Ruthenium-Catalyzed Isomerization of Bioactive Organoboron Compounds for Stereoselective Synthesis of Functional Molecules in Medicinal Chemistry

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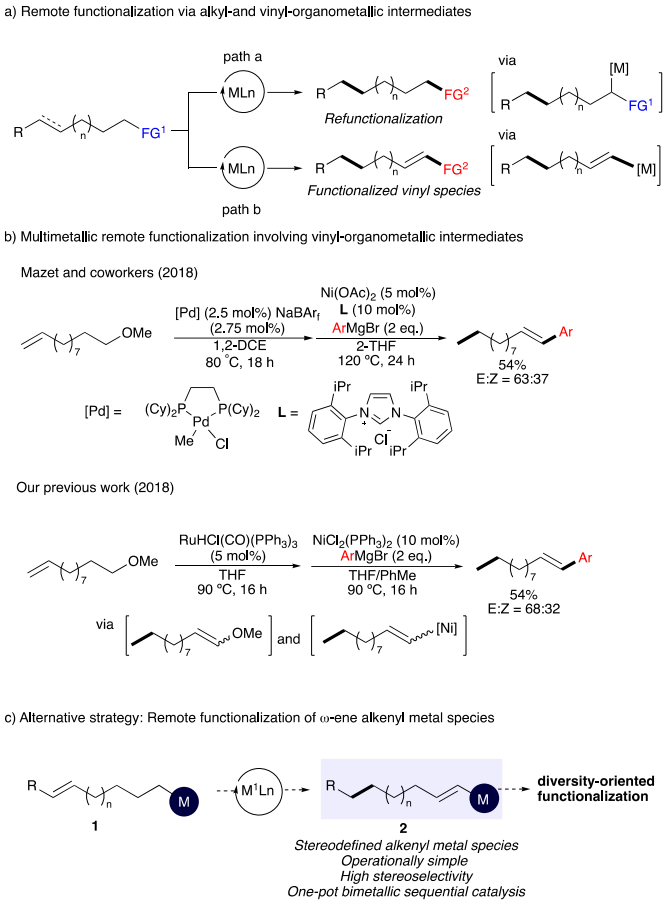
The stereoselective preparation of synthetically versatile vinylboronates from ω-alkenylboronates is achieved through a ruthenium-catalyzed isomerization reaction. A variety of di- and trisubstituted vinylboronates were conveniently produced and could be used as a new starting point for subsequent *in-situ* remote functionalization through either a sequential Ru/Pd or Ru/Cu double catalytic system.

Introduction

The distant and selective functionalization of unreactive C−H and C−C bonds stands as one important challenge in organic chemistry.[1] In recent years, the remote functionalization of alkenes by metal-walk along a hydrocarbon chain has attracted an increased attention as it allows the functionalization of a distant and generally unreactive position.[2] This concept paved the way to new approaches to efficiently build molecular complexity from easily accessible starting materials. From the pioneering metal-walk using stoichiometric zirconium complexes[3] to catalytic systems employing palladium,[4] nickel,[5] ruthenium,[6] rhodium,[7] iridium[8] or cobalt complexes,[9] many attractive protocols have been reported in the last decade. These chain-walking processes are usually leading either to sp^3 post-functionalization reactions[2] or to the generation of a carbonyl group[10] (Scheme 1a, path a). However, the preparation of a distant functionalized alkenyl organometallic species from an original sp^3 carbon center remains less explored (Scheme 1a, path b).[2g] In this regard, we[11] and Mazet[12] have independently reported an efficient Pd-Ni and Ru-Ni double catalytic system transforming readily available ω-alkenyl ethers into a large variety of styrenyl products (Scheme 1b). Despite these significant advances, several challenges remain to be addressed such as the moderate level of stereocontrol over the geometry of the formed enol ether as well as the low *E*/*Z*-selectivity of the final cross-coupled products.[13] Apart from the control of stereochemistry, the process is incompatible with sensitive functionalities and the final coupling products generally lack the diversity of functional groups that one might expect due to the nature of the Grignard reagent required for the final cross-coupling reactions.



Scheme 1. Strategies for remote functionalization of ω-alkenes.

To address these shortcomings, we hypothesized that a straightforward alternative should involve a metal-catalyzed remote functionalization of ω-alkenyl organometallic derivative **1** into a synthetically versatile alkenyl organometallic species **2** with excellent stereocontrol of the olefin geometry (Scheme 1c). Alkenyl organometallic reagents are important and versatile intermediates in organic chemistry that were abundantly used for cross-coupling reactions. Among all possible organometallic candidates for this transformation, we concentrate our initial study on the formation of

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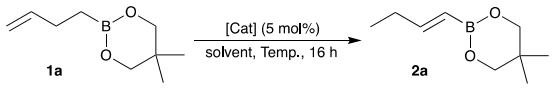
alkenyl organoboronates **2** [M = $B(OR)_2$][14] that have been recognized as the most widely used representatives due to their diverse reactivity profile, excellent functional-group tolerance, stability to air, and non-toxic nature (Scheme 1c), unique characteristics among all other organometallic reagents.[15]

However, it was also clear that this transformation would be challenging to perform as the Ru,[16] Ir,[17] Pd,[18] or Ni-catalyzed[19] isomerization of 1-alkenylboronate provide the corresponding 2-alkenylboronate (allylboronate) intermediate (the opposite of what we are planning to achieve), which react with a carbonyl group in a stereospecific way, delivering homoallylic alcohol products with excellent stereoselectivity.[20] In addition, upon proper choice of the coupling partners, the synthesis of branched-selective hydrofunctionalization could be achieved to produce α-aryl alkylboronates and 1,1-diboron compounds, respectively.[21,9c] In other words, isomerization towards the preparation of synthetically versatile vinylboronate species is highly challenging, but of high synthetic utility given the prevalence and importance of vinylboronates in cross-coupling reactions. To date, only two examples were reported and restricted to a 1-carbon migration of allyl pinacol boronates.[22] With the aim of developing an efficient alternative towards functionalized vinyl species, we decided to embark on a study and identify a metal that would be able to catalyze the migration of a remote double bond of ω-alkenylboronates **1** to stereodefined vinylboronates **2** *en route* to diversely functionalized alkenes and α-functionalized alkylboronates (Scheme 1c).

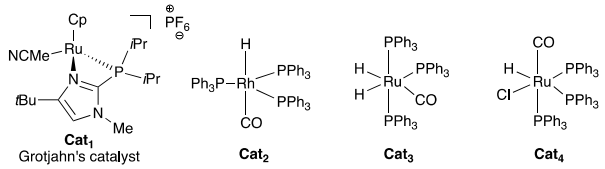
Results and Discussion

We started our study by evaluating the isomerization of our model substrate, 2-(but-3-en-1-yl)-5,5-dimethyl-1,3,2-dioxaborinane **1a**, with a selection of various commercially available well-established isomerization catalysts **Cat$_{1\text{-}4}$** (Table 1). Gratifyingly, the formation of the desired vinylboronate product **2a** was observed in all cases, albeit along with partial allylboronate isomers. For instance, the ruthenium-based "alkene zipper" Grotjahn's catalyst **Cat$_1$**,[23] successfully used for successive isomerizations of a remote double bond combined with a retro-ene reaction of ω-alkenyl cyclopropyl carbinols,[24] afforded the vinylboronate **2a** in satisfactory yield with a perfect *E*-selectivity (Table 1, entry 1). The neutral rhodium hydride complex **Cat$_2$** required higher temperature but produced **2a** in low yield, whereas ruthenium dihydride catalyst **Cat$_3$** afforded **2a** in acceptable yields with good levels of stereocontrol (Table 1, entries 2 and 3). On the other hand, the ruthenium monohydride [$RuH(Cl)(CO)(PPh_3)_3$, **Cat$_4$**] was shown to be as effective catalyst as **Cat$_1$**. Having catalyst **Cat$_4$** in hand, the nature of the solvent was briefly investigated and when toluene was replaced by dichloroethane or pinacolone, lower yields were observed (Table 1, entries 5 and 6). Ultimately, the presence of THF at 60 °C allowed the formation of **2a** in 76% yield after purification by column chromatography with an excellent *E*/*Z* ratio (Table 1, entry 7). Further reduction of the catalyst loading to 2.5 mol% didn't alter the transformation (72%, *E*:*Z* 94:6). It should be noted that subjecting pure ***E*-2a** (prepared by an independent route) to the optimized catalytic conditions (Table 1, entry 7), leads to a minor quantity of *E*- and *Z*-allylboronates indicating that the isomerization reaction of **1a** is reversible with vinylboronate product **2a** still being the major isomer.

Table 1. Reaction optimization of metal-catalyzed isomerization of alkenylboronate[a]



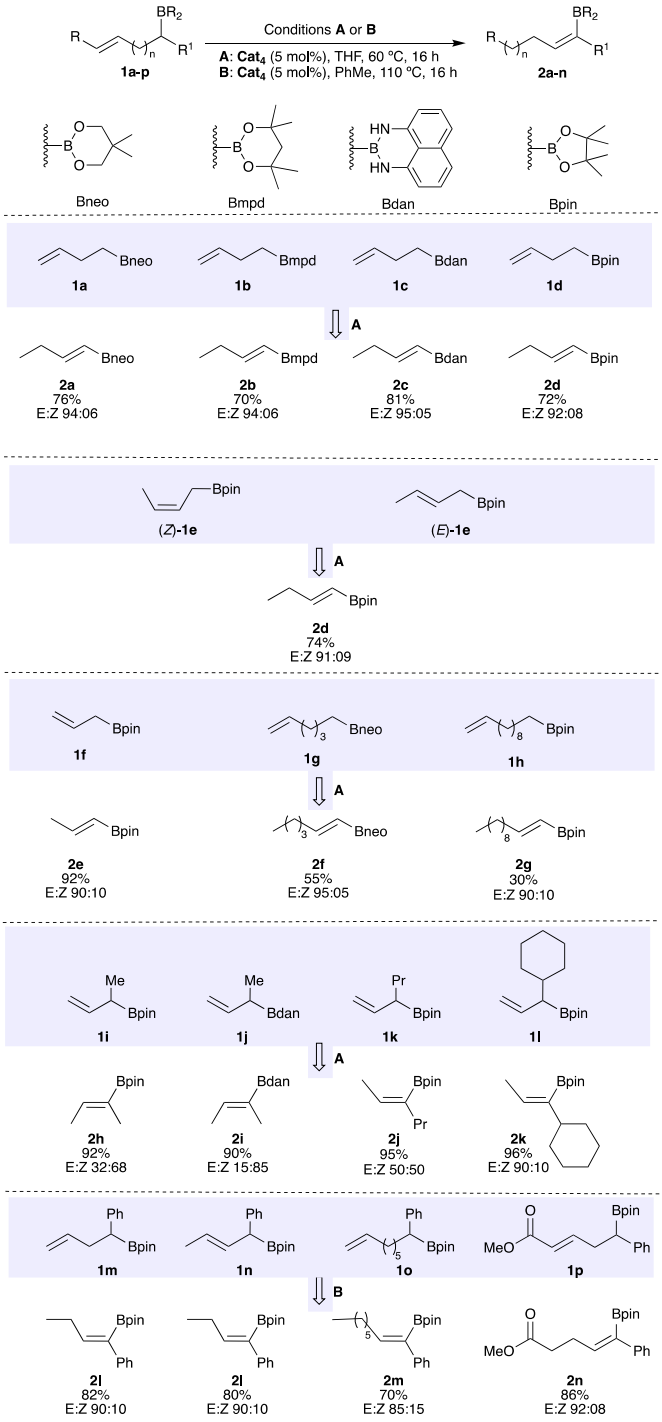
Entry	[Cat]	solvent	T (°C)	yield (%)[b]	E:Z[c]
1	Grotjahn's catalyst **Cat$_1$**	Dichloroethane	40	62	>95:5
2	$RhH(CO)(PPh_3)_3$ **Cat$_2$**	Toluene	100	29	93:7
3	$RuH_2(CO)(PPh_3)_3$ **Cat$_3$**	Toluene	100	58	91:9
4	$RuHCl(CO)(PPh_3)_3$ **Cat$_4$**	Toluene	100	64	93:7
5	$RuHCl(CO)(PPh_3)_3$ **Cat$_4$**	Dichloroethane	60	38	93:7
6	$RuHCl(CO)(PPh_3)_3$ **Cat$_4$**	Pinacolone	60	11	95:5
7	$RuHCl(CO)(PPh_3)_3$ **Cat$_4$**	THF	60	76	94:6[d]



[a] All reactions were carried out using **1a** (0.3 mmol) and catalyst (5 mol%) in 1.5 mL of solvent under Ar. [b] Yields were determined after filtration of the crude reaction mixture through a short pad of silica gel (pentane/ether, 20/1). [c] The *E*/*Z* ratio was determined by ^{1}H NMR of the crude reaction mixture. [d] The catalytic loading could be decreased to 2.5 mol% without altering the reaction.

With the optimal conditions in hand (Table 1, entry 7), we set out to explore the scope of this transformation as summarized in Scheme 2. Terminal alkenyl boronates **1a–d** with various masked boron groups were all compatible under this experimental condition, providing the corresponding isomerized products **2a–d** in good yields with good *E*/*Z* selectivities (Scheme 2). As expected, both *cis*- and *trans*-internal alkenyl boronates (*Z*)- and (*E*)-**1e** appeared to be equally tolerated, delivering the same product **2e** in similar yields and selectivity (Scheme 2). Substrates with longer tether (n = 1-4) between the unsaturation and the sp^3-centered boron atom still afforded the desired products **2a**, **2e** and **2f** in excellent to moderate yields with high *E*/*Z* selectivities. However, the isomerization of **1h**, possessing 9 methylene units between the unsaturation and the boron atom, provides **2g** in lower yield despite the good stereoselectivity. A significant amount of internal double-bond isomers was observed in the crude reaction mixture.

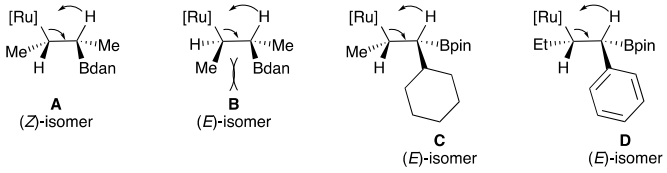
α-Branched allylboronates **1i**–**o** with different alkyl groups were also successfully engaged in this transformation for two different types of boronates species, (*i.e.,* Bpin, Bdan). Although Bdan presents a slightly higher selectivity (Scheme 2, **2h** versus **2i**), Bpin has been preferentially investigated as easier to manipulate for subsequent transformation. It is interesting to note that the selectivity of the formed double bond is very dependent of the steric hindrance of either the substituent on the boron atom (Scheme 2, compare **2h** and **2i**) or of the nature of the alkyl group (Scheme 2, compare **2h** with **2j** and **2k**).



Scheme 2. Substrate scope for the Ru-catalyzed isomerization of ω-alkenylboronates.

When α-phenyl ω-alkenylboronates **1m**–**o** having different olefin geometry and chain lengths were subjected to the condition B in toluene at 110 °C, the synthetically challenging (*E*)-trisubstituted vinylboronates **2l**–**m** were obtained in good yields with high stereoselectivities (Scheme 2). When α-phenyl alkenylboronates **1m–p** were subjected to the condition A (THF, 60 °C), the desired vinylboronates were obtained in acceptable yields with high levels of stereocontrol but with a significant amount of allyl isomers. These results suggested that the α-phenyl substituent has a pronunced influence on the C=C bond reactivity towards Ru-H insertion during the transformation of allylboronate intermediate into vinylboronate. Switching the solvent to toluene at 110 °C (condition B) was required to convert allylboronate intermediate into conjugated vinylboronate. The stereochemistry of (*E*)-**2l** was determined by comparison with reported data[25] and could be rationalized by the relative bulkiness of substituents in the Ru-H β-syn elimination (Scheme 3, **D**). It should be noted that metal-catalyzed hydroboration of internal alkynes and allenes usually produces the (*Z*)-vinylboronates[26] whereas the (*E*)-isomer could only be obtained through the elegant non-classical trans-hydroboration of internal alkynes recently reported by Fürstner (excluding metal-catalyzed diboration reactions of allenes and propargyl alcohols).[27] Hence, these results demonstrated an alternative regio- and stereoselective synthesis of *E*-trisubstituted vinylboronates by ruthenium-catalyzed isomerization.

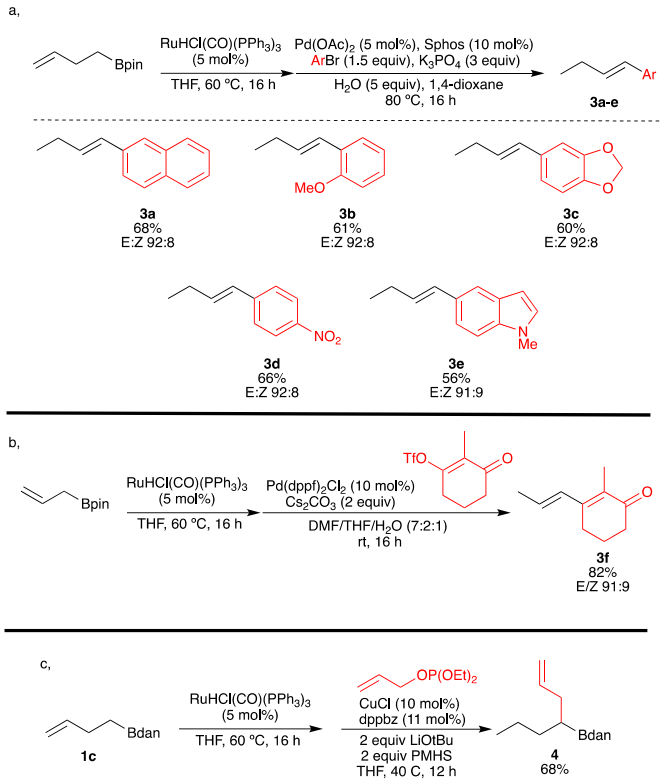
Finally, the deconjugative/reconjugative isomerization of **1p** was successfully achieved to afford the reconjugative product ***E*-2n** in good yield with excellent control over the double-bond geometry (Scheme 2). It is proposed that the steric preference of Bdan versus Bpin to produce the (*Z*)-isomer when R^1 = Me (**2h** versus **2i**) as well as the constant formation of the *E*-vinyl boronates **2k–n** as major isomer for bulkier R^1 substituents relates to the steric interactions in the *syn* Ru-H β-elimination reaction (Scheme 3). Comparing intermediates **A** and **B**, less steric interactions exist in **A** than in **B**, explaining why the isomer *Z*-is preferentially formed. When the size of the substituent increases, the trend is reversed and now intermediate **C** should be the favored intermediate before the *syn*-[Ru] β-elimination reaction (Scheme 3). Although the same explanation should hold for the intermediate **D**, one could not exclude additional potential stabilizing interactions between the aromatic ring and the [Ru] complex.[28] It should be noted that the opposite isomer (*Z*)-**2l**, prepared by an independent route (see the Supporting Information for details), treated in our standard reaction conditions, does not provide any other isomeric products including (*E*)-**2l**, indicating that the formation of (*E*)-**2l** doesn't result from subsequent isomerization processes.



Scheme 3. Mechanistic hypothesis to rationalize the stereochemistry of vinylboronates.

Motivated by merging transition-metal-catalyzed chain-walking processes with subsequent remote functionalization, we further explored the possibility of combining the ruthenium-catalyzed isomerization with a palladium-catalyzed Suzuki-Miyaura cross-coupling reaction in a single-pot operation as described in Scheme 4a. To our delight, this [Ru/Pd] catalytic combination enabled a highly *E*-selective cross-coupling reaction of the *in situ* generated (*E*)-vinylboronates that was not possible to get with our previous procedure on ω-alkenyl ethers.[11,12] Various aryl halides and alkenyl triflate were compatible furnishing the coupling products **3a–f** in

satisfying yields (based on two chemical steps) with excellent *E*:*Z* ratios. It should be highlighted that the present methodology allows the cross-coupling with partners bearing electron-withdrawing substituents, heteroaromatic or enone, which was also not allowed by our previously reported protocol (Scheme 4b).[11] An additional example to illustrate the power of this transformation is to combine the Ru-walk with a copper-catalyzed hydroallylation reaction.[29] For instance, when ω-alkenylboronate **1c** was first isomerized into **2c**, and then *in-situ* treated with an allylphosphonate in the presence of a catalytic amount of copper salt, the sp^3 *gem*-dialkylated boron species **4** was obtained in 68% yield, illustrating the compatibility of this new double catalytic system (Scheme 4c). It is remarkable that the presence of Ru catalyst doesn't interfere in the second catalytic cycle.



Scheme 4. Combined [Ru]-catalyzed isomerization with subsequent functionalization.

Conclusions

In conclusion, we have developed a regio- and stereoselective ruthenium-catalyzed isomerization of ω-alkenyl boronates into stereodefined di- and trisubstituted alkenylboronate derivatives. This method provides not only a new access to a variety of synthetically valuable alkenyl organoboronates, not always easily accessible, but serve also as an entry point for subsequent remote functionalization. These sequential catalytic processes, in a one-pot operation, could be achieved by either a subsequent palladium-catalyzed Suzuki-Miyaura cross coupling or by a copper-catalyzed hydroallylation reactions. These transformations delivered the products in practical yields with a high degree of olefin stereocontrol in the former case.

Conflicts of Interest

There are no conflicts to declare

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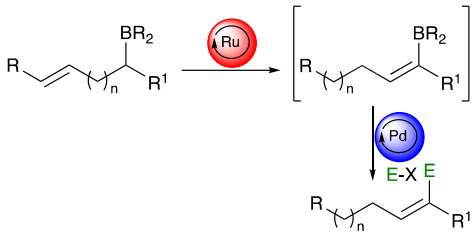

A regio- and stereoselective ruthenium-catalyzed isomerization of ω-alkenyl boronates into stereodefined di- and trisubstituted alkenylboronate derivatives is reported