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Unified Synthesis of C1−C19 Building Blocks of Halichondrins via Selective Activation/Coupling of Polyhalogenated Nucleophiles in (Ni)/Cr-Mediated Reactions

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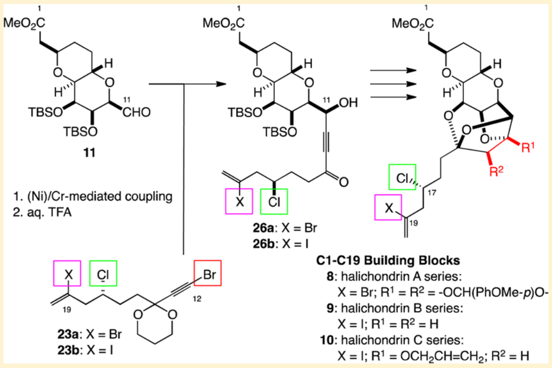
Ⓢ *Supporting Information*

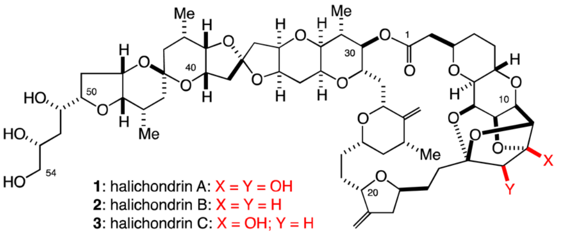
ABSTRACT: A unified synthesis of the C1−C19 building blocks **8**−**10** of halichondrins A−C was developed from the common synthetic intermediates **26a**,**b**. Acetylenic ketones **26a**,**b** were in turn synthesized via selective activation/coupling of polyhalogenated nucleophiles **23a**,**b** with aldehyde **11** in a (Ni)/Cr-mediated coupling reaction. Compared with Ni/Cr-mediated couplings of vinyl iodides and aldehydes, this (Ni)/Cr-mediated coupling exhibited two unique features. First, the coupling was found to proceed with a trace amount or no added Ni-catalyst. Second, TES-Cl, a dissociating agent to regenerate the Cr-catalyst, was found to give a better yield than $Zr(Cp)_2Cl_2$. An adjustment of the oxidation state was required to transform acetylenic ketones **26a**,**b** into C1−C19 building blocks **8** and **9** of halichondrins A and B, respectively. In the halichondrin B series, a hydroxyl-directed $(Me)_4NBH(OAc)_3$ reduction of *E*- and *Z*-*β*-alkoxy-enones **30** was found cleanly to achieve the required transformation, whereas a DMDO oxidation of *E*-vinylogous ester **27** allowed to introduce the C13 hydroxyl group with a high stereoselectivity in the halichondrin A series. In the halichondrin C series, $Hf(OTf)_4$ was used to convert the double oxy-Michael product **28** into C1−C19 building block **10**.



■ INTRODUCTION

Halichondrins are polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* by Uemura, Hirata, and co-workers (Scheme 1).[1] Several additional members, including halistatin 1, were isolated from various marine sponges.[2] This class of natural products displays interesting structure diversities at two sites, one being the oxidation state at C10, C12, and C13 of the C8−C14 polycycle and the other being the length of the carbon backbone. Thus, the halichondrin class of natural products is subgrouped into halichondrins A−C series or the norhalichondrin/halichondrin/homohalichondrin series. Due to their intriguing structural architecture and extraordinary *in vitro* and *in vivo* antitumor activity, the halichondrin class of marine natural products has received much attention from the scientific communities.[3,4] We have been engaged with the synthetic studies in this field since the late 1980s, aiming at total syntheses, coupled with development of a new synthetic strategy and discovery of new synthetic methods, with particular focus on the Cr-mediated coupling reactions.[5−8]

Scheme 1. Structure of Halichondrins A−C



We recently reported a total synthesis of halichondrin A (**1**), a phantom member in this class of natural products.[5c] Scheme 2 schematically illustrates the high convergence incorporated in the synthesis. There are two appealing aspects recognized in the synthesis. First, because of its high degree of convergence, one can expect a high overall efficiency in synthesis. Interestingly, the key two couplings have been achieved efficiently with Ni/Cr-mediated coupling reactions. Second, with a replacement of **8** with **9** and **10**, this convergent strategy can be extended to a synthesis of halichondrins B and C, respectively. Thus, we are interested in establishing a unified synthesis of C1−C19 building blocks **8**, **9**, and **10**. In this paper, we report a solution to achieve this goal, with the use of a selective activation/coupling of polyhalogenated nucleophile **23a**,**b** in the (Ni)/Cr-mediated coupling reaction as the key C−C bond-forming step.

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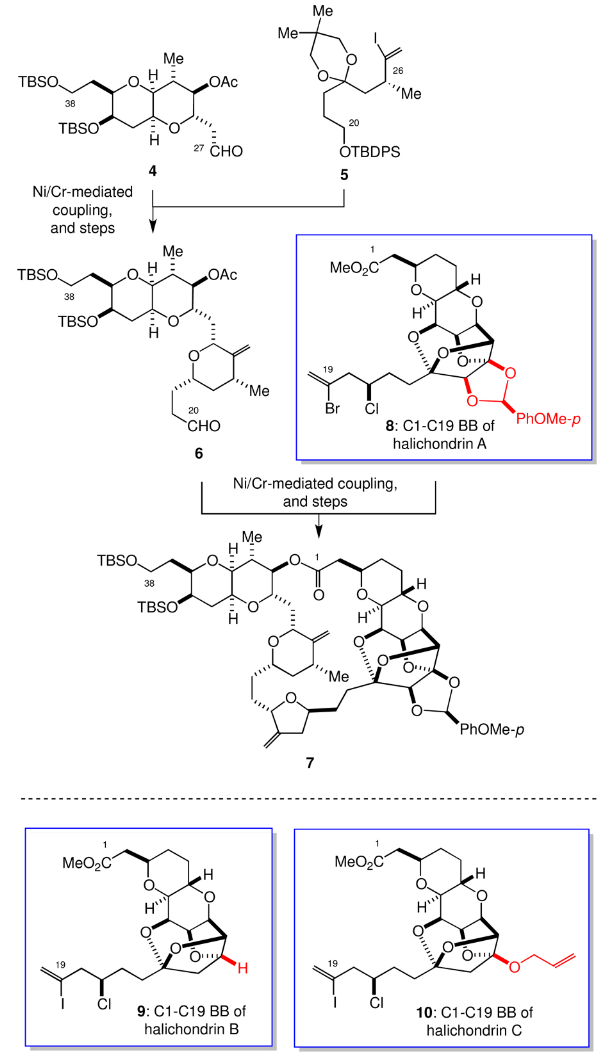
Scheme 2. Summary of the Synthesis of the Right Half of Halichondrin A and Requisite C1−C19 Building Blocks (BBs) of Halichondrins A−C

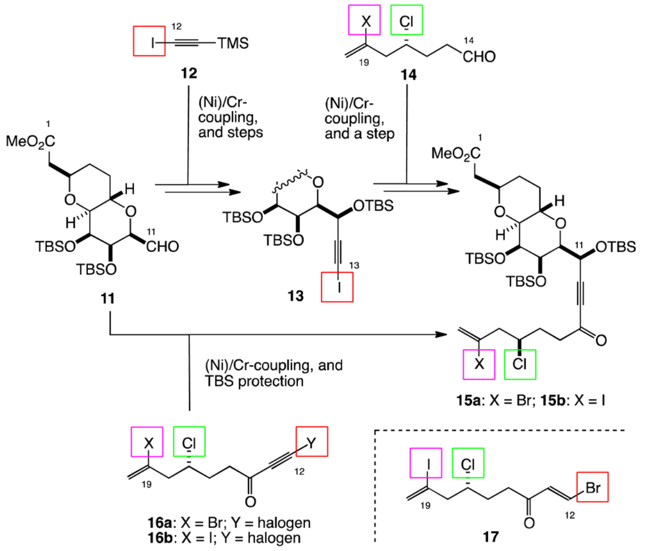


■ RESULTS AND DISCUSSION

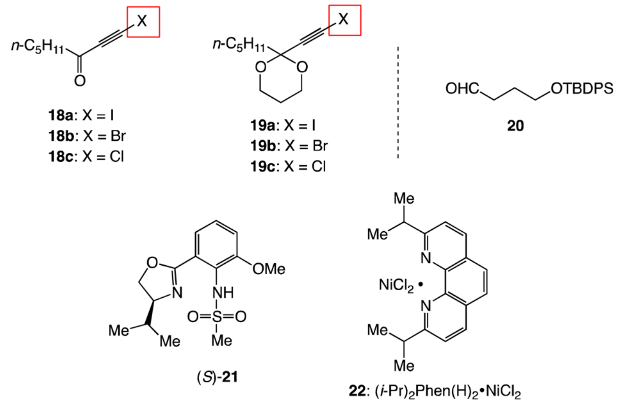
Synthetic Plan. We noticed the possibility that all of C1−C19 building blocks **8**−**10** could be synthesized from acetylenic ketone **15a,b**, by adjusting its oxidation state (Scheme 3). Indeed, C1−C19 building block **8** of halichondrin A was synthesized with this strategy.[5c]

In the halichondrin A synthesis, we synthesized acetylenic ketone **15a** via two (Ni)/Cr-mediated couplings. In light of the successful selective activation/coupling of polyhalogenated nucleophile **17** in a Ni/Cr-mediated coupling, we recognized a possibility of synthesizing **15a,b** in one step, cf., **11** + **16a,b** → **15a,b**. In the halichondrin B series, a selective activation/coupling of the *trans*-*β*-bromoenone was realized with use of a trace amount of a polyether-type Ni-catalyst.[9] For the present case, because activation of halo-acetylenes is known to require only a trace amount of Ni-catalyst or even no added Ni-catalyst, a selective activation of the halo-acetylene over the vinyl iodide or bromide and saturated chloride present in **16a,b** should not present an issue.[10,11] Thus, the remaining question was the coupling efficiency of the nucleophile generated from **16a,b** with an aldehyde, and we first addressed this issue with model compounds listed in Scheme 4.

Scheme 3. Proposed One-Step Synthesis of Acetylenic Ketones 15a,b via Selective Activation/Coupling of Halo-Acetylenic Ketones 16a,b



Scheme 4. Substrates, Sulfonamide, and Ni-Catalyst Used for the Model Study[a]



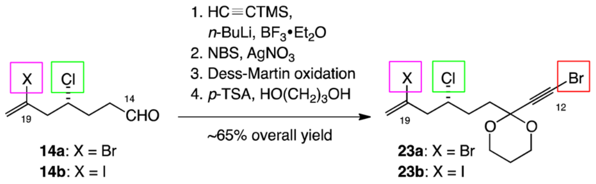
[a]The coupling was tested with the molar ratio of **18**/**19**:**20** = 1.7:1; the coupling product was isolated by silica gel chromatography and yields are based on aldehyde **20**.

Model Study on Coupling Efficiency. In order to assess the coupling efficiency, we chose six halo-acetylenes **18a**−**c** and **19a**−**c** and aldehyde **20** (Scheme 4). In this study, we first compared the coupling efficiency of halo-acetylenic ketones **18a**−**c** over halo-acetylenic ketone ketals **19a**−**c**,[12] under the coupling conditions: 10 mol % Cr-catalyst, prepared from (*S*)-sulfonamide **21**, Ni-catalyst **22** (0.05 mol %), or no added Ni-catalyst, $Zr(Cp)_2Cl_2$ (1.5 equiv), Mn (2 equiv), and LiCl (2 equiv) in MeCN ([C] 0.4M) at room temperature.[13,14] This experiment demonstrated: (1) halo-acetylenic ketones **18a**−**c** gave the desired product in only modest yields, with the order of coupling efficiency being **18b** (49%) > **18c** (20%) > **18a** (11%); (2) halo-acetylenic ketone ketals **19a,b** gave the desired product in good yields, with the order of coupling efficiency being **19b** (93%) > **19a** (82%) ≫ **19c** (8%); (3) no significant difference was detected between 0.05 mol % and no added Ni-catalyst. In addition, a brief study on solvents and concentration revealed: (1) the solvent choice being EtCN > MeCN > DME

> THF, but not DMF, and (2) the optimum concentration being a range of 0.4−0.8 M.

Coupling in the Real Series. With the results gained in the model study, we began the study on the proposed coupling. The requisite nucleophiles **23a,b** were readily prepared from the previously reported, optically pure aldehydes **14a,b** (Scheme 5).[15,16] With respect to the electrophile, several possible C8,C9-protecting groups were screened, thereby showing bis-TBS aldehyde **11** as the best option.[17]

Scheme 5. Synthesis of Nucleophiles 23a,b



14a: X = Br
14b: X = I

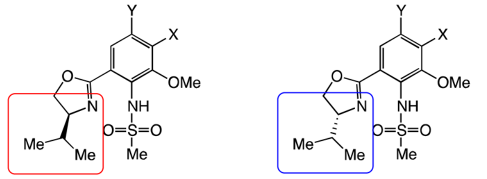
23a: X = Br
23b: X = I

For the simplicity of presentation, we will discuss first the coupling experiments in the nucleophile **23a** series, although the studies were carried out on both **23a,b** simultaneously.

In the proposed coupling, one chiral center is introduced at the C11 position. Based on the previous work, we were aware that a nucleophilic addition to an aldehyde such as **11** predominantly, often exclusively, gives the desired C11*β* alcohol.[7e,11a] With this background, we subjected **11** and **23a** to the coupling reaction under the condition used in the model study, to furnish the desired product **26a** in 55% yield, with a 10:1 stereoselectivity. The structure of **26a** was established via correlation with the authentic sample obtained in the previous route.[5c] As anticipated, we did not detect a product derived through activation of the vinyl bromide or saturated chloride present in **23a**.

In order to improve the observed stereoselectivity, we adopted the toolbox approach and screened a representative set of sulfonamides (Table 1).[7e,18] This screening showed that (1) as previously observed, the stereochemistry outcome was dictated by the substrate structure rather than the chirality present in the Cr-catalyst and (2) for this coupling, sulfonamides in the (*R*)-series gave a better stereoselectivity than the corresponding sulfonamides in the (*S*)-series. Among the tested ligands, we chose sulfonamide (*R*)-**21** and Ni-catalyst **22** for the following study.

Table 1. Sufonamides Tested for a Ligand Search with a Toolbox Approach



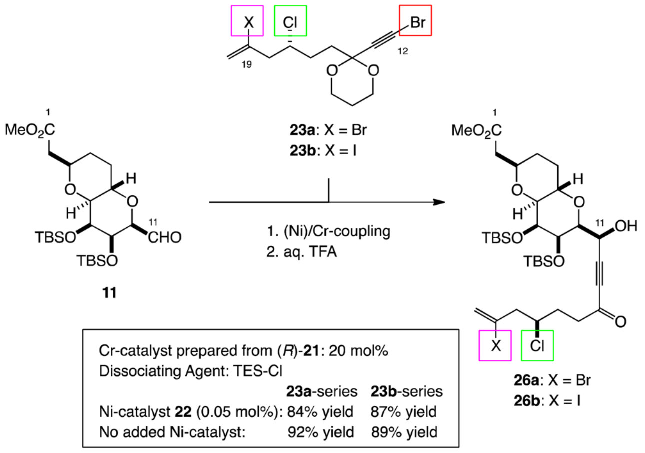
	11β:11α		11β:11α
(*S*)-**21**: X = Y = H	10:1	(*R*)-**21**: X = Y = H	20:1
(*S*)-**24**: X = OMe; Y = H	8:1	(*R*)-**24**: X = OMe; Y = H	13:1
(*S*)-**25**: X = Y = OMe	7:1	(*R*)-**25**: X = Y = OMe	16:1

Naturally, we were anxious to improve the coupling efficiency. Particularly, we wondered how we could enhance the efficiency of Cr-catalytic cycle. In a catalytic Cr-mediated carbonyl addition, it is required to dissociate a Cr/product alcohol complex and regenerate a Cr-catalyst. TMS-Cl or TES-Cl and $Zr(Cp)_2Cl_2$ are known to be effective dissociating agents.[19] Generally, the overall coupling rate with $Zr(Cp)_2Cl_2$ is significantly faster than that with TMS-Cl or TES-Cl, at least for the Ni/Cr-mediated coupling of vinyl iodides with aldehydes. In addition, it is noteworthy that, when the TMS-Cl procedure is applied for a readily enolizable aldehyde, a significant amount of aldehyde is recovered, due to a silyl enol ether formation *in situ*.

For the present case, it was found that the coupling rate with TES-Cl was slower than that with $Zr(Cp)_2Cl_2$, yet the coupling yield with TES-Cl was noticeably better than that with $Zr(Cp)_2Cl_2$, i.e., 85% with TES-Cl vs 70% with $Zr(Cp)_2Cl_2$.[20] Although its mechanistic reason was not clear, the TES-Cl condition made it possible to achieve the proposed coupling with the synthetically useful efficiency.

As noted before, Cr-mediated coupling of a halo-acetylene with an aldehyde is known to proceed with only a trace amount of Ni-catalyst or even no added Ni-catalyst.[11] For this reason, we studied the coupling of **11** + **23a** → **26a** "with" and "without" added Ni-catalyst, thereby showing the coupling efficiency to be comparable (Scheme 6). There is no definite experimental evidence to conclude whether this coupling involves activation of bromoacetylene with Ni-catalyst, followed by Cr-mediated coupling, or activation/coupling with only a Cr-catalyst. In this connection, it is worthwhile mentioning that the homodimer of bromoacetylene was isolated in ca. 0.3% yield (based on **23a**) in the coupling without added Ni-catalyst. Formation of the dimer with no added Ni-catalyst may support that Ni-catalyst, or some unknown metal, activated halo-acetylene **23a** prior to the C−C bond formation.[21] However, reflecting this ambiguity, we refer to the coupling as (Ni)/Cr-mediated reaction in this paper.

Scheme 6. (Ni)/Cr-Mediated Couplings[a]



Cr-catalyst prepared from (*R*)-**21**: 20 mol%
Dissociating Agent: TES-Cl

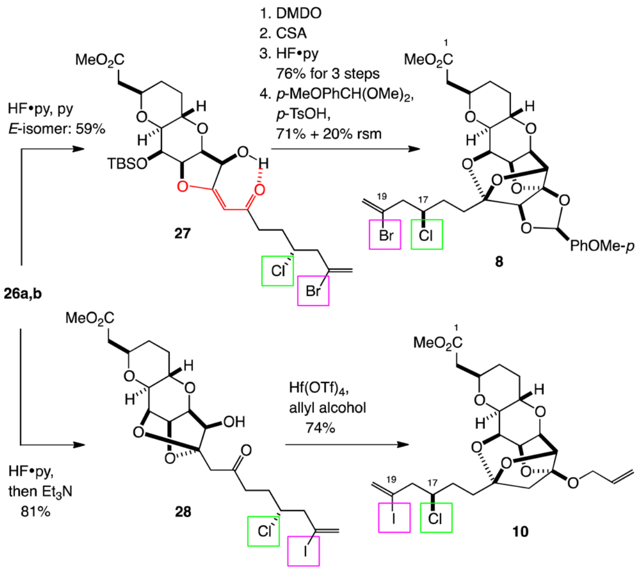
	23a-series	**23b**-series
Ni-catalyst **22** (0.05 mol%):	84% yield	87% yield
No added Ni-catalyst:	92% yield	89% yield

[a]Coupling conditions: Cr-catalyst prepared from (*R*)-**21**: 20 mol %; Ni-catalyst (0.05 mol %) or no added Ni-catalyst; TES-Cl (2.5 equiv); LiCl (4 equiv); Mn (4 equiv); EtCN ([C] 0.4 M); RT. The coupling was done with the molar ratio of **18**/**19**:**20** = 1.7:1; the coupling product was isolated by silica gel chromatography and yields are based on aldehyde **11**.

As mentioned, we carried out the coupling studies with both **23a,b** simultaneously and obtained the virtually identical results in the both series, although a small reduction in yield was noticed in the **23b** series.

Synthesis of C1–C19 Building Blocks of Halichondrins A–C from the Common Synthetic Intermediate 26. *Synthesis of C1–C19 Building Block of Halichondrin A.* In the halichondrin A synthesis, we already established the transformation of **26a** into C1–C19 building block **8** (Scheme 7).

Scheme 7. Synthesis of C1–C19 Building Blocks (BBs) in the Halichondrin A and C Series

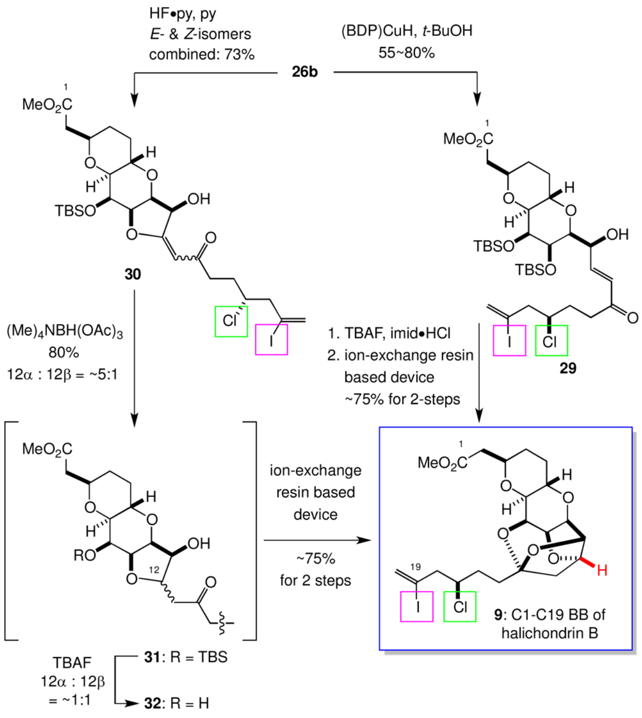


The key reactions in this transformation included: (1) a selective TBS-deprotection to form *E*-enone **27** and (2) a highly stereoselective DMDO-oxidation to introduce the C13 hydroxyl group. It should be noted that C1–C19 building block **8** bears the C19 vinyl bromide, because the corresponding vinyl iodide was not compatible with the DMDO oxidation.[5c,22]

Synthesis of C1–C19 Building Block of Halichondrin C. In the halichondrin C synthesis, we reported a synthetic route to construct the polycyclic ring system from an acetylenic ketone.[5b] Although the transformation was carried out on the macrolactone framework, we felt confident in extending this synthetic method to the present acyclic system; indeed, we had no unexpected difficulty in the transformation of **26b** to **10** in 60% overall yield (Scheme 7). The key reactions in this transformation included: (1) double oxy-Michael addition of C8,C9-hydroxyl groups to the acetylenic ketone to form ketal **28** and (2) Hf(OTf)$_4$-induced conversion of the double oxy-Michael product **28** to polycycle **10** in allyl alcohol. The structure **10** was fully supported by the spectroscopic data (HR-MS, ^{1}H and ^{13}C NMR).

Synthesis of C1–C19 Building Block of Halichondrin B. In order to synthesize C1–C19 building block **9** in the halichondrin B series from the common synthetic intermediate, we obviously needed an acetylene-to-olefin reduction and tested first the reactivity of **26b** and its C11-OTBS derivative against CuH, HN=NH, and CrCl$_2$ (Scheme 8), thereby indicating that the C11-OTBS substrate exhibited a very poor reactivity. Based on this observation, we used **26b** for a search of a satisfactory reducing reagent/condition. Among reagents tested, (BDP)CuH, a Stryker CuH modified by Lipshutz, gave a most promising result (Scheme 8).[23] Yet, we had two issues to address. First, this reduction gave a mixture of *E*- and *Z*-enones. As discussed in the preceding companion paper (DOI: 10.1021/jacs.5b03498),[9] *Z*-enone was found to form readily the furan.[9] Thus, although it was a minor product, *Z*-enone was wasted. Second, this reduction gave the desired *E*-enone **30** as the major product, but the isolated yield varied from 55% up to 80%. Apparently, the problem was over-reduction. Despite extensive efforts, we were unable to identify a condition to achieve the reduction with a high reproducibility and high yield.

Scheme 8. Synthesis of C1–C19 Building Blocks (BBs) in the Halichondrin B Series



Under this circumstance, we decided to focus on reduction of *E*-enone *E*-**30**. Once again, we attempted several known methods, including various CuH reagents, H$_2$/Crabtree catalyst, and Na$_2$S$_2$O$_4$, but with only limited success.[24] Ultimately, we found that (Me)$_4$NBH(OAc)$_3$ reduced the vinylogous ester cleanly to give **31** in 80% yield as a 5:1 mixture of 12α:12β diastereomers.

(Me)$_4$NBH(OAc)$_3$ is well recognized as an excellent hydride donor in a so-called hydroxyl-directing setting.[25] However, a literature search revealed that no example was reported for reduction of a vinylogous ester with (Me)$_4$NBH(OAc)$_3$. Nonetheless, we would assume that, like the case of β-hydroxyl ketones,[26] the reduction was facilitated via a ligand exchange of (Me)$_4$NBH(OAc)$_3$ with the C11-hydroxyl group, followed by an intramolecular hydride delivery in a conjugated fashion, to yield the 12α-alcohol as the major product. Consistent with this suggestion, we found that the substrate with the C11-OH masked with a TBS was inert to the reduction.

We anticipated that the intramolecular hydride delivery should yield predominantly 12α-stereoisomer, which is the undesired stereoisomer. However, we were aware that it should not be an issue, because the C12-configuration is prone to isomerization via a retro oxy-Michael/oxy-Michael process; indeed, the ratio of 12α:12β stereoisomers varied from one experiment to other, likely due to a different degree of isomerization during workup.

As expected from the above consideration, we observed that (Me)$_4$NBH(OAc)$_3$ reduction of the corresponding *Z*-enone *Z*-**30** gave **31** as a mixture of 12α:12β stereoisomers. Thus, for the preparative purpose, it was not necessary to separate *E*- and *Z*-enones **30**.

On TBAF treatment, **31** furnished **32** as a ~1:1 mixture of 12α:12β diastereomers. With an ion-exchange resin-based device,[27] this mixture was transformed cleanly to C1−C19 building block **9** of halichondrin B without isolation/separation/equilibration of intermediates. On comparison of spectroscopic data (^{1}H and ^{13}C NMR, MS, TLC), **9** thus obtained was found to be superimposable on the authentic sample.[9]

■ CONCLUSION

A unified synthesis of the C1−C19 building blocks **8**−**10** of halichondrins A−C was developed from the common synthetic intermediates **26a**,**b**. Acetylenic ketones **26a**,**b** were in turn synthesized via selective activation/coupling of polyhalogenated nucleophiles **23a**,**b** with aldehyde **11** in a (Ni)/Cr-mediated coupling reaction. Compared with Ni/Cr-mediated couplings of vinyl iodides and aldehydes, this (Ni)/Cr-mediated coupling exhibited two unique features. First, the coupling was found to proceed with a trace amount or no added Ni-catalyst. Second, TES-Cl, a dissociating agent to regenerate the Cr-catalyst, was found to give a better yield than $Zr(Cp)_2Cl_2$.

An adjustment of the oxidation state was required to transform acetylenic ketones **26a**,**b** into C1−C19 building blocks **8** and **9** of halichondrins A and B, respectively. In the halichondrin B series, a hydroxyl-directed $(Me)_4NBH(OAc)_3$ reduction of *E*- and *Z*-β-alkoxy-enones **30** was found cleanly to achieve the required transformation, whereas a DMDO oxidation of *E*-vinylogous ester **27** allowed to introduce the C13 hydroxyl group with a high stereoselectivity in the halichondrin A series. In the halichondrin C series, $Hf(OTf)_4$ was used to convert double oxy-Michael product **28** into C1−C19 building block **10**.

Lastly, we note that an application of the synthetic method developed in the halichondrin A synthesis[5c] should allow us to transform C1−C19 building blocks **8**−**10** into halichondrins A−C, respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization data, and copies of spectra data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03499.

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Notes

The authors declare no competing financial interest.

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(10) Cr-mediated couplings of halo-acetylenes with aldehydes were first reported by Takai, Nozaki, and coworkers: Takai, K.; Kuroda, T.; Nakatsukasa, S.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5585. It should be noted, however, that the work had been done before a special role of Ni-salt was recognized in the Cr-mediated coupling reactions.

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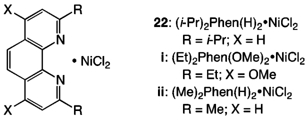
(12) Dimethyl ketal, ethylene glycol ketal, and 2,2-dimethyl-1,3-propylene glycol ketal were also tested as a ketone protecting group of **19a–c**.

(13) The standard coupling conditions used in the toolbox approach; see ref 7e.

(14) Three Ni-complexes were screened for this coupling, thereby showing that the order of effectiveness was **22** ∼ **i** > **ii**. Based on this observation, **22** was chosen for this study.

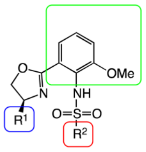


(15) Liu, S.; Kim, J. T.; Dong, C.-G.; Kishi, Y. *Org. Lett.* **2009**, *11*, 4520.

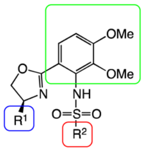
(16) (Ni)/Cr-mediated coupling of IC≡CTMS with **14** gave the desired product. However, considering its cost relative to TMS acetylene, we chose the synthesis shown in Scheme 5. We also attempted the coupling of TMS-C≡C-I with **14**, induced by tetrabutylammonium difluorotriphenylsilicate, but did not give a promising result.

(17) C8,C9-Protecting groups tested included: cyclohexylidene ketal, anisylidene acetal, methylene acetal, bis-MOM ether, diacetate, dibenzoate, carbonate, and others.

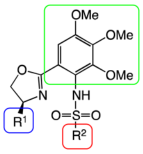
(18) We originally used sulfonamide **iii** for ligand search in the toolbox approach (see ref 7e). In order to expand the space of ligand search, we have recently added sulfonamides **iv** and **v** to this approach; see the structure highlighted by a green box. Sulfonamides (*S*)- and (*R*)-**24** and **25** were sulfonamides used in that study.



iii



iv



v

(19) (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533; *J. Am. Chem. Soc.* **1996**, *118*, 12349. (b) See ref 7d.

(20) The coupling product at this stage was a mixture of C11-OTES (major) and C11-OH (minor). On the following acid treatment, both products gave **26**.

(21) There is a paper reporting homo-dimerization of halo-acetylenes without metal; see: Chen, Z.; Jiang, H.; Wang, A.; Yang, S. *J. Org. Chem.* **2010**, *75*, 6700. For transition-metal-free homo-dimerization, see: Krasovskiy, A.; Tishkov, A.; del Amo, V.; Mayr, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5010.

(22) For the next Ni/Cr-mediated coupling to form the C19–C20 bond, the vinyl iodide at the C19 is a better nucleophile than the corresponding vinyl bromide.

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