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A Very Simple Synthesis of Chloroalkenes and Chlorodienes by Selective Suzuki Couplings of 1,1- and 1,2-Dichloroethylene

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Abstract: Chloroalkenes, important building blocks for cross-coupling reactions, are prepared in one step by the Suzuki reaction of 1,1-dichloroethylene and 1,2-dichloroethylene with alkenyl- and arylboronic acids. Under the proper reaction conditions, it is possible to obtain the monocoupling reaction to provide the corresponding chloroalkenes with good yields. This method represents an excellent route for the preparation of chloroalkenes and chlorodienes from commercially available starting materials.

Keywords: boronic acids; chloroalkenes; cross-coupling; palladium; Suzuki reaction

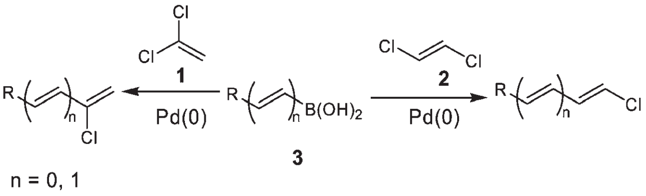
Introduction

Transition-metal catalyzed cross-coupling reactions are amongst the most powerful transformations for the formation of C–C and C–heteroatom bonds.[1] In a cross-coupling process, the formation of the new bond is achieved from two coupling partners: a *nucleophile*, typically an organometallic derivative (organoboron, organotin, organozinc) and an *electrophile*, usually an organic halide or pseudohalide. In spite of the enormous development of increasingly efficient cross-coupling protocols in recent years, the usefulness of these methodologies is very often hampered by the availability of the starting materials. In this context, the development of efficient methodologies for the preparation of organic halides appears to be a field of great interest.

We have recently disclosed the palladium-catalyzed amination of alkenyl bromides and chlorides as a new method for the synthesis of imines and enamines.[2] In particular, we have shown that the amination of 1- and 2-chlorobutadienes represents a new entry to the preparation of 1- and 2-aminobutadienes, respectively,[2c,3] versatile reagents for cycloaddition reactions.[4] In the course of our research, we surprisingly realized that simple 1- and 2-chloroethylenes and specially 1-chloro-1,3-butadienes[5] and 2-chloro-1,3-butadienes,[6] are not as readily available as one might initially imagine. Most of the methods described for their synthesis are not general, require several steps from commercial sources, and usually provide low yields and lack stereoselectivity.

A general strategy for the synthesis of 1-chloroalkenes[7] and 2-chloroalkenes[8] could be the selective cross-coupling reaction between inexpensive and commercially available 1,2-dichloroethylene and 1,1-dichloroethylene, respectively, and the corresponding organometallic derivatives (Scheme 1). Palladium-catalyzed selective monosubstitutions of 1,1- and 1,2-dihaloalkenes have been reported employing organomagnesium,[9] organozinc,[10] organoboron,[11] and organotin[12] reagents, as well as in Sonogashira couplings with acetylenes.[13] Moreover, selective monosubstitutions on mixed 1,2-dihaloethylenes such as 1-bromo-2-iodoethylene and 1-chloro-2-iodoethylene have been recently employed by Neghisi,[14] and Organ[15] for the preparation of 1-haloalkenes. However, the simplest and most readily available members of the family, 1,1- and 1,2-dichloroethylene,[16] have been less studied. The ability of 1,2-dichloroethylene to participate in selective monocouplings has been applied in Sonogashira couplings,[17] and also in Ni-catalyzed couplings with Grignard reagents,[18] in Pd-catalyzed reactions with alkenylalanes,[19] and to the best of our knowledge, only one example of reaction of 1,2-dichloroethylene with an alkenylboronic acid has been previously reported, providing only a moderate yield of the corresponding chlorodiene.[20] The use of 1,1-dichloroethylene in cross-coupling processes is more scarce, and only a Sonogashira coupling and a single example of a Pd-catalyzed coupling of a vinylalane have been previously reported.[21]

Motivated by the need for a simple and efficient method for the synthesis of structurally diverse 1-chloroalkenes and 2-chloroalkenes to broaden the scope of the alkenylamination reaction, we decided to carry out an extensive study on the Pd-catalyzed cross-coupling reactions of dichloroethylenes. We decided to focus on the Suzuki–Miyaura reaction,[22,23] owing to the wide availability and also low toxicity of the required boronic acids. Surprisingly, in spite of its popularity, the Suzuki–Miyaura cross-coupling with dichloroethylenes had remained almost unexplored.[20] In this paper, we report our findings regarding the employment of 1,1-dichloroethyene (**1**) and *trans*-1,2-dichloroethylene (**2**) as substrates in Suzuki cross-couplings oriented to the preparation of chloroalkenes and chlorodienes (Scheme 1).

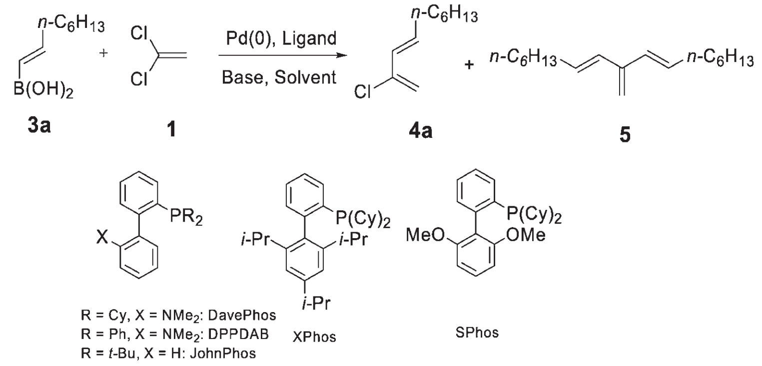


Scheme 1. General strategy for the synthesis of 1-chloroalkenes and 2-chloroalkenes.

Results and Discussion

We selected the coupling of *(E)*-1-octenylboronic acid (**3a**) with **1** as prototype reaction to develop suitable conditions. A large array of reactions was carried out using $Pd_2(dba)_3$ as metal source, different supporting ligands, solvents, and bases, and under different molar ratios of the dichloroethylene (Table 1). Preliminary experiments using 1:1 molar ratio of both coupling part-

Table 1. Reaction of alkenylboronic acid **3a** with 1,1-dichloroethylene **1**.[a] Selected data from the optimization of the reaction conditions.



Entry	Ligand	Solvent	Base	T [°C]	T [h]	Ratio **4a**:**5**[b]	Yield[c] [%]
1	PPh_3	Dioxane	CsF	100	5	32:68	not determined
2	BINAP	Dioxane	CsF	100	5	70:30	not determined
3	BINAP	Dioxane	CsF	70	7	62:38	not determined
3	DavePhos	Toluene	K_3PO_4	80	6	>95:5	40
4	DPPDAB	Toluene	K_3PO_4	80	6	>95:5	58
5	SPhos	Toluene	K_3PO_4	100	5	>95:5	16
6	JohnPhos	Dioxane	CsF	70	4	>95:5	28
7	XPhos	Toluene	K_3PO_4	100	4	>95:5	92[d]
8	XPhos	Toluene	Cs_2CO_3	100	5	>95:5	70
9	XPhos	Dioxane	K_3PO_4	100	4	–	0
10	XPhos	Dioxane	CsF	100	4	>95:5	86[d]
11[e]	XPhos	Toluene	K_3PO_4	100	5	>95:5	46
12	XPhos	Toluene	K_3PO_4	25	24	–	0
13	XPhos	Dioxane	CsF	25	24	–	0

[a] *General reaction conditions:* 0.5 mmol alkenylboronic acid; 2.0 mmol (4 equivs.) 1,1-dichloroethylene; $Pd_2(dba)_3$ 0.5 mol %; 2:1 molar relationship Pd:Ligand; 2 equivs. base; 2 mL solvent.

[b] Determined by analysis of the ^1H NMR spectra of the reaction.

[c] Isolated yields.

[d] Reaction conversion was complete.

[e] $Pd_2(dba)_3$ 0.25 mol % was used.

ners afforded always considerable amounts of triene **5**, derived from the second coupling of chloride **4a** with the boronic acid. Therefore, our optimization study was directed towards a set of reaction conditions that would maximize the conversion of the coupling reaction, but minimizing the formation of the triene **5**. It was found that a 4:1 molar ratio of dichloroethylene: boronic acid was a prerequisite to avoid the second coupling process.

The set of ligands included in the optimization round consisted of PPh_3, the chelating diphosphine BINAP, and several electron-rich bulky biphenyls. As represented in Table 1, the best results were obtained from the Pd(0)/XPhos[24] catalytic combination (entries 7 and 10), which provided high yield of the desired chlorodiene **4a** without formation of the triene **5**. Interestingly, PPh_3 and BINAP, which are expected to generate less active catalysts also promoted the cross-coupling, but the reactions always afforded mixtures of chlorodiene **4a** and triene **5**. Other ligands which are known to be very active in the Suzuki–Miyaura reaction (DavePhos, SPhos)[25] afforded the desired chlorodiene but with lower conversions and overall yield (entries 3 and 5).

On the other hand, it was observed that a proper combination of base and solvent is very important for the success of the reaction (entries 7 to 10). After some experimentation it was determined that the best combinations were K_3PO_4/toluene and CsF/dioxane. Typically, the optimized reaction conditions required 1 mol % of Pd at 100 °C. A decrease in the catalyst loading to 0.5 mol % slowed the reaction down significantly (entry 11), while the reaction at room temperature did not proceed to any extent (entries 12 and 13). Moreover, when the molar relationship of dichloroethylene: boronic acid was reduced from 4:1 to 2:1, a small amount of triene **5** was always detected.

The scope of the reaction was studied with a variety of alkenyl- and arylboronic acids (Table 2). In several cases, when XPhos was employed as supporting ligand, significant amounts of the double coupled product were obtained. After some experimentation, it was determined that in such examples reactions in the presence of JohnPhos (Table 2, Method C) provided the best results.

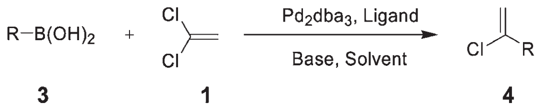
Under the optimized reaction conditions, the cross-coupling reaction could be achieved successfully with different alkenyl- and arylboronic acids **3** giving rise to the desired 2-chloro-1,3-butadienes and α-chlorostyrenes **4** (Table 2). In most of the examples the alkenyl chloride **4** was obtained cleanly as the sole reaction product as judged by ^1H and ^{13}C NMR. However, the instability of these type of compounds towards chromatography gave rise, in some examples, to relatively reduced isolated yields.

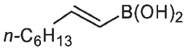
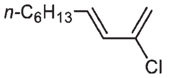
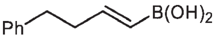
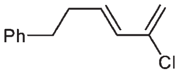
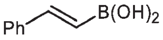
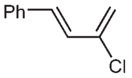
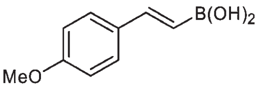
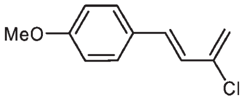
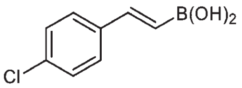
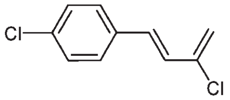
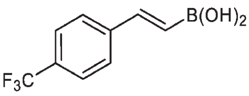
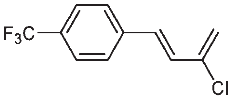
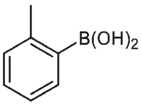
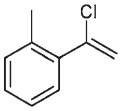
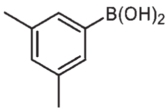
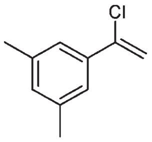
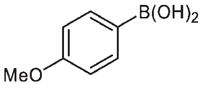
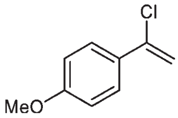
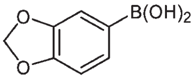
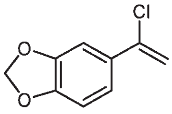
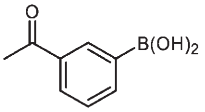
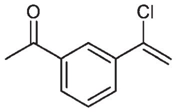
The coupling reaction provides excellent results for electron-rich and electron-neutral substitutents on the boronic acid. Moreover, the reaction can be carried out in the presence of an aryl chloride (entry 6), given the higher reactivity of vinyl chlorides over aryl chlorides towards oxidative addition reactions. However, the utilization of electron-poor arylboronic acids seemed to be a limitation of the reaction due to undesired side reactions of the boronic acid (entry 12).[25b,26] Thus, when 3-acetylphenylboronic acid was used, the reaction proceeded with very low yield, with acetophenone, coming from the protodeborination of the boronic acid, being the main product isolated. In spite of this limitation, this procedure represents a very efficient approach to a wide variety of α-chlorostyrenes and 2-chloro-1,3-butadienes, which competes favourably with the very few alternative methods available for their preparation.[6,7]

We next turned our attention to the coupling reactions with 1,2-dichloroethylene, which would allow for the preparation of 2-substituted-1-chloroethylenes. In contrast with the successful results obtained in most cases for 1,1-dichloroethylene, the coupling of 1,2-dichloroethylene turned out to be more challenging. Again, an extensive screening of ligands and reaction conditions was carried out in an attempt to overcome the limitations observed, using the coupling of 2-phenylethenylboronic acid with 1,2-dichloroethyene as prototype reaction. The best reaction conditions again consisted in $Pd_2(dba)_3$ as metal source, JohnPhos as supporting ligand, CsF as additive in dioxane at 70 °C.

As depicted in Table 3, results ranging from excellent to good were obtained for the coupling of 1,2-dichloroethylene with electron-rich alkenylboronic acids (entries 1–3 and 5) and electron-rich arylboronic acids (entries 10 and 11). In those cases, the monocoupling reaction proceeds selectively and with total retention of configuration of the *trans* double bond. However, a slight decrease in the electron-donor character of the substituents of the boronic acid gave rise to very poor results due to an increase of the double coupling product **7** as well as other undesired side products derived from protodeboronation, **8**, and homocoupling, **9**, of the boronic acids.[26] The increase in the formation of **7** can be rationalized considering the relative reactivity of the different chloroalkenes towards oxidative addition to the Pd center. Apparently, there is a very slight reactivity difference between 1,2-dichloroethyene (**2**) and the 1-chloroalkenes **6** formed in the coupling reaction. For electron-rich alkenylboronic acids, the coupling reaction gives rise to electron-donating-substituted chloroalkenes **6**, that are less reactive towards oxidative addition than 1,2-dichloroethylene, and therefore, the selective monocoupling occurs. However, the coupling of electron-neutral and electron-poor boronic acids with 1,2-dichloroethylene affords a new chloroethylene **6** which is substantially more reactive than 1,2-dichloroethylene towards oxidative addition, and therefore it was not possible to carry out the selective monocoupling under the present reaction conditions.

Table 2. Synthesis of 2-chloroalkenes by cross-coupling of 1,1-dichloroethylene (**1**) with alkenyl- and arylboronic acids **3**.



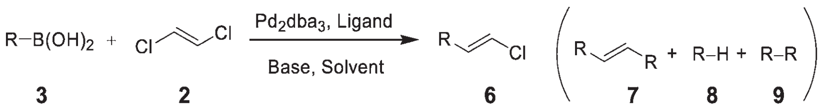
Entry	R-B(OH)$_2$		Product		Method[a]	Yield(%)[b]
1		**3a**		**4a**	A	92
2					B	86
3		**3b**		**4b**	A	87
4		**3c**		**4c**	C	76
5		**3d**		**4d**	C	72
6		**3e**		**4e**	C	49
7		**3f**		**4f**	C	61
8		**3g**		**4g**	C	64
9		**3h**		**4h**	C	87
10		**3i**		**4i**	C	66
11		**3j**		**4j**	C	83
12		**3k**		**4k**	C	21[c]

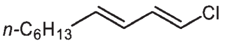
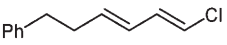
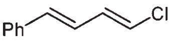
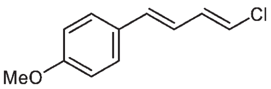
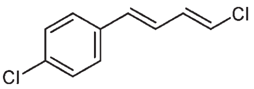
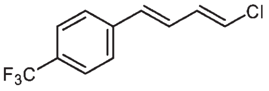
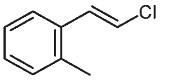
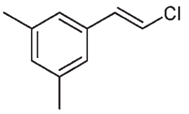
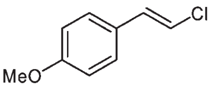
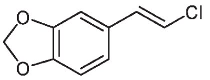
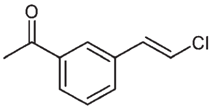
[a] *Method A:* 0.5 mmol boronic acid; 2.0 mmol (4 equivs.) dichloroethylene **1**; Pd$_2$(dba)$_3$ 0.5 mol %; XPhos 2 mol %; 1 mmol (2 equiv.) K$_3$PO$_4$; 2 mL toluene; 100 °C. *Method B:* 0.5 mmol boronic acid; 2.0 mmol (4 equivs.) dichloroethylene **1**; Pd$_2$(dba)$_3$ 0.5 mol %; XPhos 2 mol %; 1 mmol (2 equivs.) CsF; 2 mL dioxane, 100 °C. *Method C:* 0.5 mmol boronic acid; 2.0 mmol (4 equivs.) dichloroethylene **1**; Pd$_2$(dba)$_3$ 0.5 mol %; JohnPhos 2 mol %; 1 mmol (2 equivs.) CsF; 2 mL dioxane, 70 °C.

[b] Isolated yields, after flash chromatography.

[c] A **4k**:acetophenone, 31:69, mixture was obtained.

Table 3. Synthesis of 1-chloroalkenes by cross-coupling of 1,2-dichloroethylene (**2**) with alkenyl- and arylboronic acids **3**.



Entry	Product		Method[a]	Ratio **6**:**7**:**8**:**9**	Yield [%][b]
1		**6a**	A	100: 0:0:0	89
2			B	100:0:0:0	94
3		**6b**	A	100:0:0:0	90
4		**6c**	C	69:31:0:0	44
5		**6d**	C	79:0:21:0	65
6		**6e**	C	100:0:0:0	60
7		**6f**	C	56:22:0:22	33
8		**6g**	C	41:59::0	14
9		**6h**	C	66:32:1:0	50
10		**6i**	C	100:0:0:0	67
11		**6j**	C	100:0:0:0	82
12		**6k**	C	44:12:44:0	31

[a] *Method A:* 0.5 mmol boronic acid; 2.0 mmol (4 equivs.) dichloroethylene **2**; $Pd_2(dba)_3$ 0.5 mol %; XPhos 2 mol %; 1 mmol (2 equivs.) K_3PO_4; 2 mL toluene; 100 °C. *Method B:* 0.5 mmol boronic acid; 2.0 mmol (4 equivs.) dichloroethylene **2**; $Pd_2(dba)_3$ 0.5 mol %; XPhos 2 mol %; 1 mmol (2 equivs.) CsF; 2 mL dioxane, 100 °C. *Method C:* 0.5 mmol boronic acid; 2.0 mmol (4 equivs.) dichloroethylene (**1** or **2**); $Pd_2(dba)_3$ 1 mol %; JohnPhos 2 mol %; 1 mmol (2 equivs.) CsF; 2 mL dioxane, 70 °C.

[b] Isolated yields, after flash chromatography.

Conclusion

In summary, we have carried out an extensive study of the usefulness of 1,1- and *trans*-1,2-dichloroethylene in selective Suzuki couplings with boronic acids. The coupling reaction of 1,1-dichloroethylene represents a very general and efficient method for the preparation of α-chlorostyrenes and 2-chloro-1,3-butadienes in one step and from commercial starting materials. On the other hand, the selective coupling of *trans*-1,2-dichloroethylene with alkenylboronic acids and electron-rich arylboronic acids, is a very straightforward and efficacious method for the stereoselective synthesis of *trans*-1-chloro-1,3-butadienes and *trans*-β-chlorostyrenes, respectively. In both cases, the present methodology compares favourably with the existing methods for the preparation of these types of chlorides, important building blocks for cross-coupling reactions.

Experimental Section

General Remarks

All reactions were carried out under nitrogen atmosphere in an RR98030 12 place Carousel Reaction Station^{TM} from Radleys Discovery Technologies, equipped with gas-tight threaded caps with a valve, cooling reflux head system, and digital temperature controller. Toluene, dioxane, pentane and hexanes were continuously refluxed and freshly distilled from sodium/benzophenone under nitrogen. $Pd_2(dba)_3$ was purchased form Strem Chemical Co. and used without further purification. All phosphine ligands used are commercially available from Strem or Aldrich and were used without further purification. K_3PO_4 and CsF were purchased from Aldrich Chemical Co., stored in a flask purged with nitrogen and weighed in the air. The boronic acids employed are commercially available from Aldrich or Acros, and were used without further purification. The boronic acid 3b was prepared according to a literature procedure.[27] 1,1-Dichloroethylene and 1,2-dichloroethylene are commercially available from Fluka and Acros, respectively, and were used without further purification.

General Procedure for the Cross-Coupling of Boronic Acids 3 with 1,1-Dichloroethylene (1) or *trans*-1,2-Dichloroethylene (2)

Method A: A carousel reaction tube under nitrogen atmosphere was charged with dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) (0.02 mmol, 2 mol %), tris(dibenzylideneacetone)dipalladium(0) (0.005 mmol, 1 mol %), potassium phosphate (2 mmol), the boronic acid **3a**, **b** (1 mmol) and toluene (4 mL). After 1 minute, the dichloroethylene **1** or **2** (4 mmol) was added. The system was heated at 100 °C with stirring and reflux until the starting boronic acid had been completely consumed as judged by TLC analysis. The mixture was allowed to cool to room temperature, taken up in dry pentane or hexanes (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure. The residue was redissolved in dry hexanes (15 mL), filtered again through Celite, concentrated under reduced pressure and dried under high vacuum to afford a residue which consisted of the essentially pure chlorodiene **4a**, **b** or **5a**, **b**.

Method B: This is the same as that of Method A, using CsF (2 mmol) instead of K_3PO_4 as base and dioxane (4 mL) as solvent.

Method C: A carousel reaction tube under nitrogen atmosphere was charged with 1,1′-bis(di-*tert*-butylphosphino)biphenyl (JohnPhos) (0.02 mmol, 2 mol %), tris(dibenzylideneacetone)dipalladium(0) (0.005 mmol, 1 mol %), cesium fluoride (2 mmol), the boronic acid **3c**–**k** (1 mmol) and dioxane (4 mL). After 1 minute, the dichloroethylene **1** or **2** (4 mmol) was added. The system was heated at 70 °C with stirring and reflux until the starting boronic acid had been completely consumed as judged by TLC analysis. The mixture was allowed to cool to room temperature, taken up in dry pentane, hexanes or dichloromethane (15 mL), and filtered through Celite. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography. In some cases, the crude residue was heated neat at 42–65 °C in a kugelröhr apparatus at 10^{-3} Torr for 1–3 hours to eliminate the protodeborination product.

Specific experimental details and characterization data for compounds **4** and **6** are available in the Supporting Information.

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