

An Efficient Synthesis of Stereodefined Enynes and Dienes via Pd-Catalyzed Reaction of Chloroenynes and Chlorodienes with Grignard Reagents

Parfait Ramiandrasoa,^a Bernard Bréhon,^b Armelle Thivet,^a
 Mouâd Alami^{*a,b} and Gérard Cahiez^a

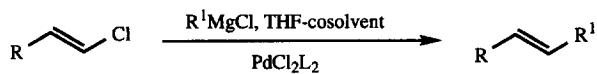
^a/ Département de Chimie, Ecole Supérieure de Chimie Organique et Minérale, 13 bd de l'Hautil, 95092 Cergy-Pontoise, France.
 Fax: (+33) 1 01 30 75 60 21

^b/ Ecole Normale Supérieure, Département de Chimie associé au CNRS, 24 rue Lhomond, 75231 Paris Cedex 05, France.

Key Words: chlorodienes, chloroenynes, enynes, dienes, dienynes, trienes, palladium.

Abstract: In the presence of PdCl₂(PPh₃)₂ and Et₃N, chloroenynes and chlorodienes react rapidly under mild conditions with various Grignard reagents to give isomerically pure conjugated enynes, dienes, dienynes and trienes in good isolated yields. © 1997 Published by Elsevier Science Ltd.

Transition metal-catalyzed cross coupling reactions of organometallic compounds with organic halides, offer an attractive method for carbon-carbon bond formation.¹ Although the substitution of vinyl halides mostly vinyl iodides or bromides under palladium catalysis is now well documented,² Less common are Pd-catalyzed coupling reactions of organometallic reagents with vinyl chlorides³ since these compounds are considered generally poor reactants and show low reactivity toward oxidative addition in the catalytic cycle except for the nickel-catalyzed coupling with Grignard reagents.⁴ We have recently reported that vinyl chlorides⁵ including chloroenynes and chlorodienes undergo rapid coupling with 1-alkynes when performing the reaction under appropriate conditions (PdCl₂(PhCN)₂-CuI in piperidine). The use of these compounds would be interesting in synthesis since they are considerably more accessible,⁶ less photosensitive and thus more stable than the corresponding iodides or bromides. Herein we report that chloroenynes and chlorodienes react easily and rapidly under mild conditions with Grignard reagents in the presence of PdCl₂(PPh₃)₂, thus providing an efficient access to stereodefined substituted enyne and diene derivatives. Such structures are of great interest since they are found in various biologically active compounds.⁷



R = alkenyl, alkynyl R¹ = alkenyl, aryl, alkyl

A first series of experiments was effected with (*E*)-chloroenyne **1a** and phenyl magnesium chloride as partners to establish the best reaction conditions (Table I). It is noteworthy that both the nature of catalyst and the cosolvent show a critical influence for the success of the reaction. Thus, when treating (*E*)-chloroenyne **1a** at room temperature with phenyl magnesium chloride (2 equiv), in THF, in the presence of PdCl₂(PPh₃)₂ (5%) a 68% isolated yield of (*E*)-enyne **2a** was obtained (entry 1). It may be pointed out that all our attempts to improve this result by using other palladium catalyst resulted in similar or lower yields (23 to 71%, entries 2 to 9). However, by adding triethylamine or TMEDA to the reaction mixture, the (*E*)-enyne **2a** was obtained stereospecifically in high isolated yield (90-91%, entries 13 and 14) within 15 min.

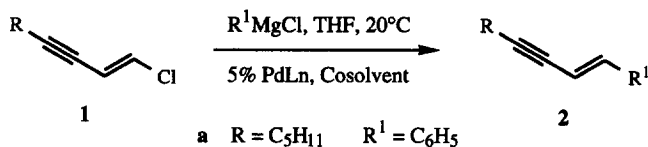


Table I

Entry	PdLn	Cosolvent	Isolated yield of 2a (%)
1	PdCl ₂ (PPh ₃) ₂	-	68
2	PdCl ₂ (bipy)	-	37
3	PdCl ₂ (<i>o</i> -phen)	-	67
4	PdCl ₂ (AsPh ₃) ₂	-	66
5	PdCl ₂ (dppe) ^a	-	23
6	PdCl ₂ (dppp) ^b	-	71
7	PdCl ₂ (dppb) ^c	-	40
8	Pd(OAc) ₂	-	45
9	Pd(OAc) ₂ + 2PPh ₃	-	38
10	PdCl ₂ (PPh ₃) ₂	DME	57
11	"	Sulfolane	82
12	"	<i>i</i> -Pr ₂ NEt	83
13	"	Et ₃ N	91
14	"	TMEDA	90

a/ dppe: 1,2-bis(diphenylphosphino)ethane. b/ dppp: 1,3-bis(diphenylphosphino)propane. c/ dppb: 1,4-bis(diphenylphosphino)butane.

As can be seen from table II, the reaction described above has been successfully applied to various chloroenynes and chlorodienes. Good yields of geometrically pure unsaturated compounds (enyne, dienes, dienynes and trienes) have been obtained when using aryl and alkenylmagnesium halides. However, with alkylmagnesium halides containing β-hydrogen(s), the cross coupling was less successful and gives as side product reduction of the vinyl chloride even by using PdCl₂(dppf) as catalyst⁹ (entry 19).

Table II: Pd-catalyzed cross coupling reaction of unsaturated vinyl chlorides with Grignard reagents.^a

Entry	Vinyl chloride ^b	RMgCl	Product ^c	Yield (%) ^d
15		ClMg-		95
16	"	BrMg-		90
17	"	ClMg-		71
18	"	BrMg-		62
19	"	ClMgOct		42 ^e
20		ClMgC ₆ H ₅		86 ^f
21	"			63 ^g
22		ClMgC ₆ H ₅		70
23		ClMgC ₆ H ₅		93
24		ClMgC ₆ H ₅		76
25		ClMgC ₆ H ₅		77
26		ClMgC ₆ H ₅		51
27		ClMgC ₆ H ₅		81
28	"	BrMg-		70
29	"	BrMg-		55
30		ClMgC ₆ H ₅		81

^a Unless otherwise stated, all reactions were performed with 2 equiv of RMgCl, 8 equiv of Et₃N and 5% of PdCl₂(PPh₃)₂. For a typical procedure see ref. 8. ^b Chloroenynes were prepared from the corresponding 1-alkynes and (*E*) or (*Z*)-dichloroethylene, see ref. 6. Chlorodienes were prepared according to ref. 6a. ^c Satisfactory spectral data were obtained for all new compounds, see ref. 8. ^d Isolated yields. ^e Yield using PdCl₂(dppf) (dppf: 1,1'-bis(diphenylphosphino)ferrocene); a 15% were obtained when using PdCl₂(PPh₃)₂. ^f Yield using PdCl₂(dppp) as a 95:5 mixture of *Z*:*E* isomers. ^g Isolated in a 92:8 mixture of *Z*:*E* isomers.

In conclusion, the Pd-catalyzed cross coupling reaction of vinyl chlorides with Grignard reagents provides a simple and alternative route to stereodefined unsaturated compounds. Furthermore, the use of chloroenynes and chlorodienes is more attractive than the corresponding bromides and iodides since they are easily accessible, and can be stored at -20°C for several months without isomerisation.

Acknowledgements: The authors wish to thank Dr. G. Linstrumelle for fruitful discussions.

References and notes

- (a) Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic Press: London, **1985**. (b) Kalinin, V.N. *Synthesis* **1992**, 413-432 and references cited therein.
- (a) Tamao, K. in *Comprehensive Organic Synthesis*, Vol. 3; Trost, B.M.; Fleming, I.; Pattenden, G. Ed.; Pergamon Press: Oxford, **1991**, pp 435-480. (b) Knight, D.W. in *Comprehensive Organic Synthesis*, Vol. 3; Trost, B.M.; Fleming, I.; Pattenden, G. Ed.; Pergamon Press: Oxford, **1991**, pp 481-520.
- For the coupling of vinyl chlorides with Grignard reagents under palladium catalysis see: (a) Ratovelomanana, V.; Linstrumelle, G. *Synth. Comm.* **1984**, *14*, 179-187. (b) Hoffmann, R.W.; Giesen, V.; Fuest, M. *Liebigs Ann. Chem.* **1993**, 629-639. (c) Sugihara, Y.; Ogasawara, K. *Synlett* **1994**, 665-666. For the coupling of polychloroolefins see: (d) Linstrumelle, G.; Alami, M. (*E*) and (*Z*)-dichloroethylene in *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L., Ed., Wiley, Chichester, **1995**, 3, 1710-1712. (e) Ratovelomanana, V.; Linstrumelle, G. *Tetrahedron Lett.* **1981**, *22*, 315-318. (f) Ratovelomanana, V.; Linstrumelle, G.; Normant, J.F. *Tetrahedron Lett.* **1985**, *26*, 2575-2576.
- The coupling of vinyl chlorides with Grignard reagents under nickel catalysis has been described see: (a) Corriu, R.J.P.; Masse, J.P. *J. Chem. Soc. Chem. Comm.* **1972**, 144. (b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.I.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Soc. Chim. Jpn.* **1976**, *49*, 1958-1969. (c) Hosoni, A.; Saito, M.; Sakurai, H. *Tetrahedron Lett.* **1979**, 429-432. (d) Babudri, F.; Fiandanese, V.; Mazzone, L.; Naso, F. *Tetrahedron Lett.* **1994**, *35*, 8847-8850. For the coupling under iron catalysis see: (e) Cahiez, G.; Marquais, S. *Tetrahedron Lett.* **1996**, *37*, 1773-1776.
- Alami, M.; Linstrumelle, G. *Tetrahedron Lett.* **1991**, *32*, 6109-6112.
- (a) Chemin, D.; Linstrumelle, G. *Tetrahedron* **1994**, *50*, 5335-5344. (b) Alami, M.; Gueugnot, S.; Domingues, E.; Linstrumelle, G. *Tetrahedron* **1995**, *51*, 1209-1220.
- (a) Jones, E.R.H.; Thallez, V.; *The Chemistry of Carbon-Carbon Triple Bond*, part II; Patai, S., Interscience, New York, **1978**, pp 621. (b) Bohlmann, F.; Burkhardt, T.; Zdero, C. *Naturally Occurring Acetylenes*, Academic Press, New York, **1973**.
- Typical Procedure: preparation of (1E)-1-phenyl-1-nonen-3-yne (2a, Table 1, entry 15)*: To a solution of $\text{PdCl}_2(\text{PPh}_3)_2$ (0.05 mmol, 35 mg), chloroenyne **1a** (1 mmol, 157 mg), triethylamine (8 mmol, 1.1 mL) in 3 mL of anhydrous THF was added dropwise at 20°C a solution of PhMgCl (2 mmol, 0.8N in THF). After stirring at room temperature for 20 min, the reaction was hydrolyzed at 0°C with aqueous hydrochloric acid (1M) and extracted with Et_2O . The organic extract was dried over MgSO_4 and the solvent was removed *in vacuo*. Filtration through silica gel (eluent: petroleum ether) gave 181 mg (91%) of pure enyne **2a**: ^1H NMR (270 MHz, CDCl_3) δ 7.25 to 7.39 (5H, m), 6.87 (1H, d, $J = 16.2$ Hz), 6.16 (1H, dt, $J = 16.2$ and 2.3 Hz), 2.36 (2H, td, $J = 6.9$ and 2.3 Hz), 1.60 to 1.52 (2H, m), 1.46 to 1.33 (4H, m), 0.92 (1H, t, $J = 6.9$ Hz); ^{13}C NMR (67.8 MHz, CDCl_3) δ 139.95, 136.55, 128.60, 128.20, 126.00, 108.90, 93.10, 79.70, 31.15, 28.50, 22.25, 19.65, 14.00.
- $\text{PdCl}_2(\text{dppf})$ is described to depress side reactions particularly β -elimination see: Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158-163.

(Received in France 23 December 1996; accepted 21 February 1997)