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Suzuki−Miyaura Cross-Coupling of 1,1-Dichloro-1-alkenes with 9-Alkyl-9-BBN

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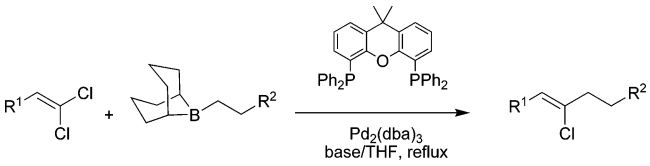
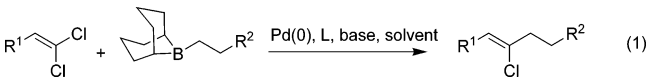


We addressed an unexplored application of the Suzuki−Miyaura protocol to the cross-coupling of 1,1-dichloro-1-alkenes with 9-alkyl-9-BBN. The use of bisphosphine ligands with a large P−Pd−P bite angle allowed us to synthesize *Z*-chlorinated internal alkenes in good yields resulting from a selective monocoupling process, a recurrent challenge with 1,1-dichloro-1-alkenes. Moreover, these monochlorinated olefins could be further transformed providing stereospecifically trisubstituted olefins.

Palladium-catalyzed cross-coupling reactions represent one of the most popular and efficient chemical tools used for the formation of C−C or C−heteroatom bonds. Many electrophilic coupling partners (typically halogenated C_{sp^2}) can react with a wide variety of organometallic species from which alkyl, alkenyl, aryl, or alkynyl groups are transferred.[1] During the course of our investigations on the total synthesis of the macrolactone haterumalide NA[2] (Figure 1), we planned to use a retrosynthetic disconnection implying a yet unexplored Suzuki−Miyaura[3] cross-coupling between 1,1-dichloro-1-alkenes and 9-alkyl-9-BBNs leading to *Z*-chloroalkenes as represented in eq 1.



(1)

Such a new cross-coupling process would provide a straightforward access to molecules bearing a *Z*-chloroalkene function, which also occurs in some other natural products such as pinnaic acid[4] or halichlorine[5] (Figure 1). Starting from these *Z*-chloroalkenes, we could attempt the challenging synthesis of stereospecifically trisubstituted alkenes by making use of recently developed palladium catalysts.[6]

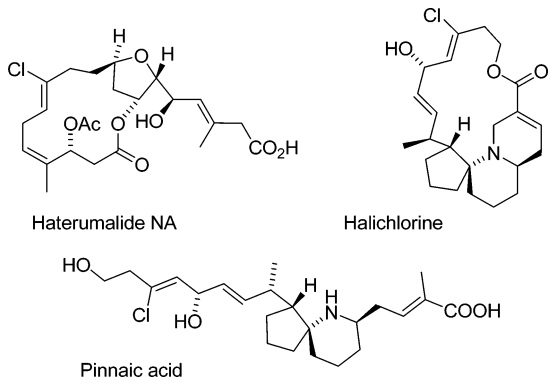


FIGURE 1. Some examples of natural products bearing a chlorovinyl function.

Whereas the reactivity of 1,1-dibromo-1-alkenes has been extensively studied,[7] only a few successful metal-catalyzed cross-couplings involving 1,1-dichloro-1-alkenes are known in the literature. Thus, only a few examples of C_{sp^3} nucleophilic coupling partners have been reported (organozincs[8−10] or Grignards[8,11]) along with some C_{sp^2} (organozincs,[8,9] Grignards,[11] organoboranes,[12] organoalanes[13]) and C_{sp} partners.[13] However, it is important to notice that 1,1-dibromo-1-alkenes and 1,1-dichloro-1-alkenes do not behave the same way in palladium-catalyzed cross-coupling reactions. Thus, whereas it is easy to be selective of monosubstitution with 1,1-dibromo-1-alkenes, 1,1-dichloro-1-alkene electrophiles, in similar classical reaction conditions, lead always to 2-fold substitution. As monochloroolefins are usually regarded as being unsuitable electrophilic coupling partners, the involvement of the remaining chloride appears anomalous. As an explanation, Negishi suggested[10] the

[†] ICSN.
[‡] ENSCP.
[§] ENS.

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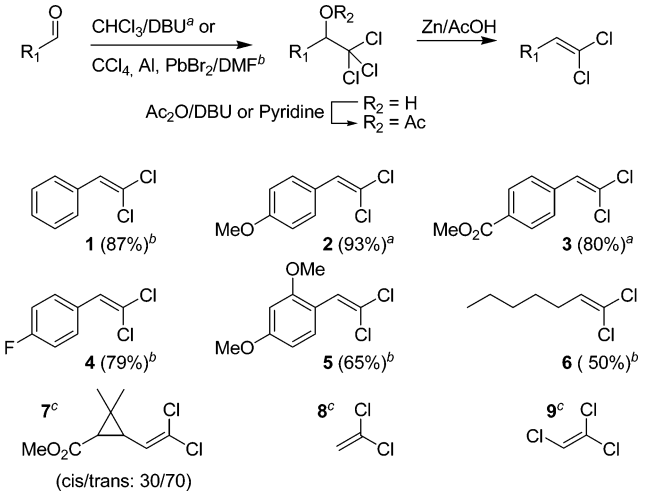
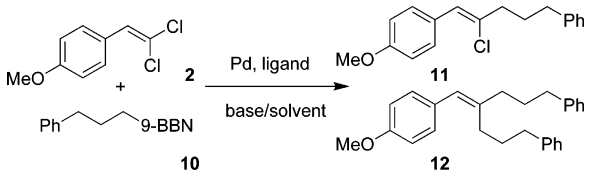
SCHEME 1. 1,1-Dichloro-olefins



[a] Method A. [b]Method B. [c]Commercially available.

SCHEME 2. Cross-Coupling Test Reaction



persistence of the usually transitory palladium(0)−olefin complex generated at the reductive elimination step. Within this complex, a subsequent second oxidative insertion in the C−Cl bond would be facilitated. With 9-alkyl-9-BBN nucleophiles, as in the case of alkylzinc nucleophiles,[8] we observed that dppf or dppp bisphosphines mainly promoted biscoupling. TLC monitoring showed only traces of the monocoupled product during the course of the reaction suggesting a one-step process that matches well the Negishi's mechanistic suggestion. On the other hand, we also observed that the dppp ligand can promote cross-coupling reactions with monochloro-olefins (Table 3), showing that a concurrent pathway can also yield biscoupled products starting from 1,1-dichloro-olefins. Thus, as we started our investigations, it appeared that the recurrent challenge with 1,1-dichloro-1-alkene electrophiles was to achieve monocoupling selectively.

In a first stage, we prepared a set of 1,1-dichloro-1-alkenes from various aldehydes by adapting known procedures (Scheme 1). From nonenolizable aldehydes, the reaction with chloroform in DBU led to 1,1,1-trichloroalkan-2-ols that were subjected to a subsequent one-pot acetylation followed by an elimination promoted by zinc in acetic acid (method A).[14] From all other aldehydes, the 1,1,1-trichloroalkan-2-ol key intermediates were obtained under milder conditions utilizing the reaction of CCl_4 in the presence of aluminum and a catalytic amount of lead(II) salt in DMF (method B).[15] Subsequent acetylation and elimination steps gave 1,1-dichloro-olefins.

To establish the best Suzuki−Miyaura cross-coupling conditions, we evaluated a broad range of phosphine ligands, palladium catalyst precursors, bases, and solvents. As a model

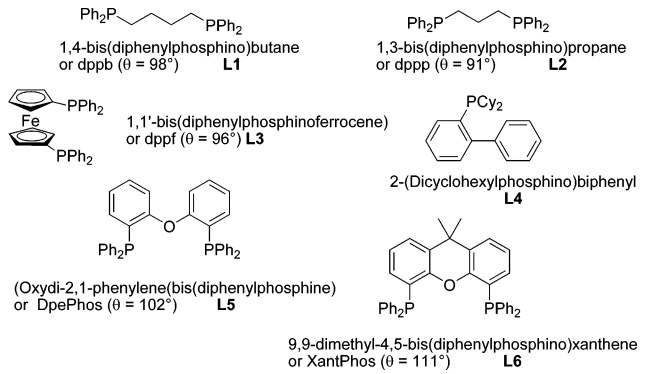


FIGURE 2. Phosphine ligands used for our investigations.

TABLE 1. Influence of the Solvent[a]

entry	solvent	T [°C]	conversion [%][b]	**11** [%][b]	**12** [%][b]
1	Et_2O	20	nd	28	9
2	Et_2O	36	35	18	5
3	benzene	80	85	14	9
4	THF	20	nd	27	1
5	DMF	66	64	2	31

[a] Reactions conducted with $PdCl_2$(dppf) (2 mol %), **10** (1 equiv), K_3PO_4, and KF (3 equiv). [b] Isolated yield.

reaction, we chose the coupling of 1,1-dichloro-1-alkene **2** with 1 equiv of 9-(3-phenylpropyl)-9-BBN **10** (Scheme 2). The $PdCl_2$(dppb) catalyst was reported to give double substitution with alkylzinc nucleophiles.[8] In our case, this catalyst led to decomposition along with the formation of only a small amount of the 2-fold substituted product **12**.

With $PdCl_2$(dppf) in solvents of low polarity such as THF, Et_2O, or benzene (Table 1), more satisfactory results were obtained as the monochlorinated product **11** was the major product formed (**11**/**12** ratio between 14:9 and 27:1), whereas in DMF (Table 1, entry 5), the bissubstituted product **12** was formed almost exclusively. At this point, nonpolar solvents thus appeared instrumental in providing monoalkylated products. Moreover, when using $PdCl_2$(dppf) as the catalyst, the nature of the 1,1-dichloro-1-alkene strongly influenced the mono/biscoupling selectivity. Indeed, the coupling of electron-rich 1,1-dichloro-1-alkenes such as **2** or **5** with alkyl-9-BBN **10** in THF led to larger amounts of biscoupled products (**12** and **28**), whereas under the same conditions, electron-poor substrates such as **3** or **4** led to the exclusive formation of monocoupled products. This observation seems in opposition with the assumption that electron-rich electrophilic coupling partners are less reactive, but it makes sense if the persistent palladium(0)/monochloro-olefin complex is more stable when the olefin is electron rich.

Accordingly,[8] monodentate ligands such as PPh_3 or 2-(dicyclohexylphosphino)biphenyl (Figure 2, **L4**)[16] only led to product **12** with poor yields (Table 2, entries 1 and 2). This demonstrated that selective monosubstitution requires bidentate bisphosphine ligands. Moreover, the use of bisphosphines with a small P−Pd−P bite angle θ and with a less rigid skeleton such as dppp also led mainly to product **12** (Table 2, entry 4) and, even worse, to decomposition in the case of dppb (entry 5).

We then focused on bidentate ligands with larger P−Pd−P bite angles θ.[17] Indeed, Negishi recently demonstrated by using

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TABLE 2. Influence of the Catalyst[a]

entry	palladium catalyst	conversion [%][b]	**11** [%][b]	**12** [%][b]
1	$PdCl_2(PPh_3)_2$	60	5	30
2	$Pd(OAc)_2$, **L4**	78	0	19
3	$PdCl_2$(dppf)	64	2	31
4	$PdCl_2$(dppp)	92	6	45
5	$PdCl_2$(dppb)	100	0	trace
6	$Pd_2(dba)_3$-DpePhos	100	58−65	<1
7	$Pd_2(dba)_3$-**XantPhos**	**100**	**72**	<**1**

[a] Reactions conducted in refluxing THF, with 2 mol % of Pd and with KF and K_3PO_4 (3 equiv). [b] Isolated yield.

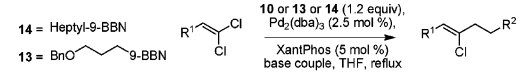
DpePhos that a larger θ provides a good selectivity of monocoupling of alkylzinc with 1,1-dichloro-1-alkenes.[10]

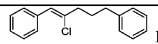
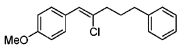
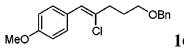
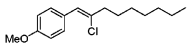
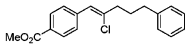
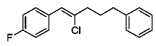
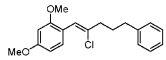
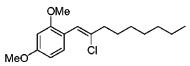
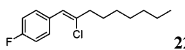
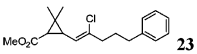
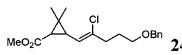
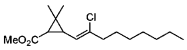
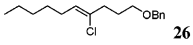
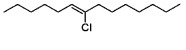
In our case, the use of DpePhos in the cross-coupling of 9-alkyl-9-BBN with 1,1-dichloro-1-alkenes had a dramatic effect: not only the yield increased but also the second coupling was suppressed (Table 2, entry 6). We also performed experiments with XantPhos, which has an even larger bite angle θ, and we selectively obtained monocoupled *Z*-chloro-olefin[18] with a significantly better yield (Table 2, entry 7, *Z*/*E* 96:4). However, with DMF as solvent, the mono-/biscoupling ratio fell.

The effect of the base is significant. Using the KF−K_3PO_4 combination turned out to be a good solution in most cases. Replacement of KF by NaF led to lower cross-coupling yields. With KF or K_3PO_4 alone in THF, no reaction took place, and the addition of water led, in both cases, to a slow and incomplete coupling reaction, thus establishing the need of a concomitant use of a fluoride anion source along with a higher pH. In some cases, the Cs_2CO_3−CsF couple appears to be a good alternative to K_3PO_4−KF as it allows significantly better yields (Table 3, entries 1, 9, 10, and 12) and *E*/*Z* selectivities (entries 1, 4, and 12) and/or higher reaction rates (entries 3, 11, and 12). The reaction rate being already quite slow, the use of lower palladium loads was not studied.

As demonstrated by the cross-couplings of various 9-alkyl-9-BBNs with various 1,1-dichloro-1-alkenes (Table 3), the conditions we established ($Pd_2(dba)_3$, (2.5 mol %), couple F^--base and XantPhos (5 mol %) in refluxing THF) are general. The observed yields are generally good, and the selectivity of monocoupling is almost total in every case. The *Z*/*E* ratio is generally excellent, being in most cases superior to 95:5. As it could be expected, the nature of the 1,1-dichloro-1-alkene has some effects. The higher reaction rate is observed with electron-poor styrene substrates (Table 3, entries 1 and 6). Electron-rich styrene 1,1-dichloro-1-alkenes such as compounds **2** and **5** gave negligible amounts of 2-fold coupled compounds **12** and **28** (entries 2, 3, and 8). This correlates with the observation previously made with the dppf ligand. With vinylidene chloride **8**, we failed to give any coupling product, but trichloroethylene **9** reacted when using our conditions. Previous investigations demonstrated the capricious nature of trichloroethylene **9** as an electrophile in cross-coupling reactions. Depending on the reaction conditions, coupling took place at the bischlorinated extremity[19] or at the monochlorinated extremity.[20] Under our conditions (Scheme 3), with KF−K_3PO_4 as the bases couple,

TABLE 3. Cross-Coupling of Various 1,1-Dichloro-olefins with Various 9-Alkyl-9-BBNs



entry	electrophile	9-alkyl-9-BBN	product, method, reaction time, yield[a], *Z*/*E* ratio[b]
1	**1**	**10**	 **15** **A**[c]: 5 h, 69%, 88/12. **B**[d]: 17h, 80%, 97/3
2	**2**	**10**	 **11** **A**[c]: 20 h, 86%, 91/9.[e] **B**[d]: 18h, 88%, 93/7
3	**2**	**13**	 **16** **A**[c]: 41 h, 83%, >98/2. **B**[d]: 15h, 79%, 93/7
4	**2**	**14**	 **17** **A**[c]: 24 h, , 83%, 92/8. **B**[d]: 22h, 61%, 98/2
5	**3**	**10**	 **18** **A**[c]: 5 h, , 65%, 94/6. **B**[d]: 4h, 73%, 92/8
6	**4**	**10**	 **19** **A**[c]: 48 h, 82%, 84/16. **B**[d]: 16h, 68%, 98/2
7	**5**	**10**	 **20** **A**[c]: 44 h, 82%, 94/6.[f] **B**[d]: 20h, 57%, 94/6
8	**5**	**14**	 **21** **A**[c]: 23 h, , 80%, 92/8. **B**[d]: 22h, 79%, 95/5
9	**4**	**14**	 **22** **A**[c]: 23 h, , 74%, 93/7 **B**[d]: 23h, 87%, 90/10
10	**7**	**10**	 **23** **A**[c]: 160h, 58%, 93/7. **B**[d]: 166h, 79%, 93/7
11	**7**	**13**	 **24** **A**[c]: 160 h, 59%, 96/4. **B**[d]: 75h, 65%, 98/2
12	**7**	**14**	 **25** **A**[c]: 140 h, 63%, 88/12. **B**[d]: 72h, 70%, 98/2
13	**6**	**13**	 **26** **A**[c]: 110 h, 65%, 96/4. **B**[d]: 114h, 46%, 97/3
14	**6**	**14**	 **27** **A**[c]: 110 h, 74%, 94/6. **B**[d]: 114h, 65%, 96/4

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy. [c] KF−K_3PO_4 couple. [d] CsF−Cs_2CO_3 couple. [e] 1% of biscoupling adduct **12** was isolated. [f] 2% of biscoupling adduct **28** was isolated.

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(18) Configuration determined by ^{1}H NMR NOESY experiments.
(19) Okamoto, Y.; Yoshikawa, Y.; Hayashi, T. *J. Organomet. Chem.* **1989**, *359*, 143−149.
(20) Ratovelomanana, V.; Linstrumelle, G.; Normant, J.-F. *Tetrahedron Lett.* **1985**, *26*, 2575−2576.

SCHEME 3. Coupling with Trichloroethylene 9

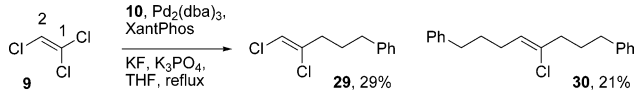
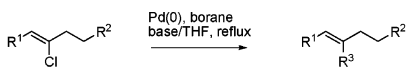
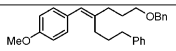
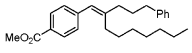
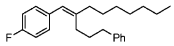
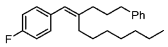
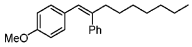
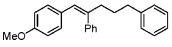


TABLE 4. Synthesis of Trisubstituted Olefins



entry	electrophile	conditions	borane	product and yield
1	**16**	**A**[a]	**10**	 **31** (69%)
2	**18**	**A**[a]	**14**	 **32** (69%)
3	**22**	**B**[b]	**10**	 **33-*Z*** (74%)
4	**19**	**B**[b]	**14**	 **33-*E*** (74%)
5	**17**	**B**[b]	**34**	 **35** (58%)
6	**11**	**B**[b]	**34**	 **36**[c] (66%)

[a] Conditions A: $PdCl_2$(dppp), (7 mol %), borane, KF and K_3PO_4 (3 equiv), THF, reflux. [b] Conditions B: $Pd_2(dba)_3$, (2.5 mol %), 2-(dicyclohexylphosphino)biphenyl (5 mol %), borane, KF, K_3PO_4 (3 equiv), THF, reflux. [c] 26% of **11** was recovered.

we observed the formation of two products of *Z*-configuration: 1,2-dichloro-1-alkene **29** resulting from the coupling of one borane unit at C-1 and monochloro-olefin **30** in which one borane unit was coupled at both the C-1 and C-2 positions.[18]

Having established efficient and selective Suzuki−Miyaura conditions affording monochlorinated olefins, we briefly studied the preparation of stereospecifically trisubstituted alkenes. The 2-(dicyclohexylphosphino)-biphenyl ligand (Figure 2), well-known to promote coupling with chlorinated electrophilic coupling partners,[16] allowed cross-couplings of some of our *Z*-chloroalkenes with various boron nucleophiles as shown in Table 4. Surprisingly, $PdCl_2$(dppp) also proved to be a suitable catalyst for this reaction. The coupling of monochlorinated olefins **17** and **11** with phenylboronic acid **34** yielded compounds **35**[21] and **36** which are analogues of the antiangiogenic agent combretastatin.

Conclusion

We have developed a new application of the Suzuki−Miyaura cross-coupling reaction between 9-alkyl-9-BBNs and 1,1-dichloro-1-alkenes. This required the use of a large bite angle bisphosphine ligand to obtain an efficient preparation of chlorinated internal alkenes of *Z*-configuration along with suppression of the 2-fold substitution side reaction. This could result from a faster decomposition rate of the unusually persistent palladium(0)−chloro-olefin complex due to the geometrical constraints imposed by a large bite angle and rigid bisphosphine ligand. Moreover, this approach leads to an efficient synthesis of trisubstituted alkenes with control of the geometry.

Experimental Section

Typical Procedure for Stereoselective Monocoupling. A terminal alkene (1.2 mmol) was added to a solution of 9-BBN (0.5 M in THF, 2.4 mL, 1.2 mmol). The solution was stirred at room temperature for 1 h under an argon atmosphere. A solution of the 1,1-dichloro-1-alkene (1.0 mmol) in THF (2 mL) was added followed by $Pd_2(dba)_3$ (23.1 mg, 2.5 mol %), XantPhos (28.5 mg, 5 mol %), KF (180 mg, 3.0 mmol), and K_3PO_4 (635 mg, 3.0 mmol) (method A). Alternatively, CsF (454.4 mg, 3.0 mmol) and Cs_2CO_3 (979.6 mg, 3.0 mmol) were used instead of KF and K_3PO_4 (method B). The solution was refluxed under argon until completion (see Table 3 for reaction times). After cooling to room temperature, the reaction mixture was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by column chromatography affording the monocoupled product.

(*Z*)-2-Chloro-1-(4-methoxyphenyl)-5-phenylpent-1-ene (11): prepared according to typical procedures from allylbenzene (495 μL, 4.17 mmol) and 1,1-dichloro-1-alkene **2** (609 mg, 3.00 mmol). Purification by column chromatography (heptane/CH_2Cl_2, 85:15) afforded **1** as a colorless solid (741 mg, 86%, method A; 758 mg, 88%, method B). Mp 95−96 °C; IR (solid) 2931, 2360, 1605, 1508, 1247, 1176, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 2.00 (m, 2H), 2.49 (t, J = 7.2 Hz, 2H), 2.67 (t, J = 7.5 Hz, 2H), 3.81 (s, 3H), 6.39 (s, 1H), 6.88 (dd, J = 2.1, 6.6 Hz, 2H), 7.20 (d, J = 6.9 Hz, 2H), 7.25−7.32 (m, 3H), 7.57 (dd, J = 2.1, 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 29.1, 34.6, 40.5, 55.2, 113.5, 124.1, 125.9, 127.7, 128.3, 128.5, 130.3, 132.5, 141.8, 158.8; MS (EI) *m*/*z* 288 (M^+, ^{37}Cl), 286 (M^+, ^{35}Cl), 181, 159, 147, 145, 131, 121, 115. Anal. calcd. for $C_{18}H_{19}ClO$: C, 75.38; H, 6.68. Found: C, 75.32; H, 6.86.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) For a closely related homologue of compound **35**: Yamanoi, S.; Seki, K.; Matsumoto, T.; Suzuki, K. *J. Organomet. Chem.* **2001**, *624*, 143−150.