Palladium(0)-Catalyzed Cross-Coupling of Potassium (Z)-2-Chloroalk-1-enyl Trifluoroborates: A Chemo- and Stereoselective Access to (Z)-Chloroolefins and Trisubstituted Alkenes

ARTICLE *in* CHEMISTRY - A EUROPEAN JOURNAL · JUNE 2009

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Palladium(0)-Catalyzed Cross-Coupling of Potassium (*Z*)-2-Chloroalk-1-enyl Trifluoroborates: A Chemo- and Stereoselective Access to (*Z*)-Chloroolefins and Trisubstituted Alkenes

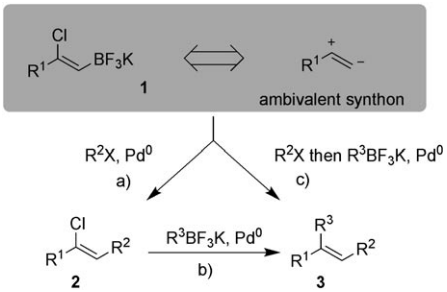
Xavier Guinchard, Xavier Bugaut, Cyril Cook, and Emmanuel Roulland*[a]

Abstract: We describe the preparation of a series of new potassium trifluoroborates **1** and the study of their behaviour in a Pd^0-catalyzed cross-coupling reaction. We found that compounds **1** are endowed with original properties as they behave as nucleophilic cross-coupling partners chemoselectively but also as ambivalent synthons. The usefulness of this methodology has been successfully illustrated by the first total synthesis of an *N*-acyl spermidine.

Keywords: alkenes · boron · cross-coupling · palladium · vinyl chloride

Introduction

The (*Z*)-chloroolefin functionality occurs in numerous natural or synthetic biologically active or pharmaceutically relevant compounds, making the development of methods for the synthesis of this structural motif an interesting area of investigation. Among the natural products bearing a (*Z*)-chloroolefin functionality are, for instance, the biselide and haterumalide family,[1] chagosensine,[2] spongistatin,[3] aurantosides,[4] halichlorine[5] and pinnaic acid.[6] Among synthetic and biologically active products one can find, for instance, pyrethroids that are widely used selective insecticides.[7] Since the Pd^0-catalyzed cross-coupling reaction of chlorinated olefins has been rendered efficient thanks to the development of new ligands,[8] (*Z*)-chloroolefins **2** (Scheme 1) may also be regarded as suitable intermediates for the still challenging stereoselective synthesis of trisubstituted olefins **3**.[9] Furthermore, the Suzuki–Miyaura cross-coupling[10] has received an important improvement with the use of organotrifluoroborates chemistry as demonstrated by Genet et al.[11] and as widely implemented by Molander et al.[12] Combining these two considerations, we reasoned that potassium (*Z*)-2-chloroalk-1-enyltrifluoroborate derivatives **1** (Scheme 1) would behave as ambivalent cross-coupling partners in Pd^0-catalyzed reactions. As underlined in a recent review by Negishi et al.,[13] the chemistry of 2-halo-1-boro-1-alkene derivatives remains hitherto not fully exploited in the context of the Pd^0 cross-coupling chemistry. We wish to report herein the synthesis of compounds **1** and the study of their reactivity in Pd^0-catalyzed cross-coupling reactions and its application in the total synthesis of an *N*-acyl spermidine. This study is a part of our program on the development of new synthetic methods to access (*Z*)-chloroolefins **2** and their applications to natural product total synthesis. In a previous paper,[14] we described a first efficient stereoselective access to (*Z*)-chloroolefins **2** by the Suzuki–Miyaura cross-coupling of 1,1-dichloro-1-alkenes **4** with 9-alkyl-9-BBN **5**; further transformation of compounds **2** led stereoselectively to the corresponding trisubstituted alkenes **3** (Scheme 2). The efficiency of this methodology was illustrated by our total syn-



Scheme 1. Transformations of potassium (*Z*)-2-chloroalk-1-enyltrifluoroborates **1**. a) Chemoselective Pd^0-catalyzed cross-coupling involving the nucleophilic pole of **1** to yield **2**. b) Substitution of the chlorine atom of **2** giving **3**. c) One-pot access to trisubstituted alkenes giving **3** from **1**.

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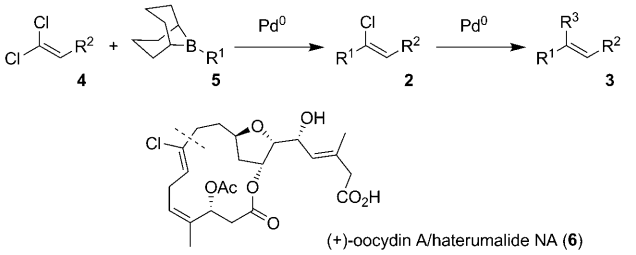
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900425.

thesis of (+)-oocydin A/haterumalide NA **6** (Scheme 2).[15] One must notice that Negishi et al. reported an alternative cross-coupling of 1,1-dichloro-1-alkenes **4** with alkylzinc reagents.[16] Nevertheless, the synthetic methods for (*Z*)-chloroolefins **2** described above suffer from some limitations: i) they are restricted to alkyl nucleophilic coupling partners, ii) starting material **4** is neither commercially available nor straightforwardly accessed, iii) these cross-coupling reactions require the use of a somewhat expensive ligands (XantPhos or DpePhos).

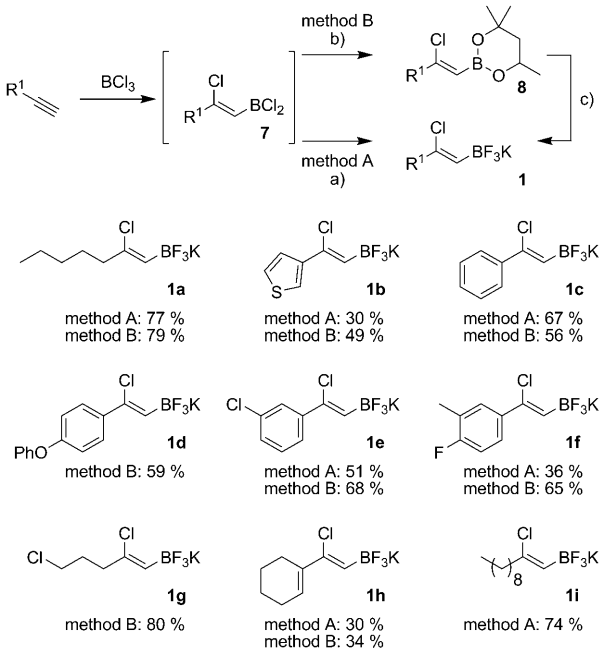


Scheme 2. Our previous study on the synthesis of chlorovinylic compounds **2** and our target (+)-oocydin A/haterumalide NA (**6**).

Compounds such as **1** are new and not previously described potassium trifluoroborate derivatives. Very few analogues of **1** have been reported in the literature and even less studied in Pd^0-catalyzed chemistry. Among these, 2-iodo- and 2-bromo-1-vinyl-9-BBN derivatives were synthesized by haloboration of alkynes, while the corresponding chlorinated olefin could not be obtained this way because 9-chloro-9-BBN do not react with alkynes.[17] Furthermore, 2-bromo-1-vinyl-9-BBN and their corresponding cyclic esters of 2-bromo-1-vinyl-borane were tested as coupling partners with no success.[17] Only the products of bromoboration of alkynes by BBr_3 were successfully engaged in Pd^0-catalyzed reactions.[17,18] Thus, with alkylzinc reagents as coupling partners, the substitution of the bromine atom furnished the corresponding sensitive boronic halides that were directly submitted to Suzuki–Miyaura cross-coupling conditions yielding trisubstituted alkenes. Closely related to this is the polyene synthesis methodology developed by Burke et al. using B-protected *trans*-haloalkenylboronic acid derivatives.[19] Whilst efficient for preparation of trisubstituted alkenes, these methods do not furnish access to halogenated alkenes.

Results and Discussion

Synthesis of potassium (*Z*)-2-chloroalk-1-enyltrifluoroborate derivatives 1: The main goal of our study was to synthesize (*Z*)-chlorovinylic derivatives **2** from (*Z*)-2-chloroalk-1-enyltrifluoro-borates **1** by Pd^0 cross-coupling. Hence, we expected to establish reaction conditions allowing the nucleophilic pole of **1** to react chemoselectively while the chlorine atom would remain intact. Before this, we investigated reaction conditions to access potassium (*Z*)-2-chloroalk-1-enyltrifluoroborate derivatives **1** (Scheme 3) starting from the well-known chloroboration reaction of terminal alkynes by BCl_3.[17] This reaction is stereospecific as it results from the *syn* addition of BCl_3 to the C–C triple bond. Furthermore this reaction is highly regioselective as it always delivers the boron atom at the terminal position leading to intermediate **7** (Scheme 3).[20] The transformation of intermediates **7** into their corresponding potassium trifluoroborate salts **1** was performed by a treatment with an aqueous solution of KHF_2 (Scheme 3, method A). With most alkynes, yields were nevertheless increased by synthesizing the cyclic boronic ester of 2-methylpentane-2,4-diol[21] **8** as an intermediate which was subsequently transformed into **1** by treatment with KHF_2 in water (Scheme 3, method B). Thus, we obtained a series of pure (*Z*)-potassium trifluoroborate salts **1** in poor to good yields (34 to 80%) from both aromatic or aliphatic terminal alkynes.[22] The poor yields being mostly due to purification problems. This inexpensive process was easily performed on large scale (40 mmol), furnishing **1** as stable salts that can be kept on the shelf for a long period of time. As we were writing this article, the synthesis of a brominated analogue of **1c** (Scheme 3) has been reported through a similar method, but no mention of its reactivity was made.[23]



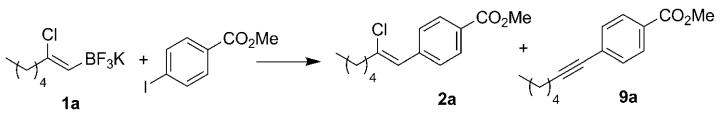
Scheme 3. Synthesis of potassium (*Z*)-2-chloroalk-1-enyltrifluoroborates **1**: a) BCl_3, CH_2Cl_2, RT, then H_2O, 0 °C, KHF_2. b) BCl_3, CH_2Cl_2, RT, then 2-methylpentane-2,4-diol. c) KHF_2, H_2O/MeOH, RT.

Studies of the palladium-catalyzed reaction of potassium (*Z*)-2-chloroalk-1-enyltrifluoroborate derivatives 1: We then focused on the study of the Pd^0-catalyzed cross-coupling of these new organotrifluoroborates **1**. With potassium trifluoroborate **1a** as a test compound facing methyl 4-iodobenzoate as coupling partner, we targeted vinylic chloride **2a**. The first trials (Table 1) readily demonstrated that classical

Suzuki–Miyaura reaction conditions were not suitable (Table 1, entries 1,2). We shifted towards large bite angle phosphines[24] such as XantPhos or DpePhos, assuming that the intermediate stemming from the reductive elimination step should be similar to the one formed in the course of the cross-coupling of 1,1-dichloroalkenes **4** which we previously studied (Scheme 2).[14] Actually, using one molecule of XantPhos per palladium, we succeeded in performing the desired coupling but with the formation of the unwanted alkyne derivative **9a** (Table 1, entries 3, 5). When using two molecules of XantPhos per palladium, the reaction was cleaner (Table 1, entry 7) but was difficult to reproduce with other substrates. Surprisingly, DpePhos gave no reaction (Table 1, entry 8). The Buchwald's ligand RuPhos, known to allow the coupling of potassium trifluoroborates,[25] was used but furnished **2a** in poor yield (Table 1, entry 9). Finally, we tried the P(tBu)$_3$ ligand developed by Fu.[26] Various palladium sources were tried, and the combination of [Pd$_2$(dba)$_3$] (1.5 mol%) with P(tBu)$_3$·HBF$_4$ (3 mol%) turned out to give the best yields particularly at 120°C in a sealed tube with more concentrated conditions (0.7 mol L^{-1}) offering then a markedly shortened reaction time (Table 1, entry 13). The Z configuration of **2a** was confirmed by comparison with the NMR data of known analogues with very closely related structures.[14] Lower palladium loads led to lower yields. Other solvents (DMF, dioxane, toluene, EtOH) and other bases (K_3PO_4, CsF, CsOH, KOH, TMSOK) were also tried but with no satisfactory results. It is important to note that the reaction conditions that we have established here are unexpectedly chemoselective. Despite the use of the strongly activating P(tBu)$_3$ ligand, we actually observed that **1a** is neither reactive enough to cross-couple with itself, nor with any chlorinated electrophilic coupling partner. We assume that for both steric and electronic reasons, each pole of the ambivalent synthon **1** deactivate the other: i) the double bond that is electron-enriched by the trifluoroborate group, might render oxidative insertion of Pd^0 into the C–Cl bond more difficult. ii) the nucleophilicity of the trifluoroborate function might also be diminished probably because of the chlorine atom's electron-withdrawing effect, leading to a more difficult transmetallation step.

We obviously also explored the behaviour of cyclic boronic ester **8a**[27] (Scheme 3) and obtained coupling product **2a**, unfortunately always accompanied by an important proportion of the side product **9a** despite numerous conditions investigated. This experiment seems to indicate that potassium trifluoroborates **1** are superior to their boronic ester analogues **8** at least as reagents for the synthesis of (Z)-chloroolefins **2**.

Table 1. Optimization of the cross-coupling conditions on a test reaction.



1a **2a** **9a**

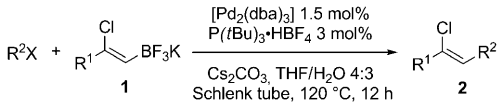
Entry	Pd source, ligand	Base[b], solvent[c]	T, reaction time	Isolated yield [%] **2a** (**9a**)
1	[PdCl$_2$(dppf)][a]	K_3PO_4, THF	reflux, 48 h	n.r.
2	[PdCl$_2$(dppf)][a]	K_3PO_4, THF/H_2O	reflux, 48 h	n.r.
3	[Pd$_2$(dba)$_3$], XantPhos[e]	K_3PO_4, THF/H_2O	90°C, 16 h[j]	50 (25)[k]
4	[Pd$_2$(dba)$_3$], XantPhos[e]	KOH, THF/H_2O	90°C, 90 h[j]	50[k]
5	[Pd$_2$(dba)$_3$], XantPhos[e]	Cs_2CO_3, THF/H_2O	90°C, 36 h[j]	70 (20)[k]
6	[Pd$_2$(dba)$_3$], XantPhos[e]	K_3PO_4, PhMe/H_2O	90°C, 20 h[j]	n.r.
7	[Pd$_2$(dba)$_3$], XantPhos[f]	Cs_2CO_3, THF/H_2O	90°C, 20 h[j]	85
8	[Pd$_2$(dba)$_3$], DpePhos[e]	Cs_2CO_3, THF/H_2O	90°C, 16 h[j]	n.r.
9	PdCl$_2$, RuPhos[g]	Cs_2CO_3/THF/H_2O	reflux, 60 h	36
10	[Pd$_2$(dba)$_3$], P(tBu)$_3$·HBF$_4$[h]	Cs_2CO_3, THF/H_2O	90°C, 20 h[j]	63
11	PdCl$_2$, P(tBu)$_3$·HBF$_4$[g]	Cs_2CO_3, THF/H_2O	reflux, 60 h	72
12	[Pd$_2$(dba)$_3$], P(tBu)$_3$·HBF$_4$[h]	Cs_2CO_3, THF/H_2O	reflux, 90 h	81
13	[Pd$_2$(dba)$_3$], P(tBu)$_3$·HBF$_4$[i]	Cs_2CO_3, THF/H_2O[d]	120°C, 12 h[j]	92

[a] (5 mol%). [b] Base: 3 equiv [c] conc. 0.15 M, THF/H_2O or PhMe/H_2O 9:1. [d] conc. 0.7 M, THF/H_2O 3:4. [e] [Pd$_2$(dba)$_3$] (1.5 mol%), phosphine (3 mol%). [f] [Pd$_2$(dba)$_3$] (1.5 mol%), XantPhos (6 mol%). [g] PdCl$_2$ (5 mol%), phosphine (10 mol%). [h] [Pd$_2$(dba)$_3$] (2.5 mol%), P(tBu)$_3$·HBF$_4$(5 mol%). [i] [Pd$_2$(dba)$_3$] (1.5 mol%), P(tBu)$_3$·HBF$_4$ (3 mol%). [j] Sealed tube. [k] ^{1}H NMR estimated yield. dba = dibenzylidene acetone, dppf = 1,1′-Bis(diphenylphosphino)ferrocene, XantPhos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, DpePhos = (Oxydi-2,1-phenylene)bis(diphenylphosphine), RuPhos = 2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl.

In order to explore the scope of this reaction, we conducted cross-couplings upon **1a** with various halogenated coupling partners (Table 2, entries 1–10). Thus, the reactions proceeded with moderate to good yields (46 to 91%) with a large variety of both iodinated (Table 2, entries 1, 9, 10) or brominated (Table 2, entries 1–6) aromatic compounds, as iodinated (Table 2, entry 7) or brominated (Table 2, entry 8) olefins, demonstrating that this reaction is compatible with electron-rich (Table 2, entries 2, 4, 5, 9, 10) and electron-poor (Table 2, entries 1, 3, 6) aromatic substrates. Interestingly, the coupling of **1a** with 2-iodophenol furnished 2-pentylbenzofurane **2j** (58%, Table 2, entry 10). This product likely originates from a domino process in the course of which the expected Suzuki coupling occurs followed by an intramolecular Ullmann-type reaction. However, the coupling of **1a** with 2-iodoaniline only gave aniline derivative **2i** (74%, Table 2, entry 9) and not the corresponding 2-pentylindole.

The cross-coupling of potassium (Z)-2-chloroalk-1-enyltrifluoroborates **1b** to **1g** also proceeded successfully using methyl 4-iodobenzoate as coupling partner (Table 2, entries 11, 14–18) giving mostly satisfactory yields (36 to 81%). Interestingly, the coupling of chlorinated electrophiles failed despite the use of P(tBu)$_3$ as ligand (Table 2, entries 1, 6) correlatively, potassium (Z)-2-chloroalk-1-enyltrifluoroborate **1e** yielded the dichlorinated compound **2p** in 81% (Table 2, entry 16). In all these above described cross-couplings, the geometry of the double bond remained intact.[28]

Table 2. Synthesis of (*Z*)-chloroalkenes **2** by coupling of potassium (*Z*)-2-chloroalk-1-enyltrifluoroborates **1**.



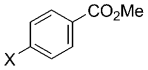
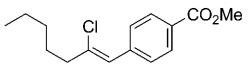
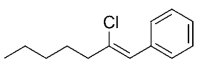
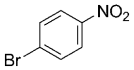
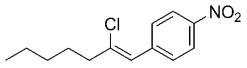
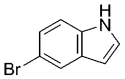
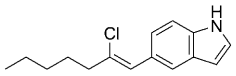
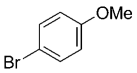
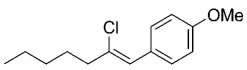
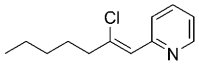
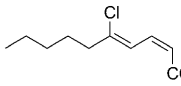
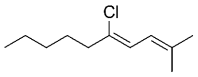
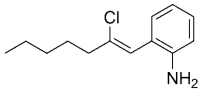
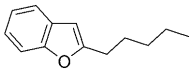
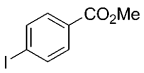
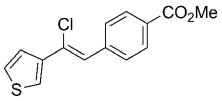
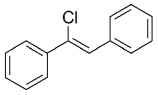
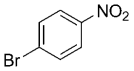
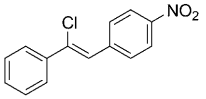
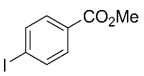
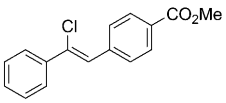
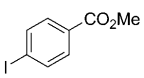
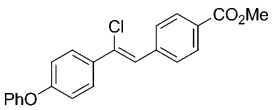
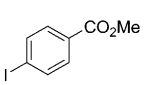
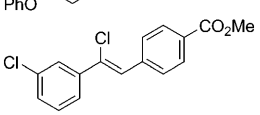
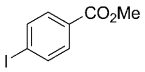
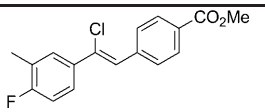
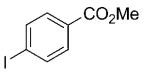
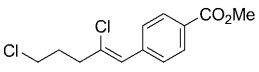
Entry	**1**	Halide	Product	Yield [%][a]
1	**1a**			**2a**, X = I, 91 X = Br, 63[b] X = Cl, 0
2	**1a**			**2b**, 70
3	**1a**			**2c**, 46
4	**1a**			**2d**, 77[c]
5	**1a**			**2e**, 56[c]
6	**1a**			**2f**, X = Br, 25[f] X = Cl, deg.
7	**1a**			**2g**, 81[d]
8	**1a**			**2h**, 70[e]
9	**1a**			**2i**, 74
10	**1a**			**2j**, 58
11	**1b**			**2k**, 36
12	**1c**			**2l**, 70
13	**1c**			**2m**, 46
14	**1c**			**2n**, 80
15	**1d**			**2o**, 52
16	**1e**			**2p**, 81

Table 2. (Continued)

Entry	**1**	Halide	Product	Yield [%][a]
17	**1f**			**2q**, 79
18	**1g**			**2r**, 50[g]

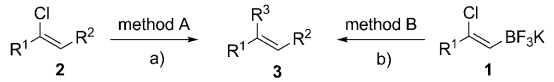
[a] Isolated yields. [b] Reaction time: 48 h. [c] Reaction time: 36 h. [d] Reaction time: 72 h in a sealed tube with 2.5 mol% of $[Pd(P(tBu)_3)_2]$ catalyst at 80 °C. [e] Due to its high volatility 2 equiv of 1-bromo-2-methylprop-1-ene were used. [f] The corresponding alkyne derivative **9b** was formed in 16% yield. [g] Obtained as a *Z*/*E* 62:38 separable mixture.

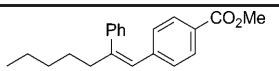
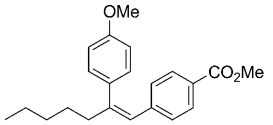
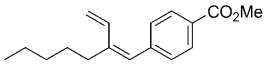
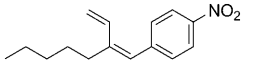
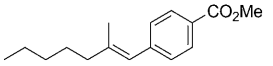
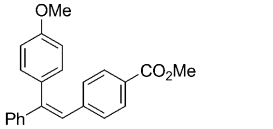
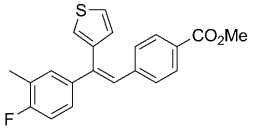
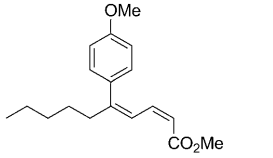
Synthesis of trisubstituted alkenes 3: We investigated conditions in order to obtain trisubstituted alkenes **3** by substitution of the chlorine atom of chloroalkenes **2** by coupling with commercially available potassium trifluoroborates (Table 3). Various studies[25,29] described the coupling of aryl or vinyl potassium trifluoroborates with arylchlorides but, to the best of our knowledge, no cross-coupling of vinylic chloride was reported. Inspired by these, we found out that using RuPhos as palladium ligand with Cs_2CO_3 as base, in a mixture of THF and water at 80 °C, provided trisubstituted alkenes **3** in good yield (69 to 99%) and importantly with full conservation of the double-bond geometry.[30] We also demonstrated that we could efficiently substitute the chlorine atom by a methyl group using trimethylboroxine as demonstrated by the synthesis of olefin **3e** from chloroalkene **2a** (Table 3, entry 5). The few precedents involved activated aromatic electrophilic coupling partners[31] and, to the best of our knowledge, only one cross-coupling methodology was described which involved non-activated aryl chlorides.[32] This useful transformation offers an interesting stereoselective access to the 1,2-disubstituted (*E*)-prop-1-enylidene motif and thus to the class of polyenes natural products which is a important and large family.[33]

We also investigated the conditions of a one-pot–two-steps sequence targeting a rapid elaboration of trisubstituted alkenes by assembling our ambivalent synthon **1** with two other components (Table 3, method B). We have already established above that the RuPhos ligand is not suitable for the first step involving the nucleophilic pole of **1**. We found that palladium with $P(tBu)_3$ as ligand, allowed the two steps to proceed. Thus, once the first coupling step achieved, the introduction in the reaction medium of a third component such as an aryl or a vinyl potassium trifluoroborate along with more $[Pd_2(dba)_3]$ and $P(tBu)_3$, led to the substitution of the chlorine atom furnishing the desired trisubstituted alkenes **3** in a range of 26 to 56% yield.

Application of the methodology in total synthesis: In order to illustrate the usefulness of our methodology, we performed a short and efficient total synthesis of the *N*-acyl spermidine **11** (Scheme 4). This natural product isolated from the soft coral *Sinularia* sp.[34] bears a (*E*,*Z*)-dienic

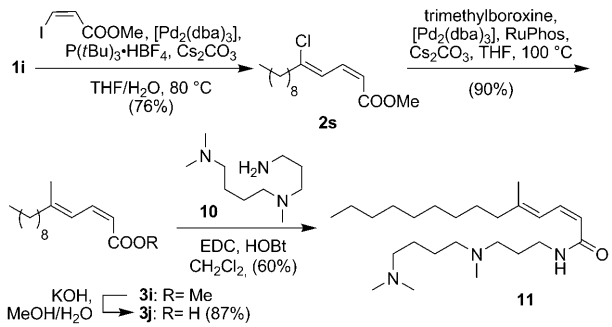
Table 3. Synthesis of trisubstituted alkenes from **1** or **2**.[a]



Entry	Product		Method A: Yield [%]	Method B: Yield [%]
1		**3a**	87	26[c]
2		**3b**	89	38
3		**3c**	87	42
4		**3d**	69[b]	56[d]
5		**3e**	67[c]	–
6		**3f**	84	44
7		**3g**	97	43
8		**3h**	99	33

[a] Reaction conditions: a) R_3BF_3K, 2.5 mol% $[Pd_2(dba)_3]$, 10 mol% RuPhos, 3 equiv Cs_2CO_3, THF/H_2O 9:1, 80 °C, 12 to 36 h; b) R_2X, 1.5 mol% $[Pd_2(dba)_3]$, 3 mol% $P(tBu)_3{\cdot}HBF_4$, 3 equiv Cs_2CO_3, THF/H_2O 4:3, 120 °C, 12 h, then, R_3BF_3K, 2.5 mol% $[Pd_2(dba)_3]$, 10 mol% $P(tBu)_3{\cdot}HBF_4$, THF/H_2O 9:1, 100 °C, 48 h. [b] Obtained as a *Z*/*E* mixture 85:15. [c] Contaminated by methyl biphenyl-4-carboxylate. [d] Obtained as a *Z*/*E* mixture 60:40. [e] Using general reaction conditions but without H_2O.

motif and is endowed with cytotoxicity against various human tumour cells[34] and an H^+-pyrophosphatase inhibition activity.[35] Using our methodology, we straightforwardly obtained intermediate **3j** in four steps (50% overall yield) from undecyne with full control of the conjugated diene configuration. The coupling with amine **10**[36] supplied the targeted *N*-acyl spermidine derivative **11**, the characterization data of which were similar to those of the naturally occurring compound.



Scheme 4. Total synthesis of *N*-acyl spermidine **11**.

Conclusions

We have prepared and described a series of new potassium trifluoroborates **1**, and studied their behaviour in the context of a Pd^0-catalyzed cross-coupling. We found out that those compounds **1** are endowed with original and versatile properties as they behave as nucleophilic cross-coupling partners in a chemoselective manner and also as ambivalent synthons. Thus, the nucleophilic pole of **1** has reacted chemoselectively furnishing a series of chloroalkenes **2** with pure *Z* geometry. A one-pot–two-steps rapid elaboration of valuable trisubstituted alkenes **3** has been performed involving both poles of the synthon **1** successively. The usefulness of this methodology has been successfully illustrated by the first total synthesis of the *N*-acyl spermidine **11**.

Experimental Section

General procedure for the synthesis of potassium trifluoroborates 1: To a solution of BCl_3 (4 mmol, 1 M in hexane) in CH_2Cl_2 (6 mL) under argon at room temperature was slowly added a solution of the alkyne (1 equiv) in CH_2Cl_2 (4 mL). The resulting solution was stirred for 1 h and then cooled to 0 °C. Anhydrous Et_2O was added (4 mL), followed by a solution of 2-methylpentan-2,4-diol (1.2 equiv) in Et_2O (4 mL). The resulting solution was allowed to stir at room temperature for 30 min and transferred to a separating funnel. The organic phase was washed twice by water, then dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum. The resulting crude boronic ester was dissolved in MeOH (4 mL) under argon, and solid KHF_2 (3 equiv) was added. H_2O (4 mL) was added dropwise to this mixture over 5 min. The resulting mixture was stirred at room temperature for 2 h and then fully evaporated under vacuum. The solids were washed three times by refluxing acetone and the combined acetone phases were evaporated. The resulting solid was washed washed by Et_2O and dried under vacuum to yield potassium trifluoroborate **1**.

General procedure for the palladium catalysed cross-coupling of potassium trifluoroborates: A mixture of the potassium trifluoroborate **1** (0.5 mmol), halide (0.5 mmol), $[Pd_2(dba)_3]$ (6.8 mg, 0.0075 mmol), $P(tBu)_3{\cdot}HBF_4$ (4.3 mg, 0.015 mmol), Cs_2CO_3 (489 mg, 1.5 mmol) was placed in a Schlenk tube equipped with a magnetic bar. The tube was purged by three vacuum–argon flush cycles. Freshly distilled THF (0.4 mL) and degassed H_2O (0.3 mL) were added and the Schlenk tube was sealed and heated at 120 °C for 12 h (unless otherwise noted). The reaction mixture was cooled and filtered through a short pad of silica gel (elution by EtOAc). The solvents were removed under vacuum and the residue **2** was purified by chromatography on silica gel.

Representative procedure for the synthesis of trisubstituted alkenes from vinyl chlorides—Synthesis of 3b from 2a: A mixture of the vinyl chloride **2a** (87 mg, 0.327 mmol), potassium 4-methoxyphenyltrifluoroborate (84 mg, 0.39 mmol), $[Pd_2(dba)_3]$ (4.4 mg, 8.2 μmol), RuPhos (15 mg, 33 μmol), Cs_2CO_3 (320 mg, 0.98 mmol) was placed in a Schlenk tube equipped with a magnetic bar. The tube was purged by three vacuum–

argon flush cycles. Freshly distilled THF (3 mL) and degassed H_2O (0.3 mL) were added and the Schlenk tube was sealed and heated at 80 °C for 12 h. The reaction mixture was then cooled and filtered through a short pad of silica gel (elution by EtOAc). The solvents were removed under vacuum and the residue was purified by chromatography on silica gel (EtOAc/heptane 1:19) to afford **3b** as a colourless oil (98 mg, 0.29 mmol, 89 %). $R_f = 0.18$ (EtOAc/heptane 1:9). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, $J = 7.2$ Hz, 3H), 1.25–1.46 (m, 6H), 2.48 (t, $J = 7.3$ Hz, 2H), 3.80 (s, 3H), 3.84 (s, 3H), 6.42 (s, 1H), 6.81 (d, $J = 8.7$ Hz, 2H), 6.99 (d, $J = 8.4$ Hz, 2H), 7.04 (d, $J = 8.7$ Hz, 2H), 7.76 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$, 22.6, 27.7, 31.5, 40.8, 52.0, 55.3, 114.1, 125.1, 127.3, 129.0, 129.3, 129.7, 133.0, 142.9, 146.1, 158.9, 167.1 ppm; IR (neat): $\tilde{\nu} = 1107$, 1177, 1246, 1276, 1510, 1604, 1719, 2856, 2929 cm^{-1}; LRMS (ESI): m/z: 361 $[M+Na]^+$; HRMS (ESI): m/z: calcd for $C_{22}H_{26}NaO_3$: 361.1780; found: 361.1716 $[M+Na]^+$.

Representative one-pot procedure for the synthesis of trisubstituted alkenes 3 from (*Z*)-2-chloroalk-1-enyltrifluoroborate derivatives 1—Synthesis of 3a from 1a: A mixture of the potassium trifluoroborate **1a** (119 mg, 0.5 mmol), methyl 4-iodobenzoate (130 mg, 0.5 mmol), $[Pd_2(dba)_3]$ (6.8 mg, 0.0075 mmol), $P(tBu)_3{\cdot}HBF_4$ (4.3 mg, 0.015 mmol), Cs_2CO_3 (489 mg, 1.5 mmol) was placed in a Schlenk tube equipped with a magnetic bar. The tube was purged by three vacuum–argon flush cycles. Freshly distilled THF (0.4 mL) and degassed H_2O (0.3 mL) were added and the Schlenk tube was sealed and heated to 120 °C for 14 h. The reaction mixture was then cooled and potassium phenyltrifluoroborate (110 mg, 0.6 mmol) was added to the reaction mixture, $[Pd_2(dba)_3]$ (6.8 mg, 0.0075 mmol), $P(tBu)_3{\cdot}HBF_4$ (4.3 mg, 0.015 mmol) and additional THF (2.6 mL). The Schlenk tube was sealed and heated at 100 °C for 36 h. The reaction mixture was then cooled and filtered through a short pad of silica gel (elution by EtOAc). The solvents were removed under vacuum and the residue was purified by chromatography on silica gel (EtOAc/heptane 1:19) to afford **3a** as a yellow oil (40 mg, 0.13 mmol, 26 %). $R_f = 0.30$ (EtOAc/heptane 1:19). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 0.87 (t, $J = 7.2$ Hz, 3H), 1.25–1.48 (m, 6H), 2.50 (t, $J = 7.2$ Hz, 2H), 3.84 (s, 3H), 6.45 (s, 1H), 6.95 (d, $J = 8.5$ Hz, 2H), 7.08–7.14 (m, 2H), 7.24–7.30 (m, 3H), 7.74 ppm (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.2$, 22.6, 27.7, 31.6, 40.9, 52.0, 125.5, 127.3, 127.5, 128.5, 128.7, 129.0, 129.3, 141.0, 142.5, 146.6, 167.1 ppm; IR (neat): $\tilde{\nu} = 1108$, 1180, 1276, 1434, 1605, 1720, 2928 cm^{-1}; LRMS (EI): m/z: 308 $[M]^+$; HRMS (EI): m/z: calcd for $C_{21}H_{24}O_2$: 308.1776; found: 308.1777 $[M]^+$.

Acknowledgements

We are grateful to Prof. Jean-Yves Lallemand (ICSN-CNRS) for his permanent interest and support. We want to thank Dr. Pascal Retailleau (ICSN-CNRS) for crystallographic analysis and Prof. David Aitken (ICMMO, Université Paris Sud) for fruitful scientific discussions. This study was financially supported by the CNRS.

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Received: February 16, 2009
Published online: April 25, 2009

