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Contra-thermodynamic Olefin Isomerization by Chain-Walking Hydroboration and Dehydroboration

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Abstract

We report a dehydroboration process that can be coupled with chain-walking hydroboration to create a one-pot, contra-thermodynamic, short- or long-range isomerization of internal olefins to terminal olefins. This dehydroboration occurs by a sequence comprising activation with a nucleophile, iodination, and base-promoted elimination. The isomerization proceeds at room temperature without the need for a fluoride base, and the substrate scope of this isomerization is expanded over those of previous isomerizations we have reported with silanes.

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Notes

The authors declare no competing financial interest.

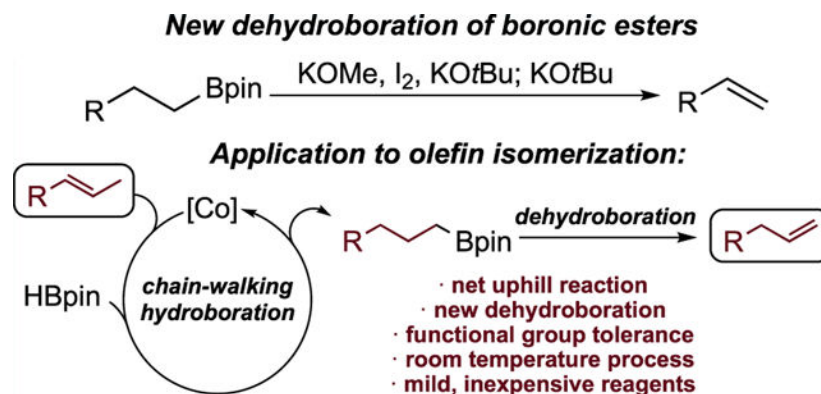
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.1c03124>.

General Methods and Materials, Preparation of Potassium Methoxide, Table S1 – Dehydroboration of Boronic Ester 2a, Scheme S1 – Dehydroboration of Boronic Ester 2b, Table S2 – Dehydroboration of 2a in the presence of reagents for hydroboration, Synthesis of Catalyst C1, Synthesis of Catalyst C2, Synthesis of Olefins, Dehydroboration of Boronic Ester 2a, Dehydroboration of Boronic Ester 2b, General Procedures for Olefin Isomerizations, Isomerization of Olefins, NMR Spectra of Olefin Isomerizations, and References. (PDF)

Graphical Abstract



Isomerizations of internal olefins to terminal olefins are endergonic and explored much less than their reverse reactions. Typically, contra-thermodynamic, positional olefin isomerizations¹ are conducted by allylic functionalization, followed by defunctionalization with allylic transposition or by photodeconjugation.² These strategies enable translocation of a double bond, but by a maximum of one carbon unit and often under harsh conditions.

Only a small number of long-range (through at least two carbon units), contra-thermodynamic olefin isomerizations have been reported.³ Typically, these reactions form terminal olefins in low yields, low selectivities, or both. Because long-range, contra-thermodynamic olefin isomerizations could enable the valorization of mixtures of internal olefins formed by catalytic cracking of heavy vacuum gasoil to constitutionally pure terminal olefins or the late-stage derivatization of complex molecules containing internal olefins to analogs containing terminal olefins for the remote installation of functional groups, our group has worked to develop mild contra-thermodynamic, long-range olefin isomerizations.

We have reported strategies for conducting such isomerizations through chain-walking hydrofunctionalization followed by dehydrofunctionalization.⁴ In theory, many systems for chain-walking hydrofunctionalization could be coupled to dehydrofunctionalizations to design such olefin isomerizations.⁵ However, few dehydrofunctionalizations have been developed.⁶

In 2019, we published a one-pot process for the selective, long-range isomerization of internal olefins to terminal olefins by platinum-catalyzed, chain-walking hydrosilylation, followed by a novel, formal dehydrosilylation (Scheme 1A).^{4b} We also developed a catalytic dehydrosilylation (Scheme 1B).^{4a} However, the substrate scope of these processes was limited by the strongly reducing conditions of the chain-walking hydrosilylation with trichlorosilane at elevated temperatures. Heteroatom-containing functional groups were not tolerated, and only hydrocarbons underwent the isomerization. In addition, excess CsF and elevated temperatures were required to conduct both types of dehydrosilylation. Therefore, we sought to develop new isomerization sequences involving alternative chain-walking hydrofunctionalizations and dehydrofunctionalizations.

Conditions for chain-walking hydroboration are milder than those for chain-walking hydrosilylation with HSiCl_3 and Speier's catalyst.^{5b-e,7,8} We were particularly interested in several chain-walking hydroborations reported by Chirik (Scheme 1C)^{5c,d,9} because the catalysts for these reactions are capable of walking through methine units and because these hydroborations are conducted with pinacol boronic esters, which are particularly mild reagents.

Dehydroboration of boronic esters or acids is a rare reaction. Alkylboranes undergo acceptorless dehydroborations, as well as transfer dehydroborations with olefins and aldehydes.^{3a-c,10} However, alkylboranes are particularly reactive, and practical chain-walking hydroborations that produce terminal alkylboranes, as opposed to terminal alkylboronic esters, from internal olefins have not been reported. Therefore, we sought to develop a mild method for dehydroboration of alkylboronic esters. Meek and co-workers reported a dehydroboration of β -alkoxy-*gem*-dipinacolato-alkylboronic esters involving palladium (Scheme 1D),¹¹ but a dehydroboration of unactivated alkylboronic esters has not been developed.

We envisioned that alkylboronic esters could undergo dehydroboration through a sequence comprising activation of the boronic ester with a nucleophile, iodination, and base-promoted elimination (Scheme 1E). Until recently, halogenations of unactivated alkylboronic esters had only been reported with organolithiates as activating reagents.¹² In the course of our studies, Renaud and co-workers reported a method for the radical bromination of unactivated alkylboronic esters with benzenesulfonyl bromide as the halogenating reagent.^{12e} However, this reaction requires reagents, such as di-*tert*-butylhyponitrite, trimethylsilyl trifluoromethanesulfonate, methoxycatecholborane, benzenesulfonyl bromide, and *S*-phenyl benzenethiosulfonate, which might be deactivated by other reaction components from the chain-walking hydroboration step or might interfere with the elimination step of an overall isomerization, and iodinations were not reported. Therefore, we sought to develop a mild iodination of alkylpinacolboronic esters that might combine with chain-walking hydroboration to create a one-pot isomerization of internal olefins to the terminal isomers.

We began our studies on this isomerization by investigating the iodination of unactivated alkylboronic ester **2a** (Table 1). We sought to identify a mild, inexpensive nucleophile capable of activating boronic esters for the desired cascade. After surveying a variety of nucleophiles (Table 1, entries 1–13), we identified KOMe as a suitable candidate. We found that alkyl iodide **3a** formed in lower yields when the reaction was conducted with commercial KOMe than when conducted with KOMe prepared from free-flowing KH and anhydrous methanol (Table 1, entries 1–2; see SI for preparation), presumably because commercial alkoxides often contain impurities, such as carbonate, formate, and water, which can decrease yields and selectivities of reactions.¹³ Little or no product formed in the presence of various other oxygen (Table 1, entries 4–9), nitrogen (Table 1, entries 10–11), or hydride bases (Table 1, entry 13). However, alkyl iodide **3a** formed in 78% yield in the presence of CsF (Table 11, entry 12).

We discovered that adding an aliquot of KO^tBu after the addition of I₂ further increased the yield of alkyl iodide **3a** (Table 11, entry 14) beyond that in entry 2 of Table 1. When the reaction was conducted with halogenating agents other than I₂, alkyl halide **3a** formed in lower yields (Table 1, entries 15–16). Temperature had little effect on the yield of alkyl iodide **3a** (Table 1, entries 17–20). Alkyl iodide **3a** formed in lower yields under conditions more dilute (Table 1, entry 21) than those in entry 14 of Table 1 and in lower yields with equivalents of KOMe or of I₂ (Table 1, entries 23–24) greater than those in entry 14 of Table 1. A delicate balance of equivalents of these two reagents is likely required to ensure the formation of alkyl iodide **3a** in high yield, possibly due to the potential of iodine to oxidize potassium methoxide.

Having identified conditions for the iodination of alkylboronic ester **2a**, we investigated the one-pot dehydroboration of alkylboronic ester **2a** to produce terminal olefin **4a** with KO^tBu as the base (see Table S1 in the Supporting Information (SI) for details).

We also conducted the iodination of β -branched alkylboronic ester **2b** to determine whether β branching inhibits the iodination process (see Scheme S1 in the SI for details). The iodination of alkylboronic ester **2b** occurred in lower yield than that of alkylboronic ester **2a**. However, repetition of the activation–iodination sequence significantly increased the yield.

We also sought to determine whether our newly developed dehydroboration of alkylboronic esters could be conducted on the crude products of chain-walking hydroborations to enable one-pot, contra-thermodynamic, positional olefin isomerizations. Therefore, we conducted the dehydroboration of alkylboronic ester **2a** in the presence of various reagents used to conduct chain-walking hydroborations with catalysts **C1** and **C2** (see Table S2 in the SI for details). We found that HBpin and catalyst **C1** inhibited the dehydroboration process (Table S3). Therefore, when conducting the dehydroboration portions of contra-thermodynamic olefin isomerizations, we added the KOMe, I₂, and KO^tBu portionwise, in series, over three iterations. As observed for the dehydroborations of purified β -branched boronic esters, the yields of dehydroborations conducted on the crude products of chain-walking hydroborations significantly increased upon adding the reagents in this fashion.

Having developed conditions for the dehydroboration of alkylboronic esters, we conducted olefin isomerizations. We initially investigated olefin isomerizations in which the chain-walking hydroboration step was conducted in the presence of catalyst **C1** (Scheme 2). We found that both hydrocarbon (olefins **1c**, **1d**, **1e**, **1f**, and **1g**) and functionalized (olefin **1i**) linear internal olefins reacted in good yields with excellent regioselectivities. The tolerance for the oxygen-containing benzyl ether in olefin **1i** contrasts with the tolerance of only hydrocarbons of the previous olefin isomerizations we reported,⁴ because the conditions employed in these previous methods for hydrosilylation reduced even ethers. However, esters were not tolerated (olefin **1j**).

Translocation of the double bond proceeded over as many as nine carbon units (olefin **1g**). However, an isomerization through 18 methylene units (olefin **1h**) proceeded in low yield and with low terminal:internal olefin selectivity, possibly due to the poor solubility of olefin **1g** in MTBE at room temperature. Olefins **4f** and **4g** were isolated cleanly in 68% and 64%

yield, respectively. Olefin **4i** also was isolated in good yield and with good selectivity for the terminal olefin.

To conduct contra-thermodynamic olefin isomerizations in the presence of additional functional groups and on branched internal olefins, we investigated chain-walking hydroborations catalyzed by complex **C2**. Chirik initially developed catalyst **C2**,^{5c} in which the cobalt precatalyst contains 16 valence electrons, and subsequently developed catalyst **C1**.^{5d} Catalyst **C1** is more active but tolerates fewer functional groups than catalyst **C2**. The low functional-group tolerance of catalyst **C1**, presumably, originates from the conversion of the precatalyst to a highly unsaturated cobalt boryl species containing 14 valence electrons that is deactivated by Lewis basic sites, such as oxygen lone pairs. Chirik also found that certain internal olefins in 6-membered rings often did not undergo hydroborations catalyzed by complex **C1** because these olefins often reacted with the catalyst to form stable, endocyclic π -allyl complexes.^{5d}

Thus, to achieve the olefin migrations of trisubstituted alkenes and alkenes containing an acetal group, we used complex **C2** as the catalyst for the chain-walking hydroboration step (Scheme 3). Indeed, the overall isomerization occurred with trisubstituted internal olefins (olefins **1k** and **1m**), and acetal groups were tolerated (olefin **1l**). We also found that (+)- α -pinene (olefin **1m**) underwent isomerization to β -pinene (olefin **4m**) with 3:1 regioselectivity, albeit in moderate yield. Internal olefins are ubiquitous in terpenes, and an isomerization of these internal olefins to terminal olefins could enable the construction of a library of unnatural terpene analogs. The previous contra-thermodynamic olefin isomerizations we reported⁴ were incompatible with most terpenes because these molecules often underwent rearrangements as well as disproportionation to saturated and aromatic products at the elevated temperatures of Pt-catalyzed chain-walking hydrosilylation of trisubstituted olefins with trichlorosilane, a harsh reducing agent. The hydroboration protocol reported herein occurs under milder conditions, enabling the isomerization of terpenes to occur.

Finally, because of the value of catalyst **C2** for chain-walking hydroboration, we developed a route to this catalyst in 5 steps in 22% overall yield, which is two fewer steps than the route reported in the literature, and 2.74 g of the cobalt-dichloride precursor was obtained (see SI for details).

In conclusion, we have combined a novel dehydroboration with chain-walking hydroboration to create a long-range, contra-thermodynamic isomerization of internal olefins to terminal olefins that proceeds at room temperature with a mild reagent for hydrofunctionalization and without fluoride bases. The substrate scope of the isomerization was expanded, relative to that of our previous isomerizations, to include heteroatom-containing internal olefins and an example of a terpene.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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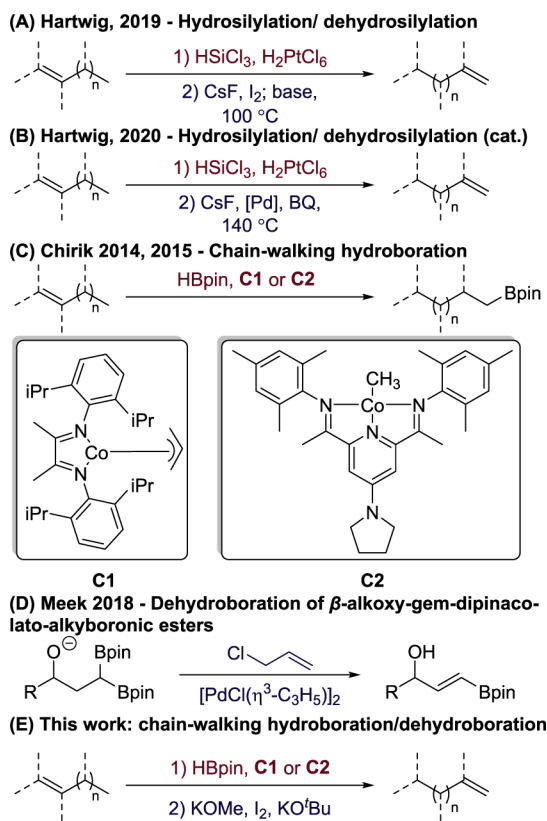
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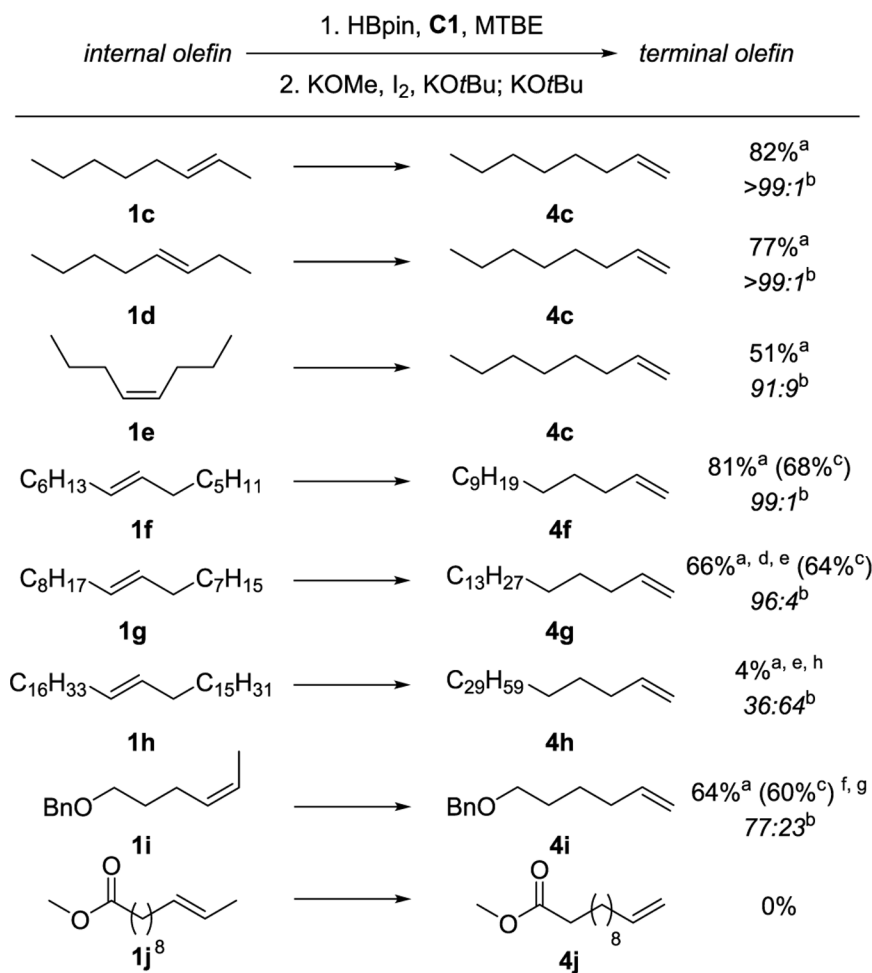
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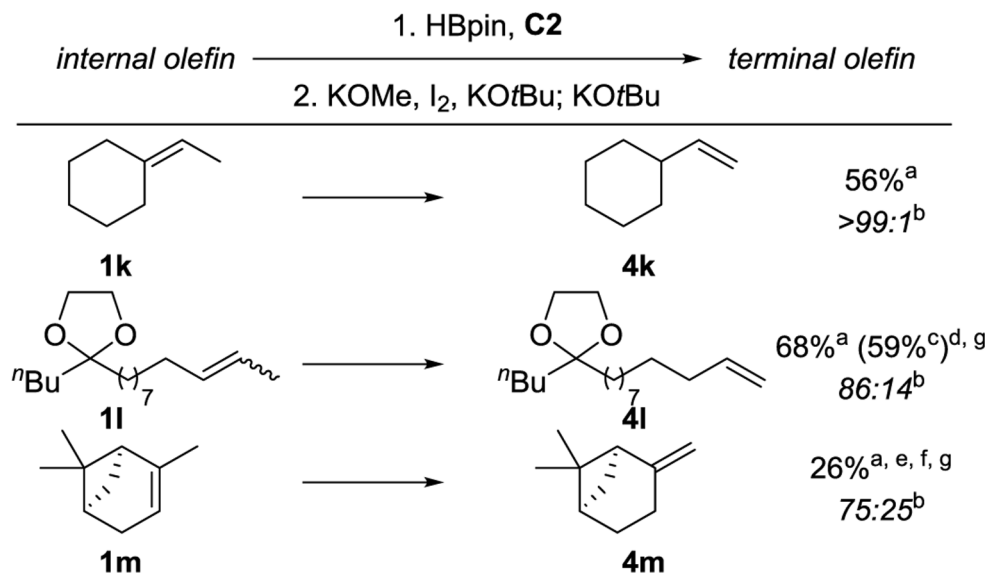
**Scheme 1.**

Development of a Long-Range, Contra-thermodynamic Olefin Isomerization through Hydroboration and Dehydroboration



Scheme 2. Contra-thermodynamic Olefin Isomerizations in the Presence of Catalyst C1

Step 1: Internal olefin (0.640 mmol), HBpin (1.05 equiv), **C1** (2 mol %), rt, 24 h, MTBE (640 μ L). Step 2: KOMe (3 equiv), I₂ (3 equiv), KO^tBu (1.5 equiv), portionwise, 3 iterations; KO^tBu (5 equiv). ^aYield of terminal olefin determined ¹H NMR spectroscopy with trichloroethylene as internal standard. ^bTerminal/internal ratio. ^cIsolated yield of terminal olefin. ^dWith 0.320 mmol of olefin, scaled accordingly. ^e5 mol % **C1**. ^f3 mol % **C1**. ^gStep 1 conducted over 72 h. ^hHydroboration, iodination, and elimination steps conducted at 65 °C.



Scheme 3. Contra-thermodynamic Olefin Isomerizations in the Presence of Catalyst C2

Step 1: Internal olefin (0.640 mmol), HBpin (1.05 equiv), C2 (3–7 mol %), rt, 24 h. Step

2: KOMe (3–4 equiv), I₂ (3–4 equiv), KO^tBu (1.5–2 equiv), portionwise, 3–4 iterations;

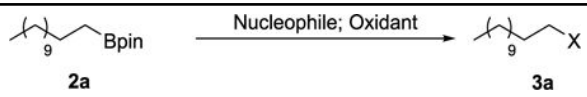
KO^tBu (5–6 equiv). ^aYield of terminal olefin determined by ¹H NMR spectroscopy with

trichloroethylene as internal standard. ^bTerminal/internal ratio. ^cIsolated yield of terminal

olefin. ^dStep 1 conducted at 50 °C for 72 h. ^eStep 1 conducted at 50 °C for 168 h.

^fHydroboration reaction mixture filtered over silica prior to dehydroboration. ^gWith 0.320 mmol of internal olefin, reagents scaled accordingly.

Table 1.

Iodination of Boronic Ester 2a^a


Entry	Nucleophile	Oxidant	Temp	Yield ^b
1	KOMe ^c	I ₂	rt	50
2	KOMe ^d	I ₂	rt	86
3	KOMe ^d + 18-c-6	I ₂	rt	89
4	KOtBu	I ₂	rt	29
5	KOEt	I ₂	rt	15
6	NaOMe	I ₂	rt	5
7	KOH	I ₂	rt	3
8	Cs ₂ CO ₃	I ₂	rt	0
9	NaOAc	I ₂	rt	0
10	LiNH ₂	I ₂	rt	8
11	KHMDS	I ₂	rt	5
12	CsF	I ₂	rt	78
13	KH	I ₂	rt	0
14	KOMe ^d + KOtBu ^e	I ₂	rt	93
15	KOMe ^d + KOtBu ^e	NBS	rt	37
16	KOMe ^d + KOtBu ^e	NIS	rt	0
17	KOMe ^d + KOtBu ^e	I ₂	50	88
18	KOMe ^d + KOtBu ^e	I ₂	65	85
19	KOMe ^d + KOtBu ^e	I ₂	80	86
20	KOMe ^d + KOtBu ^e	I ₂	100	77
21	KOMe ^d + KOtBu ^{e,f}	I ₂	rt	81
22	KOMe ^d + KOtBu ^{e,g}	I ₂	rt	63 ^h
23	KOMe ^d + KOtBu ^{e,i}	I ₂	rt	12
24	KOMe ^d + KOtBu ^{e,j}	I ₂	rt	16

^aConditions: Nucleophile (2 equiv), THF (100 μ L), 15 min, rt; Oxidant (2 equiv), THF (100 μ L), 15 min, rt.

^bDetermined by GC.

^cCommercial bottle.

^dPrepared from KH, see SI for details.

^eEntries 14–24: KO^tBu (1 equiv), THF (100 μ L), added 15 min after I₂, 1 h, rt, see SI for details.

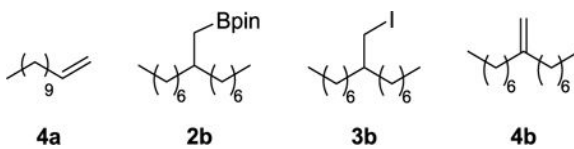
^fAt low concentration, an additional 900 μL of THF was added with the KOMe.

^gLong reaction time, 24 h after the addition of KO^tBu .

^hSome olefin formed by elimination.

ⁱ4.0 equiv KOMe.

^j4.0 equiv of I_2 .



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