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A Novel Method for the Construction of (*Z*,*E*)- or (*Z*,*Z*)-Conjugated Alkadienyl Carboxylates

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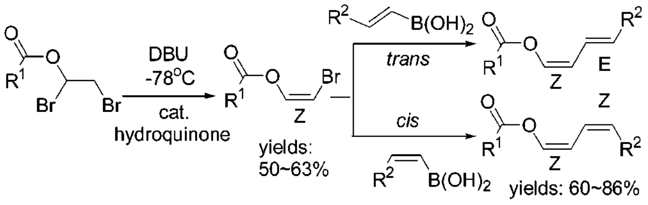
ABSTRACT



The stereocontrolled dehydrobromination of 1,2-dibromoethyl carboxylates giving (*Z*)-2-bromovinyl carboxylates could readily be approached by using DBU and a catalytic amount of hydroquinone as a base at −78 °C. The first investigation on the Suzuki-type cross-coupling of (*Z*)-2-bromovinyl carboxylates as electrophiles with stereodefined alkenylboronic acids provides a novel method for the construction of (*Z*,*E*)- or (*Z*,*Z*)-conjugated alkadienyl carboxylate moieties, which are often present in a range of natural products.

Conjugated alkadienyl carboxylate moieties not only are found in a growing class of natural products isolated from a wide spectrum of marine organisms with important physiological properties[1] but also are recognized to be important precursors to prepare a wide range of natural products by Diels−Alder reaction.[2] Among the methods for the preparation of conjugated alkadienyl carboxylates, the traditional enolacetylation of *trans*-2-alkenylal with acetic anhydride in the presence of base led to a mixture of all four isomers of alkadienyl acetate.[3a] It was found that stereodefined (*E*,*E*)- or (*E*,*Z*)-conjugated alkadienyl carboxylates could be prepared in a few steps from pyridine[1d] and (*E*,*Z*)-alkadienyl carboxylates also could be obtained by the stereocontrolled hydrogenation of (*E*)-alkynylvinyl carboxylates.[1c] Bruneau reported that ruthenium-catalyzed addition of carboxylates to terminal alkynes can afford (*Z*)-alk-1-en-yl esters including conjugated dienyl esters.[3b] However, to the best of our knowledge, the general method for the stereodefined preparation of (*Z*,*E*)- or (*Z*,*Z*)-conjugated alkadienyl carboxylates has not been reported, perhaps becuase of its thermodynamic instability.[1d,4] So, it seems important to develop an effective method for the construction of (*Z*,*E*)- or (*Z*,*Z*)-conjugated alkadienyl carboxylates. In this communication, we wish to report a novel approach to (*Z*,*E*)- or (*Z*,*Z*)-conjugated alkadienyl carboxylates.

As is well-known, the transition metal catalyzed Suzuki cross-coupling reaction is one of the most efficient methods for the construction of carbon−carbon bonds, especially for the formation of general dienes.[5] Apparently, it is a reasonable route to synthesis of (*Z*,*E*)- or (*Z*,*Z*)-conjugated alka-

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[4] (a) Söderberg, B. C.; O'Neil, S. N.; Chisnell, A. C.; Liu, J. *Tetrahedron* **2000**, *56*, 5037−5044. (b) Söderberg, B. C.; Liu, J.; Ball, T. W.; Turbeville, M. J. *J. Org. Chem.* **1997**, *62*, 5945−5952.

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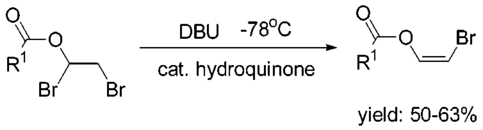
dienyl carboxylates by the Suzuki-type coupling reaction of (*Z*)-2-bromovinyl carboxylates as electrophiles with alkenylboron reagents. Accordingly, the successful preparation of (*Z*)-2-bromovinyl carboxylates and the selection of coupling conditions are the key to realize the route. Although many reports regarding cross-coupling reactions[6] of general alkenyl halides, including enol acetates of 2-bromo ketones,[6c] with aryl and alkenylboron reagents exist, the cross-coupling of (*Z*)-2-bromovinyl carboxylate as a special electrophile has not appeared in the literature, perhaps owing to its difficult availability. We improved the synthesis process of (*Z*)-2-bromovinyl carboxylate and first investigated its Suzuki-type cross-coupling reaction. Herein, we wish to report the experiment results.

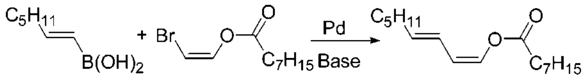
It was reported that (*Z*)-2-bromovinyl acetate could be obtained with 6.8% yield by the dehydrobromination of 1,2-dibromoethyl acetate using *N*,*N*-diethylaniline as a base.[7] Widlanski et al. described only one example of the synthesis of (*Z*)-2-bromovinyl benzoate with moderate yield.[8] The interest in (*Z*)-2-bromovinyl carboxylates as coupling precursors led us to improve the dehydrobromination of 1,2-dibromoethyl carboxylates. Fortunately, we found that DBU with a catalytic amount of hydroquinone at −78 °C could stereospecifically dehydrobrominate 1,2-dibromoethyl carboxylates to afford (*Z*)-2-bromovinyl carboxylates in moderate yields (Scheme 1).

Scheme 1



With the (*Z*)-2-bromovinyl carboxylates in hand, we optimized the coupling reaction conditions using *trans*-heptenylboronic acid and (*Z*)-2-bromovinyl octanoate as reactants. The results are shown in Table 1 and demonstrate that Pd(0) catalyst was superior to Pd(II) catalyst for the reaction (entry 11 vs 1, 8 and 13 vs 7) and dioxane appeared to be a better solvent than THF or toluene (entry 13 vs 9 and 11 vs 4). It was reported that the use of phase transfer catalysts benefited the occurrence of some coupling reactions,[9] but the addition of phase transfer catalyst NBu_4I failed to improve the yield in the reaction (entry 3). Suzuki et al. reported that thallium(I) salts effectively promoted the coupling reaction of alkylboronic esters with alkenyl or aryl halides.[10] The combinations of Ag_2O and Cu_2O with some bases could also dramatically enhance the rates of the coupling of some substrates.[11] Unfortunately, in this case, the special bases mentioned above did not make the coupling yields increase (entries 2, 5, 6, and 10). Further studies showed that $KF{\cdot}2H_2O$ and K_2CO_3 effectively promoted the cross-coupling reaction (entries 12 and 13). The satisfactory coupling yields of 84%and 86% could be achieved by carrying out the reaction in dioxane at 90 °C using $Pd(PPh_3)_4$ as the catalyst and $KF{\cdot}2H_2O$ or K_2CO_3 as a base.

Table 1. Effect of Bases and Solvents on the Coupling Reaction of *trans*-Heptenylboronic Acid with (*Z*)-2-bromovinyl Octanoate[a]



entry	conditions	yield (%)[b]
1	dioxane, $K_3PO_4{\cdot}3H_2O$, $PdCl_2dppf$	nr
2	dioxane, Tl_2CO_3, $Pd(PPh_3)_4$	32
3	dioxane, NBu_4I, $K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)_4$	14
4	toluene, $K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)_4$	33
5	dioxane, Ag_2O/Cs_2CO_3, $Pd(PPh_3)_4$	47
6	dioxane, Cu_2O/K_2CO_3, $Pd(PPh_3)_4$	3
7	dioxane, K_2CO_3, $PdCl_2(MeCN)_2$, PPh_3	43
8	dioxane, $K_3PO_4{\cdot}3H_2O$, $PdCl_2(PPh)_3$	18
9	THF, K_2CO_3, $Pd(PPh_3)_4$	32
10	dioxane, Ag_2O/K_2CO_3, $Pd(PPh_3)_4$	40
11	dioxane, $K_3PO_4{\cdot}3H_2O$, $Pd(PPh_3)_4$	64
12	dioxane, $KF{\cdot}2H_2O$, $Pd(PPh_3)_4$	84
13	dioxane, K_2CO_3, $Pd(PPh_3)_4$	86

[a] All reactions were carried out using a mixture of *trans*-heptenylboronic acid (1.2 mmol), (*Z*)-2-bromovinyl octanoate (1 mmol), 3% catalyst, and base (3 equiv) in 4 mL of solvent, for 10 h, at 90 °C (except for entry 9, the reaction was carried out under reflux). [b] Yields of isolated product based on the amount of (*Z*)-2-bromovinyl octanoate used.

The reactions of various alkenylboronic acids with (*Z*)-2-bromovinyl carboxylates were explored under optimized conditions. The results are collected in Table 2.

As shown in Table 2, the cross-coupling reaction of *trans*- or *cis*-alkenyl boronic acids with various (*Z*)-2-bromo-vinyl carboxylates proceeded readily to give the corresponding (*Z*,*E*)- or (*Z*,*Z*)-conjugated alkadienyl carboxylates in satisfactory yields. The ^1H NMR and $^1H-^1H$ COSY spectra of the coupling products confirmed that the configurations of both double bonds of the products were the same as that of the starting materials. When phenylboronic acid as a coupling partner was coupled with (*Z*)-2-bromovinyl octanoate, it was found that the reaction afforded a part of (*E*)-phenylvinyl carboxylate except the major (*Z*)-phenylvinyl carboxylate

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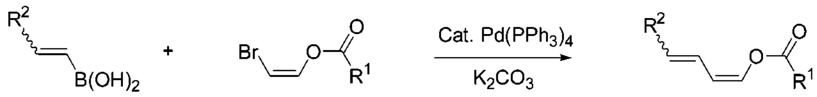
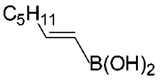
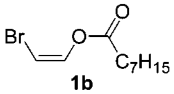
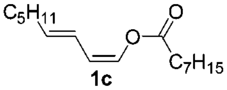
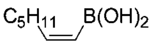
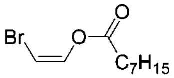
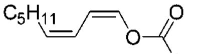
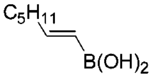
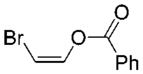
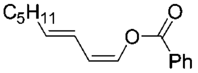
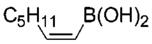
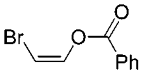
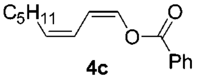
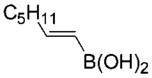
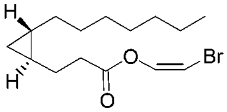
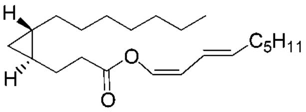
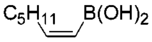
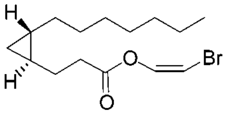
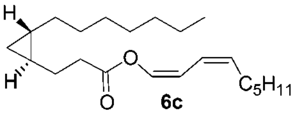
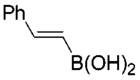
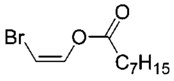
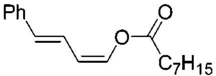
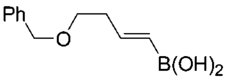
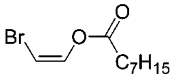
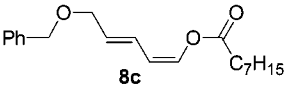
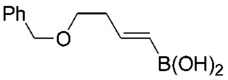
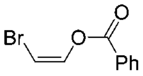
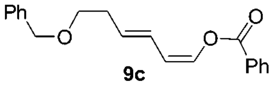
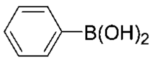
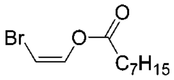
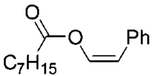
Table 2. Palladium-Catalyzed Cross-Coupling Reactions of Organoboronic Acids with Various (*Z*)-2-Bromovinyl Carboxylates[a]



entry	organoboronic acid	(*Z*)-2-bromovinyl carboxylate	product	yield
1		 **1b**	 **1c**	86%
2			 **2c**	80%
3		 **2b**	 **3c**	81%
4			 **4c**	78%
5		 **3b**	 **5c**	86%
6			 **6c**	80%
7			 **7c**	58%
8			 **8c**	70%
9			 **9c**	68%
10			 **10c**	65% b

[a] All reactions were carried out using a mixture of alkenylboronic acids (1.2 mmol) and (*Z*)-2-bromovinyl carboxylates (1 mmol), 3 equiv of K_2CO_3, and 3% $Pd(PPh_3)_4$ in 4 mL of dioxane at 90 °C under a nitrogen atmosphere for 10 h. All products were identified by ^{1}H NMR, ^{13}C NMR, IR, and mass spectra and HRMS. [b] When the reaction was carried out at 90 and 60 °C, ^{1}H NMR spectra showed that the corresponding *Z*/*E* ratios of the coupling product were 83:17 and 96:4, respectively.

(entry 10). The ^{1}H NMR spectra of the products showed the *Z*/*E* ratio to be 83:17, when the reaction was carried out at 90 °C. When the reaction took place at 60 °C, the *Z*/*E* ratio was 96:4. It seems that lower reaction temperature benefits the formation and the configuration retention of (*Z*)-form product.

In summary, the dehydrobromination conditions of 1,2-dibromoalkyl carboxylates were improved, and high stereoselective (*Z*)-2-bromoalkenyl carboxylates could be easily obtained in moderate yield. The palladium-catalyzed cross-coupling reaction of (*Z*)-2-bromoalkenyl carboxylates and alkenylboronic acids to give (*Z*,*E*)- or (*Z*,*Z*)-conjugated alkadienyl carboxylates has been first achieved. Thus, a novel practical method for the stereocontrollable construction of (*Z*,*E*)- or (*Z*,*Z*)-conjugated alkadienyl carboxylate moieties is provided. The present method has opened the door to the synthesis of some natural products having the interesting structure moieties. Further study on the scope of the reaction is currently underway in our laboratory.

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Supporting Information Available: Experimental details and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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