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Nickel-Catalyzed Double Bond Transposition of Alkenyl Boronates for *in Situ syn*-Selective Allylboration Reactions

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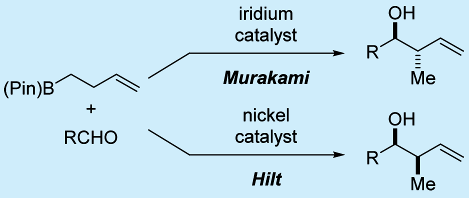
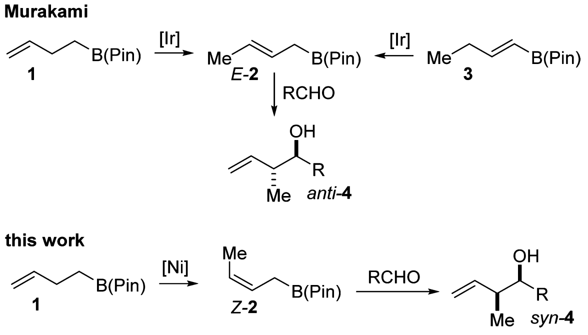
Supporting Information

ABSTRACT: The transposition of a homoallyl pinacol boronic ester was realized by a highly reactive nickel-catalyst system comprising $NiCl_2(dppp)$, zinc powder, ZnI_2, and Ph_2PH. The *in situ* generated *Z*-crotyl pinacol boronic esters were reacted with various aldehydes to form *syn*-homoallylic alcohols in high diastereoselectivities. The present nickel-catalyzed reaction is complementary to the iridium-catalyzed transposition reported by Murakami leading to the corresponding *anti*-homoallylic alcohols. Also, the multiple transposition of pentenyl pinacol boronic ester was realized.



The transposition of a carbon−carbon double bond by transition metal catalysts along a carbon chain can be achieved in two different ways. The double bond migrates either toward or away from a functional group.[1] Accordingly, an *E*-crotyl boron reagent (*E*-**2**) could be generated either from a homoallylic boronic ester (**1**) when transposition of the double bond is realized toward the boron functionality or from a vinyl boronic ester (**3**) away from the boronic ester group.[2] The latter was demonstrated recently by Murakami utilizing iridium catalysts.[3] The *in situ* allylboration of aldehydes then generated the *anti*-homoallylic alcohols (*anti*-**4**) in excellent yields and diastereoselectivities (Scheme 1).[3]

Scheme 1. Outline of Double Bond Transpositions of Boron-Functionalized Alkenes (Pin = pinacol)



The presence of the aldehyde is tolerated, because there is essentially no reactivity of homoallyl boronic esters (**1**) toward aldehydes. The allyl boron reagent *Z*-**2** will react readily with aldehydes whereas vinyl boronic esters (**3**) are unreactive toward aldehydes as well.

In this report, we describe the complementary allylation of aldehydes via *Z*-crotyl boronic esters (*Z*-**2**) in which the latter were generated *in situ* under mild reaction conditions by a nickel catalyzed transposition from homoallylic boronic esters (**1**).[4] Accordingly, we envisaged a transition-metal-catalyzed transposition of a double bond of a homoallylic boronic ester **1** in the presence of an aldehyde so that the reactive allyl boronic ester species **2** is quenched *in situ* for the formation of the desired *syn*-**4** product before another isomerization toward **3** could occur. For a successful and synthetically useful reaction of this type, three prerequisites must be fulfilled: first, the isomerization must be diastereoselective toward a defined double bond configuration of *Z*-**2**. Second, the isomerization must not be inhibited by the present aldehyde. Third, for achieving a high diastereoselectivity of the allylation reaction, the isomerization as well as the allylation must be performed at low temperatures.[5]

Under these circumstances, our previously described cobalt catalyst system will not be applicable, since the isomerization only takes place at room temperature and under these reaction conditions the allylboration will not be highly diastereoselective.[6] On the other hand, the corresponding nickel-catalyzed transposition process seems to be well suited for this transformation.[4]

When benzaldehyde was reacted with homoallyl boronic pinacol ester **1** in the presence of the simple and easy to handle nickel catalyst precursor $NiCl_2(dppp)$ (dppp = 1,3-bis(diphenylphosphino)propane), which was activated by zinc powder, zinc iodide, and diphenylphosphine, the desired product *syn*-**4a** could be obtained in 81% yield (Scheme 2).

Some aspects should be noted. For once, the reaction could also be accomplished in the absence of zinc iodide, but in this case the reactivity was slightly lower. As we reported before, the diphenylphosphine was crucial for the reaction. The transposition was performed at a temperature as low as −50 °C. At this temperature, the allylboration readily took place and gave the desired product *syn*-**4a** in good yield and an excellent diastereoselectivity of 98:2. This indicated that the two

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Scheme 2. Nickel-Catalyzed Transposition/Allylation of Benzaldehyde (Pin = pinacol)

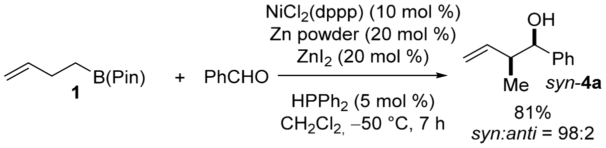
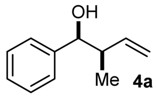
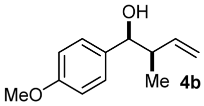
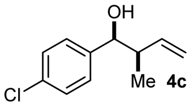
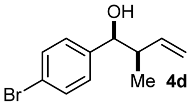
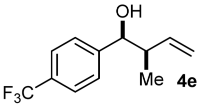
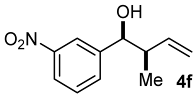
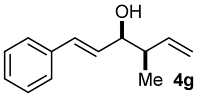
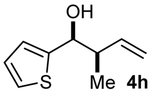
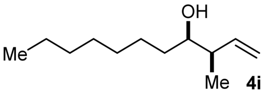


Table 1. Results of the Nickel-Catalyzed Transposition/Allylation Sequence[a]

no.	product **4**	yield temp / time *syn*/*anti* ratio
1	 **4a**	81% −50 °C / 7 h 98:2
2	 **4b**	81% −50 °C / 5 h 96:4
3	 **4c**	98% −40 °C / 1 h 97:3
4	 **4d**	77% −50 °C / 5.5 h 97:3
5	 **4e**	76% −40 °C / 7 h 95:5
6	 **4f**	61% −40 °C / 7 h 98:2
7	 **4g**	96% −40 °C / 6 h 92:8
8	 **4h**	56% −50 °C / 2 h 86:14
9	 **4i**	78% −50°C / 5 h ~95:5

[a] Reaction conditions: $NiCl_2$(dppp) (10 mol %), Zn, ZnI_2 (20 mol % each), Ph_2PH (5 mol %), **1** (0.5 mmol, 1.0 equiv), CH_2Cl_2; different reaction temperatures and times are listed in the table. The reaction temperature was adjusted with a dry ice/isopropanol bath. The *syn*/*anti* ratios were determined by ^{1}H NMR spectroscopy.

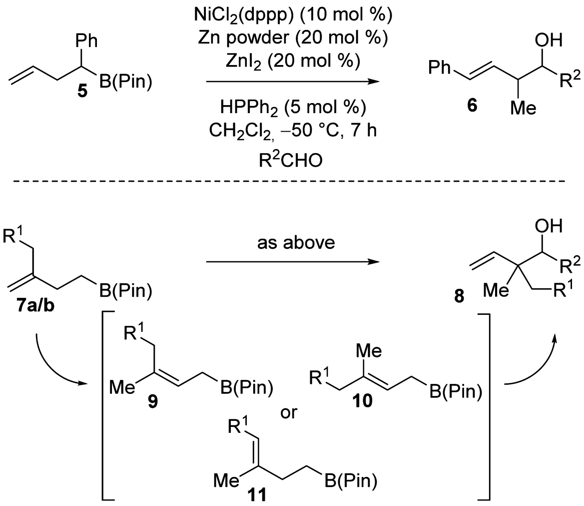
processes, the nickel-catalyzed isomerization as well as the allylboration, were highly diastereoselective. As mentioned above, *syn*-**4a** was generated predominantly, thereby indicating that also in the presence of benzaldehyde, which obviously did not inhibit the isomerization reaction, the isomerization gave the *Z*-isomer of type **2** in high excess. The low temperatures also prohibited a nickel-catalyzed isomerization of the homoallylic alcohol **4a** toward an allylic alcohol. These results prompted us to investigate a number of functionalized aldehydes in the nickel-catalyzed transposition/allylation process in order to identify the scope and limitations. The results of these reactions are summarized in Table 1.

Besides the Ph_2PH, which had to be kept under oxygen-free conditions, the other components of the catalyst system are easy to handle as well as rather inexpensive compared to other catalyst systems utilizing other metals and additives.[1−4] Functional groups such as a methoxy group (**4b**), halide functionalities (**4c** and **4d**), a trifluoromethyl group (**4e**), and a nitro substituent on the benzene ring (**4f**) are well accepted and do not interfere with the nickel-catalyzed isomerization process. Also, heterocycles, such as thiophene (**4h**) and α,β-unsaturated aldehydes (**4g**), are tolerated. The products **4a**−**4g** were obtained in good overall yields, and the *syn*-products were often formed with a high degree of diastereoselectivity (>92:8). Only the product derived from thiophene-2-carbaldehyde (**4h**) led to a lower yield of 56% and an inferior diastereoselectivity of only 86:14. Noteworthy is the observation that the carbon−carbon double bonds were not found to undergo a hydrophosphonylation which would have consumed the $HPPh_2$. Also, the aliphatic aldehyde octanal led to the desired product **4i**, which was isolated in a good yield of 78%; however, the determination of the diastereoselectivity of the overall process was problematic, since diagnostic ^{1}H NMR signals overlapped significantly. Nevertheless, we estimate the diastereoselectivity for the formation of **4i** to be >95:5 (GCMS analysis). Besides the products of type **4**, no other side products generated by follow-up transposition reactions were detected at these low temperatures. Accordingly, the methyl substituent in **4** inhibits coordination to the nickel catalyst or the hydrogen transfer of the sterically more hindered **4** is hampered at low temperatures which allows the selective formation of products **4**. When the reaction toward **4a** was performed at +40 °C, follow-up transpositions toward vinyl pinacol boronic ester **3** were observed (~14%) indicating that under elevated temperatures a fast transposition outruns the allylboration reaction. The product **4a** was obtained in moderate yield (27%) but lower diastereoselectivity (*syn*/*anti* = 80:20). However, transposition of **4a** toward a corresponding allylic alcohol was not observed.

In a second set of experiments, we were interested in investigating if the double bond transposition process could also be performed with more complicated homoallylic pinacol boronic esters (Scheme 3). Therefore, the phenyl-substituent starting material **5** or homoallylic starting material **7** with substituent R^1 was used to investigate the influence. At this point we would like to comment that the corresponding cobalt-catalyst system for the transposition of double bonds for the latter type of substrates proved to be unreactive.

The choice for the phenyl substituent at the α-carbon was rationalized by the expectation that the phenyl would preferentially adopt an *E*-configuration in the corresponding product **6** in order to minimize the number of stereoisomers formed in the reaction sequence. The substituent R^1 (**7**) was chosen to be a hydrogen and a methyl group for two instances. Initially, we intended to investigate the possibility of realizing an isomerization of an *exo*-chain double bond toward the boron functionality and thereby generate a *geminal*-dimethyl subunit (**7a**, R^1 = H).[5] If R^1 was not hydrogen but a different group, such as a methyl group, an interesting scenario would occur. The introduction of an ethyl group (**7b**, R^1 = CH_3) would allow the formation of a quaternary chiral carbon center in the proposed product **8**. Also the nickel-catalyzed transposition could either proceed toward the boron functional group to

Scheme 3. Transposition/Allylation of Substituted Homoallyl Boronic Esters (Pin = pinacol)

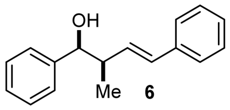
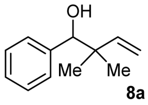
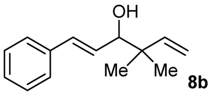
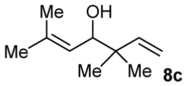
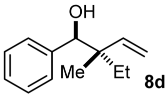
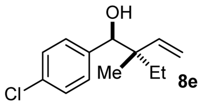
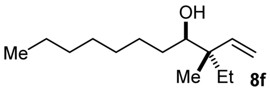


generate the proposed intermediate **9**/**10** or lead to intermediate **11**. While **9**/**10** would react with aldehydes to generate **8**, intermediate **11** would probably resemble a dead-end and lead to a dramatic loss in efficiency. Both intermediates possess a trisubstituted double bond that likely does not exhibit a significant reactivity for the nickel catalyst or a driving force toward one or the other transposition to convert **9**/**10** into **11**, or *vice versa* might be found. The results of these nickel-catalyzed reactions are summarized in Table 2.

The reaction of **5** led exclusively to the *E*-configured **6** in excellent yield (97%) in very good diastereoselectivity (95:5). The *exo*-chain double bond derivatives **7a** and **7b** reacted very slowly in the cold; however, at room temperature after somewhat longer reaction times, the desired homoallylic alcohols of type **8** were obtained in acceptable yields. Noteworthy, the natural product *artemisia alcohol* **8c** could be isolated in 80% yield. Moreover, the transpositions of starting material **7b** gave the *anti*-configured products **8e**−**8f** predominantly. The rationale for the formation of the *anti*-products is that the transposition proceeds predominantly via intermediate **10**; however, the diastereomeric ratios are only moderate.

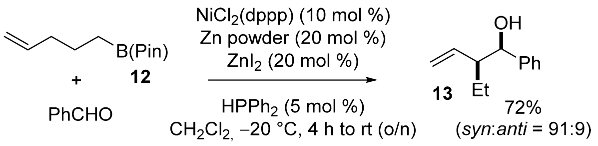
Finally, we were interested in investigating if the double bond transposition could be realized along a longer carbon chain under relatively mild reaction conditions. This would allow the introduction of longer alkyl substituents other than a simple methyl group next to the hydroxyl group in **4** (compare Scheme 2). Accordingly, as a prototype substrate, 1-pentenyl pinacol boronic ester **12** was reacted with the nickel catalyst system in the absence of benzaldehyde at low temperature (−20 °C), and a mixture of homoallylic and allylic pinacol boronates were detected (Scheme 4). In the presence of benzaldehyde even at temperatures, as low as −20 °C, the double bond transposition proceeded twice and the desired product **13** could be obtained in an acceptable yield of 72% and diastereoselectivity (91:9).

Table 2. Results of the Nickel-Catalyzed Transposition of Substituted Allyl Boronic Esters and *Exo*-Chain Double Bonds[a]

no.	products of type **6** and **8**	yield temp / time *syn*/*anti* ratio
1	 **6**	97% −20 °C / 2 h then rt o/n 95:5
2	 **8a**	75% rt /16 h -
3	 **8b**	81% rt /16 h -
4	 **8c**	80% rt /16 h -
5	 **8d**	43% rt / 48 h 19:81
6	 **8e**	73% rt / 48 h 33:67
7	 **8f**	52% rt / 16 h 31:69

[a] Reaction conditions: $NiCl_2(dppp)$ (10 mol %), Zn, ZnI_2 (20 mol % each), Ph_2PH (5 mol %), **5** or **7a**/**b** (0.5 mmol, 1.0 equiv), CH_2Cl_2; different reaction temperatures and times are listed in the table. The reaction temperature was adjusted with a dry ice/isopropanol bath. Unreacted starting material and other isomers were not separated and are included in the yield. Conversion were determined by GC/MS analysis, and *syn*/*anti* ratios were determined by ^1H NMR spectroscopy.

Scheme 4. Double Bond Transposition/Allylation of Benzaldehyde and Pentenyl Pinacol Boronic Ester 12 (Pin = pinacol)



In conclusion, we were able to apply the nickel-catalyzed double bond transposition reaction in the presence of aldehydes at low temperatures. Thereby the desired homoallylic alcohols were generated in good yields and high diastereoselectivities without further transposition of the double bonds. Also, *exo*-chain double bonds could be isomerized, but in these cases the *anti*-products were formed predominantly albeit in lower diastereoselectivities. Finally, the nickel-catalyzed isomerization of a pentenyl pinacol boronic ester was performed and led to the introduction of an ethyl group with good diastereoselectivity.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03585.

Synthesis, analytical data, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(6) The identical reaction performed with $CoBr_2$(dppp) instead of the nickel catalyst in the presence of benzaldehyde at ambient temperatures gave no conversion while in the absence of the aldehyde a transposition occurs; see: Schmidt, A.; Nödling, A. R.; Hilt, G. *Angew. Chem., Int. Ed.* **2015**, *54*, 801−804.