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Versatile palladium(II)-catalyzed Negishi coupling reactions with functionalized conjugated alkenyl chlorides

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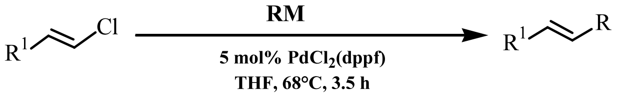
Abstract—Under palladium catalysis, we found that organozincate reagents, generated in situ, by reaction of Grignard compounds with less than molar amounts of zinc chloride, in the presence of conjugated alkenyl chlorides, give rapidly and cleanly the corresponding coupling product in high yields. In this way, aryl as well as primary and secondary alkyl substituents have been introduced successfully. The selectivity of the reaction allows to prepare various functionalized conjugated enynes and dienes from chloroenyne and chlorodiene derivatives bearing a functional group.

Due to the importance of conjugated enynes and polyenes having defined configuration,[1] the development of new approaches to the stereoselective synthesis of such unsaturated derivatives is of great interest. In this line, palladium-catalyzed cross-coupling reactions of vinyl halides (mainly vinyl iodides, bromides or triflates) with organozinc reagents (Negishi reaction) are now powerful tools in organic synthesis particularly in the stereospecific preparation of polyunsaturated molecules including enynes and dienes.[2] These reagents are intermediates of choice when functionally sensitive vinyl halides are involved since they are mild nucleophiles and well-known for their compatibility with most functional groups. Furthermore, their excellent transmetallation ability to organopalladium(II) complexes allows to perform, under mild conditions, a number of high yield reactions with organic electrophiles.

Usually, the palladium-catalyzed Negishi coupling reaction is efficiently performed with the more reactive vinyl iodides, bromides or triflates.[3] However, vinyl chlorides which show a lower reactivity than bromo and iodo analogs have been rarely used. This low reactivity is ascribed to their much lower tendency to undergo oxidative addition to palladium(0) in the catalytic cycle. To our knowledge, except for two examples reported in the literature regarding the stereoselective mono-substitution of 1,1-dichlorostyrene[4] with organozinc chloride reagents, the use of these mild organometallic compounds in the palladium-catalyzed cross coupling reaction with vinyl chlorides appears to be unprecedented.

Previously we reported that in the presence of a catalytic amount of bis(triphenylphosphine)palladium chloride, chlorodienes and chloroenynes react rapidly and cleanly under mild conditions with Grignard reagents.[5] In this way, aryl and alkenyl substituents are easily introduced in good yields. Nevertheless, alkyl substituents containing β-hydrogen(s) gave unsatisfactory results due to the formation of the reduced vinyl chloride as a side product even by using $PdCl_2(dppf)$[6]as catalyst. Hayashi et al.[6] reported that the association of this bidentate catalyst with alkylzinc chlorides in the cross-coupling reaction with aryl and vinyl bromides allows to obtain efficiently and selectively the coupling product in good yields. Consequently, we undertook to investigate the reactivity of these conjugated alkenyl chlorides towards organozinc compounds. We now report that readily available functionalized conjugated



R^1 = alcynyl, alkenyl
R = alkyl, aryl
RM = R_3ZnLi, R_3ZnMgX or RMgBr, $ZnCl_2$

Scheme 1.

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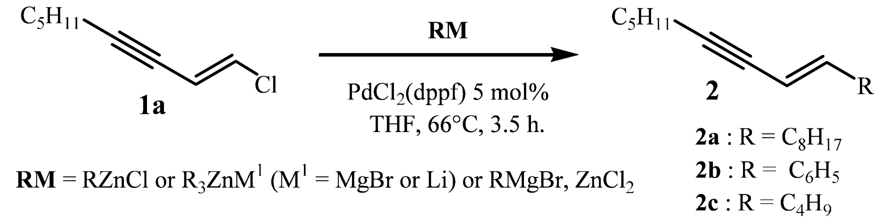
chlorodienes and chloroenynes can indeed be used as substrates in the Negishi type coupling reactions, affording stereoselectively the coupling products in high yields in the presence of a palladium catalyst that incorporates a bidentate ligand such as 1,1′-bis-(diphenylphosphino)ferrocene (Scheme 1).

At first we studied the Pd-catalyzed reaction of chloroenyne **1a** with alkylzinc reagents as a model system. The required chloroenynes **1** were readily prepared by Pd-catalyzed coupling of (*E*)-1,2-dichloroethylene with 1-alkynes.[7] Reaction of **1a** at reflux of THF in the presence of $PdCl_2(dppf)$ (5 mol%) with preformed *n*-octylzinc chloride (1.5 equiv.), prepared from *n*-octylmagnesium bromide and anhydrous $ZnCl_2$, was encouraging and afforded the enyne **2a** in moderate yield (50%, Table 1, entry 1) without any side product resulting from β-elimination. Most of the starting material **1a** unreacted was recovered at the end of the reaction. A similar result was obtained when using phenylzinc chloride instead of *n*-octylzinc chloride (entry 2). Increasing both the amount of zinc reagent (2.5 equiv.) and the reaction time (7 h instead of 3.5 h) has a positive effect since the yield of **2a** was improved to 73% (entry 3). It is well known that a marked increase in reactivity towards electrophiles occurs when organozincate-complexes were used instead of organozinc halides.[8] Consequently, we turned our efforts regarding the cross coupling reaction of **1a** with more reactive species such as magnesium trioctylzincate reagent (1.5 equiv.), prepared from the addition of 3 equiv. of Grignard reagent to zinc chloride. Under these conditions, the reaction proceeds rapidly within 3.5 h at 66°C and affords **3a** in excellent yield (85%, entry 4). It may be noted that the reaction can be performed with zincate species prepared from either Grignard or organolithium reagents (entries 4–6). Moreover, at least two of three octyl groups bonded to zinc participate in the reaction since treatment of **1a** with 0.5 equiv. of $(nC_8H_{17})_3ZnMgCl$ afforded **2a** with a similar result (82%, entry 5).

In order to simplify the coupling process from the point of view of the synthetic chemist, we also investigated the coupling reaction in which the organozinc species are generated in situ in the presence of an electrophile. Thus, when adding *n*-octylmagnesium bromide (2.5 equiv.) at 66°C to a THF solution containing $ZnCl_2$ (2.5 equiv.), the chloroenyne **1a** (1 equiv.) and $PdCl_2(dppf)$ (5 mol%), the coupling reaction was completed within 3.5 h and afforded **2a** in excellent yields whatever the nature of the Grignard reagent used (alkyl or aryl group, entries 7 and 8, Table 1). A higher temperature is essential for a rapid and complete cou-

Table 1. Optimization of the $PdCl_2(dppf)$-catalyzed cross coupling reaction of chloroenyne **1a** with organozinc reagents



RM = RZnCl or R_3ZnM^1 (M^1 = MgBr or Li) or RMgBr, $ZnCl_2$

2a : R = C_8H_{17}
2b : R = C_6H_5
2c : R = C_4H_9

Entry	RM (equiv.)	$ZnCl_2$ (equiv.)	Molar ratio $RM/ZnCl_2$	Yield of **2** (%)[a]	Product
1	$C_8H_{17}ZnCl^{b,c}$ (1.5)	–	–	50	**2a**
2	$C_6H_5ZnCl^{b,c}$ (1.5)	–	–	48	**2b**
3	$C_8H_{17}ZnCl^{b,c}$ (2.5)	–	–	73[d]	**2a**
4	$(C_8H_{17})_3ZnMgCl^{b,e}$ (1.5)	–	–	86	**2a**
5	$(C_8H_{17})_3ZnMgCl^{b,e}$ (0.5)	–	–	82	**2a**
6	$(C_4H_9)_3ZnLi^{e}$ (1.0)	–	–	85	**2c**
7	$C_8H_{17}MgBr^{f}$ (2.5)	2.5[h]	1	95[g]	**2a**
8	$C_6H_5MgCl^{f}$ (1.5)	1.5[h]	1	95	**2b**
9	$C_8H_{17}MgBr^{f}$ (1.5)	1.5[h]	1	95	**2a**
10	$C_8H_{17}MgBr^{f}$ (3.0)	1.5[h]	2	97	**2a**
11	$C_8H_{17}MgBr^{f}$ (1.5)	0.6[h]	2.5	97[i]	**2a**
12	$C_8H_{17}MgBr^{f}$ (1.5)	0.1[h]	15	20	**2a**

[a] Isolated yield based on **1a**.

[b] Reactions were performed at reflux of THF within 3.5 h using 1 equiv. of **1a** in the presence of 5 mol% of $PdCl_2(dppf)$.

[c] Prepared by transmetallation from stoichiometric amount of Grignard reagent and $ZnCl_2$.

[d] Reaction time 7 h.

[e] The formulae of the reagents are attributed in respect to the ratio of the reactants: RM (3 equiv., M = MgBr or Li) and anhydrous $ZnCl_2$ (1 equiv.). However, an equilibrium between several organozinc species cannot be discarded.

[f] Reactions were performed at reflux of THF within 3.5 h using 1 equiv. of **1a** and a THF solution of $ZnCl_2$ (0.5 M in THF) in the presence of 5 mol% of $PdCl_2(dppf)$.

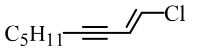
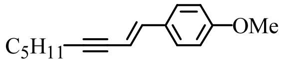
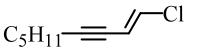
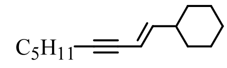
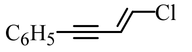
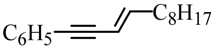
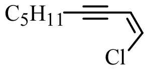
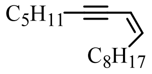
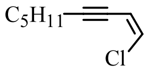
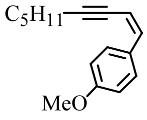
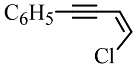
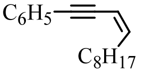
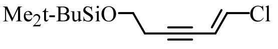
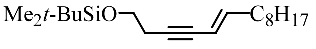
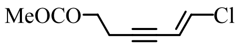
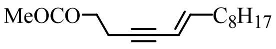
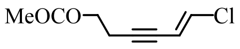
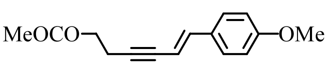
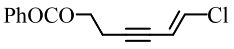
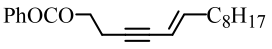
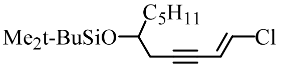
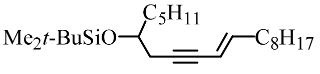
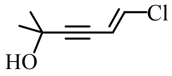
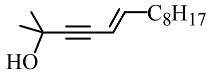
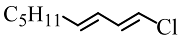
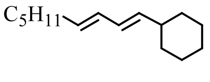
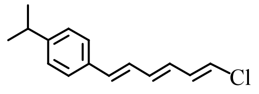
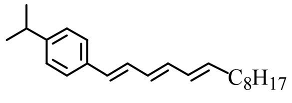
[g] An 81% yield was obtained when using freshly dried solid $ZnCl_2$ instead of a 0.5 M THF solution of $ZnCl_2$.

[h] A THF solution of $ZnCl_2$ (0.5 M in THF) was used.

[i] Without $ZnCl_2$, only 42% of coupled product **2a** were obtained.

pling reaction, since at room temperature a poor yield (~10%) of the enyne **2a** was obtained after 16 h. Moreover, the use of only 1.5 equiv. of Grignard reagent was enough to efficiently achieve the reaction (entry 9). The results presented above clearly showed that the reaction did not involved an organozinc chloride reagent to proceed even when using a 1/1 ratio of Grignard reagent/$ZnCl_2$, and prompted us to determine the best molar ratio of *n*-octylmagnesium chloride/zinc chloride necessary to perform this coupling. Increasing the ratio RM/$ZnCl_2$ from 1/1 to 2/1 or 2.5/1 resulted in similar yields of **2a** (entries 10 and 11). In the latter

Table 2. Cross coupling reactions of Grignard reagents with functionalized unsaturated vinyl chlorides **1** mediated by $PdCl_2$(dppf) and zinc chloride[a]

Entry	Vinyl chlorides 1[b]	Coupling product 2[c]	Yield (%)[d]
1	 **1a**	 **2d**	95
2	 **1a**	 **2e**	96
3	 **1b**	 **2f**	91
4	 **1c**	 **2g**	90
5	 **1c**	 **2h**	83
6	 **1d**	 **2i**	96
7	 **1e**	 **2j**	70
8	 **1f**	 **2k**	90
9	 **1f**	 **2l**	60
10	 **1g**	 **2m**	91
11	 **1h**	 **2n**	96
12	 **1i**	 **2o**	70[e,f]
13	 **1j**	 **2p**	83
14	 **1k**[g]	 **2q**	71

[a] All reactions were performed with 1.5 equiv. of RMgBr, 0.6 equiv. of a THF solution of $ZnCl_2$ (0.5 M) and 5 mol% of $PdCl_2$(dppf) in reflux of THF. For a general procedure see Ref. 10.

[b] Prepared according to Ref. 7.

[c] All new compounds exhibited satisfactory spectral properties and isomeric purity (>97%).

[d] Isolated yield based on **1**.

[e] 2.5 equiv. of RMgBr were used.

[f] Less than 10% of coupling product were obtained in the absence of $ZnCl_2$.

[g] Prepared according to Ref. 11.

case, it should be noted that only 0.6 equiv. of $ZnCl_2$ were necessary to provide **2a** in excellent yield (entry 11). All our efforts to perform this coupling reaction in the presence of a catalytic amount of $ZnCl_2$ (10 mol%) resulted, however, in a disappointing 20% yield (entry 12).

Another parameter that should have a significant influence on the course of the reaction was phosphine ligands around palladium catalyst. Consequently, we examined the catalytic activity of palladium catalysts bearing commercial bidentate phosphines on the course of the zinc chloride promoted coupling of **1a** with *n*-octylmagnesium bromide. The use of palladium catalysts coordinated with bidentates phosphines such as dppe or dppp was almost inactive however, the addition of $PdCl_2$(dppb) was found to catalyze the coupling process efficiently offering the coupling product **2a** in a similar yield (90%) than that achieved with $PdCl_2$(dppf). Finally, the influence of cosolvent additive was also briefly examined and no modification of the yield of **2a** was observed when the reaction was carried out in THF with Et_3N (8 equiv.) as cosolvent, whereas the addition of NMP or DMPU[9] dramatically decreased the yield of the reaction (10–15%).

In order to demonstrate the efficiency of this new palladium–zinc chloride mediated coupling reaction of **1** with Grignard reagents, a variety of functionalized polyunsaturated molecules were thus synthesized in good to excellent yields. As shown in Table 2, the coupling reaction was successful from various functionalized unsaturated vinyl chlorides and allows to introduce efficiently aryl substituents as well as primary and secondary alkyl substituents without formation of side products arising from β-elimination process (isomerization in the case of secondary alkyl groups and/or reduction/dimerization of the vinyl chloride). Interestingly, these reactions are highly stereoselective (>97%) since the cross coupling reactions with either (*E*)- or (*Z*)-chloroenynes furnishes either (*E*)- or (*Z*)-coupling products in excellent yields (entries 1–6). In addition, it should be noted that the cross coupling reaction tolerates sensitive functional groups in the substrates and is even successful with conjugated alkenyl chlorides having a free hydroxyl group (entry 12) or a homopropargyl acetate or benzoate (entries 8–10).

In summary, we have demonstrated for the first time that organozincate reagents generated in situ by reaction of Grignard compounds with less than molar amounts of zinc chloride lead to an efficient carbon–carbon bond formation reaction with various functionalized conjugated alkenyl chlorides. The use of these substrates for the elaboration of polyunsaturated molecules appears to be interesting since they are less photosensitive and thus more stable than the corresponding iodo and bromo analogs.

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10. Typical procedure: To a mixture containing a THF solution of $ZnCl_2$ (0.5 M, 0.6 mmol, 1.2 mL), alkenyl chloride **1** (1 mmol) and $PdCl_2$(dppf) (5 mol%) in 2 mL of THF, was added, at 65°C, Grignard reagent (1.5 mmol). The reaction was stirred at 65°C and monitored by TLC until complete consumption of starting materials (3.5–4 h). The reaction

was hydrolyzed at 0°C with aqueous HCl (1N), extracted with Et$_2$O, the organic extract was dried over MgSO$_4$ and the solvent was removed in vacuo. Purification by chromatography on silica gel afforded pure product **2**.

2d: ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.32–1.42 (m, 4H), 1.43–1.61 (m, 2H), 2.35 (dt, J=2.2, 6.6 Hz, 2H), 3.80 (s, 3H), 6.00 (dt, J=2.2, 16.2 Hz, 1H), 6.82 (d, J=16.2 Hz, 1H), 6.84 (d, J=8.9 Hz, 2H), 7.29 (d, J=8.9 Hz, 2H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 13.9, 19.5, 22.1, 28.5, 31.0, 55.1, 79.9, 92.1, 106.5, 114.0, 127.2, 129.4, 139.4, 159.7.

2h: ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.93 (t, J=6.8 Hz, 3H), 1.33–1.45 (m, 4H), 1.46–1.65 (m, 2H), 2.43 (td, J=2.2, 6.8 Hz, 2H), 3.82 (s, 3H), 5.57 (dt, J=2.2, 12.0 Hz, 1H), 6.48 (d, J=12.0 Hz, 1H), 6.87 (d, J=8.8 Hz, 2H), 7.83 (d, J=8.8 Hz, 2H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 13.9, 19.8, 22.2, 28.3, 31.5, 55.2, 79.4, 97.1, 105.7, 114.0, 129.80, 129.9, 139.7, 159.4.

2l: ^{1}H NMR (200 MHz, CDCl$_3$) δ 2.09 (s, 3H), 2.70 (td, J=2.1, 6.9 Hz, 2H), 3.81 (s, 3H), 4.21 (t, J=6.9 Hz, 2H), 5.98 (dt, J=2.2, 16.0 Hz, 1H), 6.84 (d, J=8.8 Hz, 2H), 6.85 (d, J=16.0 Hz, 1H), 7.30 (d, J=8.8 Hz, 2H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 20.1, 20.9, 55.3, 62.5, 81.4, 86.9, 105.8, 114.1, 127.4, 129.2, 140.5, 160.0, 170.8.

2j: ^{1}H NMR (200 MHz, CDCl$_3$) δ 0.07 (s, 6H), 0.90 (broad s, 12H), 1.26 (broad s, 12H), 2.06 (q, J=7.0 Hz, 2H), 2.49 (td, J=1.9, 7.3 Hz, 2H), 3.73 (t, J=7.3 Hz, 2H), 5.42 (dt, J=1.6, 15.8 Hz, 1H), 6.05 (dt, J=6.9, 15.8 Hz, 1H). ^{13}C NMR (50 MHz, CDCl$_3$) δ −5.3, 14.0, 18.3, 22.6, 23.8, 25.9, 28.8, 29.1, 29.2, 29.4, 31.9, 32.9, 62.1, 80.4, 85.2, 109.6, 143.8.

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