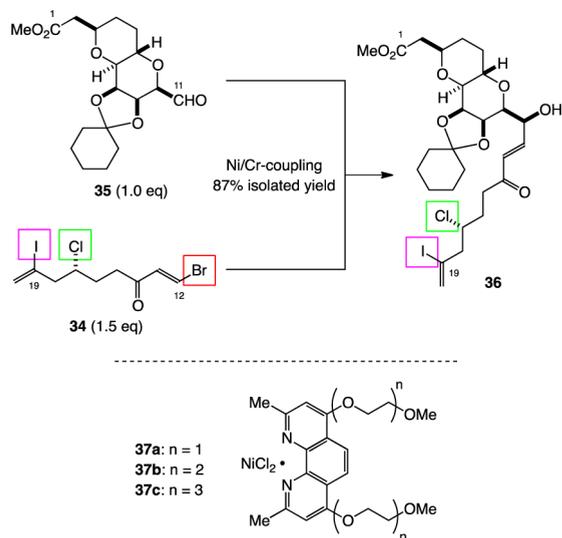
Aldehyde 35 was subjected to the Ni/Cr-coupling reaction (10 mol % Cr-catalyst, prepared from sulfonamide 12, and 0.05

**Scheme 6. Synthesis of Polyhalogenated Nucleophile 34**

mol % Ni-catalyst **13b**), to furnish a single coupling product in 46% yield. The spectroscopic analysis (HR-MS,  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR) demonstrated that the isolated product was the desired coupling product **36**. In particular, the C10–C11 vicinal proton spin-coupling constant (1.0 Hz) allowed us to assign the desired  $\beta$ -configuration to the newly introduced alcohol. Based on the previous examples similar to the present case, we anticipated the desired diastereomer to be formed in a high stereoselectivity with the Cr-catalyst prepared from (*S*)-sulfonamide **12**.<sup>24,25</sup> Nevertheless, we were delighted to observe the perfect stereocontrol for the coupling.

Naturally, we were anxious to improve the coupling efficiency. In this connection, we should comment on one technical difficulty encountered, i.e., controlling a very small amount of Ni-catalyst **13b**, which is virtually insoluble in the reaction medium. We hoped that an improvement of Ni-catalyst solubility may not only overcome the technical difficulty but also improve the coupling efficiency, because the Ni-catalyst can be homogeneously maintained at a very low concentration in the reaction medium. Along with this line of consideration, we prepared three polyether-type phenanthrene- $\text{NiCl}_2$  complexes **37a–c** (Scheme 7). As hoped, the solubility of

#### Scheme 7. Ni/Cr-Mediated Coupling of **34** with **35**, with Use of Polyether-Type Phenanthrene- $\text{NiCl}_2$ Complex **37c**<sup>a</sup>



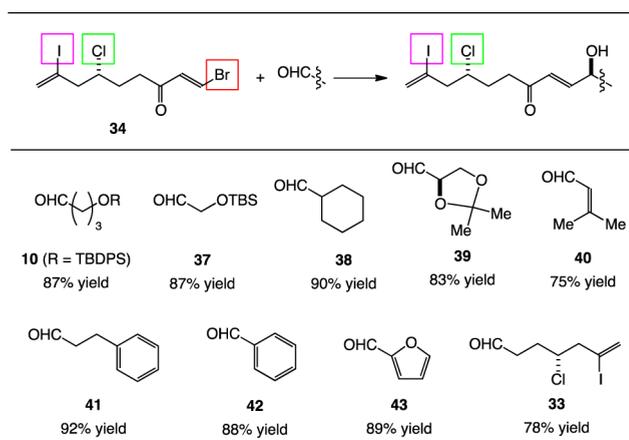
<sup>a</sup>Coupling conditions: 10 mol % Cr-catalyst, prepared from sulfonamide **12**, 0.05 mol % Ni-complex **37c**,  $\text{Zr}(\text{Cp})_2\text{Cl}_2$  (1.5 equiv), LiCl (2 equiv), and Mn (2 equiv) in MeCN ([C] 0.4 M) at room temperature for 3 h. Yield: chromatographically isolated yield in 7.1 g aldehyde scale.

these complexes, particularly **37b** and **37c**, was vastly improved. To our delight, with the use of **37c**, the coupling yield was also dramatically improved from 46% to 87%.<sup>26</sup>

Table 4 summarizes the coupling of  $\beta$ -bromoene **34** with various aldehydes under the optimized condition. The coupling efficiency of all the cases studied was very good. Among them, the result with aldehyde **33** was interesting to demonstrate that a selective activation of a  $\beta$ -bromoene over a vinyl iodide is indeed high; note that the activation of vinyl iodide in **33** induces cyclization with the aldehyde.

**Synthesis of C1–C19 Building Block of Halichondrin Bs.** As mentioned earlier, the coupling product **36** was prone to furan formation, but this instability could be overcome by

Table 4. Examples Tested for the Coupling of Polyhalogenated Nucleophile **34** with Various Aldehydes<sup>a</sup>

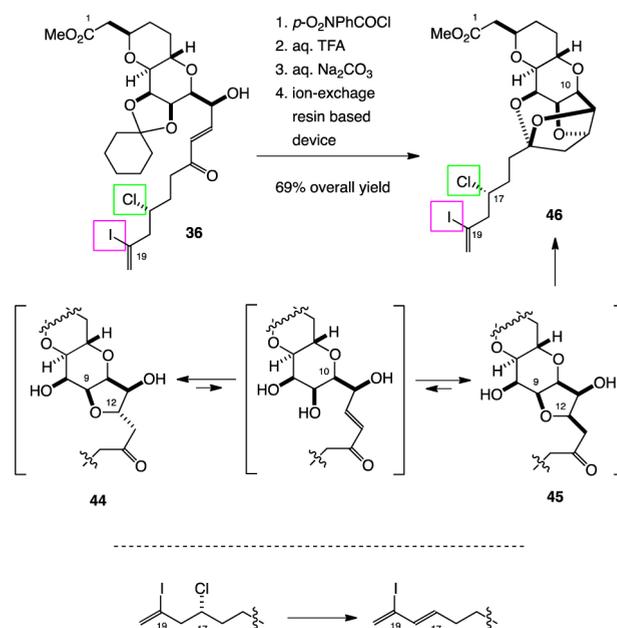


<sup>a</sup>Coupling conditions: 10 mol % Cr-catalyst, prepared from sulfonamide **12**, 0.05 mol % Ni-complex **37c**,  $\text{Zr}(\text{Cp})_2\text{Cl}_2$  (1.5 equiv), LiCl (2 equiv), and Mn (2 equiv) in MeCN ([C] 0.4 M) at room temperature for 3 h; the molar ratio of aldehyde and nucleophile was 1:1.5; product was isolated by silica gel chromatography, and indicated yields are based on aldehyde.

acylation of the resultant allylic alcohol. Among several acyl groups tested, we chose *p*-nitrobenzoate, because it was found to be stable under the aq. TFA condition required for hydrolysis of the C8,C9-cyclohexylidene group, cf., step 2 in Scheme 8.

On treatment with aqueous  $\text{Na}_2\text{CO}_3$ , the *p*-nitrobenzoate group of aq. TFA-hydrolysis product was smoothly hydrolyzed, followed by an oxy-Michael reaction of the C9 hydroxyl group to the  $\alpha,\beta$ -unsaturated ketone, to furnish a ~1:2 mixture of **44** and **45** (Scheme 8). In the previous studies, we learned the

#### Scheme 8. Completion of Synthesis of the C1–C19 Building Block **46** of Halichondrin B<sup>a</sup>

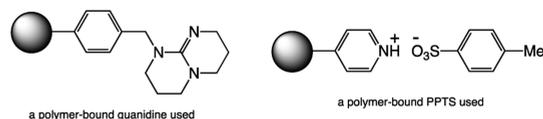


<sup>a</sup>Yield: chromatographically isolated yield in 11.4 g scale of coupling product **36**.

chemical behaviors of these oxy-Michael products, including: (1) PPTS treatment allows the C12- $\beta$  oxy-Michael product **45** to convert to the desired polycycle, cf., **46**; (2) undesired C12- $\alpha$  oxy-Michael product **44** can be recycled via retro oxy-Michael/oxy-Michael equilibration under basic condition; (3) an ion-exchange resin-based device allows the mixture of oxy-Michael products to convert to the desired polycycle without isolation and recycling of the undesired oxy-Michael product.<sup>27</sup>

With this background, we attempted to convert oxy-Michael products **44** and **45** into polycycle **46**, thereby revealing that (1) transformation of **45** into **46** under the PPTS condition was clean and facile, but (2) isomerization of **44** to **45** under the previously established basic conditions or ion-exchange-resin protocol was problematic; one problem identified was the elimination of HCl to form iodo-diene (see the lower half of Scheme 8). With this information, we searched for a reaction condition to establish the equilibrium between two oxy-Michael products without elimination of HCl and eventually found that the equilibration can be established with DBU or tetramethylguanidine in isopropanol or ethanol at room temperature, without the undesired elimination.<sup>28</sup>

Naturally, we hoped to translate some of these conditions to ion-exchange resin-based device and found that polymer-bound guanidine base, coupled with polymer-bound PPTS, was effective directly to convert a mixture of oxy-Michael products **44** and **45** to polycycle **46** in a high yield without isolation/separation/equilibration (Figure 1).<sup>29–31</sup> The structure of C1–



**Figure 1.** Polymer-bound guanidine and PPTS used for ion-exchange resin-based device.

C19 building block **46** thus synthesized was fully supported by spectroscopic data (HR-MS, <sup>1</sup>H and <sup>13</sup>C NMR), which was further confirmed by X-ray analysis of its derivative.<sup>32</sup>

The synthesis reported is easy to scale; the overall yield of **46** from **36** was 69% in a 11.4 g scale.

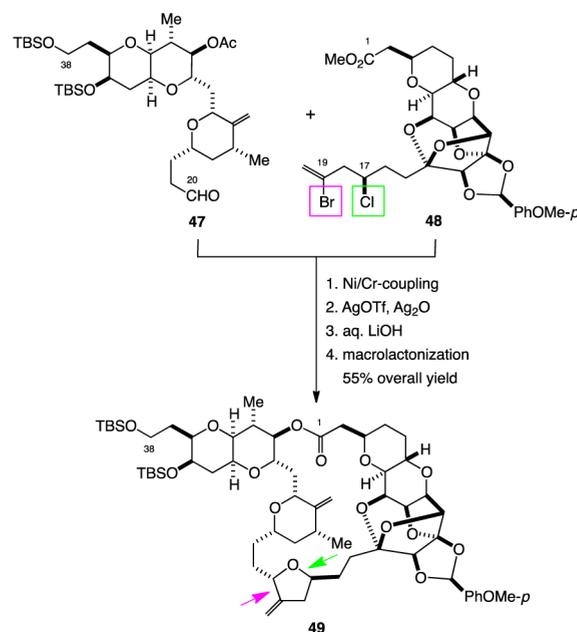
## CONCLUSION

The C1–C19 building block **46** of halichondrin Bs was synthesized via a selective activation/coupling of  $\beta$ -bromo-enone **34** with aldehyde **35** in a Ni/Cr-mediated reaction. The first phase of study was a method development to effect a coupling of a “naked” vinylogous anion with an aldehyde. The study with the coupling of **9** + **10**  $\rightarrow$  **11** revealed: (1)  $\beta$ -bromo-enone **9b** is a better nucleophile than the corresponding  $\beta$ -iodo- and  $\beta$ -chloroenones **9a,c**; (2) (Me)<sub>2</sub>Phen(OMe)<sub>2</sub>·NiCl<sub>2</sub> **13b** is a better Ni-catalyst than (Me)<sub>2</sub>Phen(H)<sub>2</sub>·NiCl<sub>2</sub> **13a**; and (3) a low Ni-catalyst loading, for example, 0.05–0.1 mol % Ni-catalyst against 10 mol % Cr-catalyst, is crucial for an effective coupling. The second phase of study was a method development to realize a selective activation/coupling of polyhalogenated nucleophiles such as **34**. The competition experiment of **10** + **9b** over **10** + **31a–c** revealed: (1) (Me)<sub>2</sub>Phen(OMe)<sub>2</sub>·NiCl<sub>2</sub> **13b** is more effective than (Me)<sub>2</sub>Phen(H)<sub>2</sub>·NiCl<sub>2</sub> **13a** for the required selective activation/coupling; (2) a low Ni-catalyst loading, for example, 0.05–0.1 mol % Ni-catalyst against 10 mol % Cr-catalyst, is crucial for discriminating  $\beta$ -bromo-enone **9b** from the three types of vinyl

iodides **31a–c**. The third phase of study was an application of the developed method to execute the proposed coupling of **34** + **35**  $\rightarrow$  **36**. For this application, a polyether-type Ni-catalyst **37c**, readily soluble in the reaction medium, was introduced to achieve the selective activation/coupling with higher efficiency. With use of ion-exchange resin-based device, the coupling product **36** was transformed to the C1–C19 building block **46** of halichondrin Bs without purification/separation of the intermediates.

Lastly, it is worthwhile noting that all of the halogens present in the nucleophile **34** are designed selectively to achieve specific bond formation in a controlled manner, as illustrated in the synthesis of right-half of halichondrin A (Scheme 9).<sup>3c</sup> Namely,

## Scheme 9. Summary of the Synthesis of the Right-Half of Halichondrin A



C19 vinyl bromide or iodide was used for the Ni/Cr-mediated coupling stereoselectively to form the C19–C20 bond, whereas C17 chloride allowed stereospecifically to form the tetrahydrofuran ring in an S<sub>N</sub>2 fashion.

## ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data, copies of spectra, and crystallographic data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03498.

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### Notes

The authors declare no competing financial interest.

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- (25) The coupling yields with **37a** and **37b** were 59% and 75%, respectively. We also prepared a Ni-catalyst with *n*-dodecyloxy substituents, i.e., X = *n*-C<sub>12</sub>H<sub>25</sub>O in **13**, but found that its solubility was roughly same as that of **13b** and the coupling yield with this Ni-catalyst was 60%.
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- (28) Basic ion-exchange resins tested included Amberlite IRA-400, Amberlite IRA-402, Amberlite IRA-900, Amberlite A-21, Amberlite A-26, and Amberlite A-27. Acidic ion-exchange resins tested included Rexny 101, Amberlite IR-120, Amberlite 15, and Amberlite IRC-86.
- (29) Both purchased from Aldrich: polymer-bound guanidine: #358754; polymer-bound PPTS: #82817.
- (30) As ethanol was used as the solvent, an ester exchange was noticed if the reaction was run over 1 day. However, it did not present an issue for preparative purpose, as the conversion was usually complete within 12 h.
- (31) See Supporting Information.