Nickel-Catalyzed Cross-Coupling of Dienyl Phosphates with Grignard Reagents in the Synthesis of 2-Substituted 1,3-Dienes

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Introduction

Conjugated dienes are important intermediates in organic synthesis.[1] We recently published a method for the synthesis of 2-substituted cyclic 1,3-dienes via a copper-catalyzed cross-coupling between dienyl triflates and Grignard reagents (eq 1).[2]
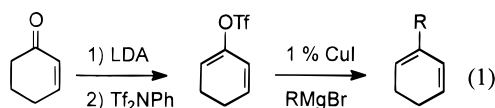
To our disappointment, dienyl phosphates, which are more stable and more readily obtained on a large scale than dienyl triflates, were not reactive under these conditions. We therefore turned our attention to the use of nickel(0) instead of copper(I) as catalyst for coupling with dienyl phosphates. Nickel- and palladium-catalyzed cross-couplings between organic halides and organometallic reagents are well-known in the literature.[3] Couplings of organic phosphates have been reported with Grignard reagents,[4] organomanganese reagents,[5] and organoaluminum reagents[4c,6] with nickel or palladium catalysis. However, little attention has been paid to the synthesis of substituted dienes via these methods. Claesson *et al.*[4a] showed that nickel-catalyzed reaction of acyclic diethyl dienyl phosphates with Grignard reagents give substituted dienes. In this paper we report on a

further investigation of this reaction with application to both cyclic and acyclic substrates and various Grignard reagents.

Results and Discussion

Dienyl phosphates were obtained from the corresponding α,β-unsaturated ketones in good yields following a literature procedure.[4b] Cross-coupling of the dienyl phosphates with Grignard reagents were studied employing catalytic amounts (1 mol %) of a nickel catalyst (NiCl$_2$(dppe) or NiCl$_2$(dppp))[7] in ether or THF. The reactions of cyclic dienyl phosphates with *n*-alkyl and aryl Grignard reagents were fast, with complete conversion usually being observed within 30 min at room temperature, to give 2-substituted dienes as the sole product (Table 1). One drawback with our previously described copper-catalyzed cross-coupling is that cyclic dienyl triflates and *n*-alkyl Grignard reagents gave moderate yields of coupling products.[2] Coupling of these structural elements can be performed more successfully with dienyl phosphates as substrates employing nickel catalysis. For example, 2-octyl-1,3-cyclohexadiene (**8**) was obtained in 86% isolated yield from the cross-coupling of 1,3-cyclohexadienyl phosphate **1**[8] with *n*-octylMgBr using NiCl$_2$(dppe) as catalyst (Table 1, entry 2), whereas the corresponding copper-catalyzed reaction employing the dienyl triflate gave only 60% yield of **8**.[2] It is noteworthy that the homocoupling product 2,2′-bis(1,3-cyclohexadienyl) that was observed as a side product in the copper-catalyzed reactions is not observed at all in the nickel-catalyzed version.

The effect of the substituent in the phosphate leaving group was examined. It was found that diphenyl phosphate **1** and the corresponding diethyl phosphate **2**[9] gave comparable yields in cross-couplings with *n*-octylMgBr using NiCl$_2$(dppe) as catalyst (Table 1, entries 2−3). Change of catalyst to NiCl$_2$(dppp) gave a similar result (Table 1, entry 4). An aryl substituent could also be easily introduced as demonstrated by the couplings of dienyl phosphates **1**, **3**, and **4** with aryl Grignard reagents (Table 1, entries 5−8). Sterically hindered phosphate **5**, however, gave a moderate yield of cross-coupling product **13** in reaction with PhMgBr (Table 1, entry 9).

The corresponding reaction with MeMgBr was slow at room temperature, but reaction between **6** and MeMgBr in refluxing ether with NiCl$_2$(dppp) as the catalyst resulted in complete conversion within 5 h, and 5,5-diphenyl-2-methyl-1,3-cyclohexadiene (**14**)[2] was isolated in 63% yield (Table 1, entry 10). Cross-coupling of dienyl phosphates with secondary alkyl Grignard reagents such as 2-butylMgBr or 2-octylMgBr was slower than the corresponding coupling with *n*-alkyl Grignard reagents. NiCl$_2$(dppe) and NiCl$_2$(dppp) should be suitable catalysts for coupling with secondary alkyl Grignard reagents since they do not promote isomerization of the alkyl group.[10]

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(7) dppe = diphenylphosphinoethane, dppp = diphenylphosphinopropane.

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Table 1. Nickel-Catalyzed Cross-Coupling of Cyclic Dienyl Phosphates with Grignard Reagents[a]

entry	substrate	RMgBr	L$_2$	product	yield[b] (%)
1	1	*n*-butylMgBr	dppe	7	(85)[c] 66
2	1	*n*-octylMgBr	dppe	8	86
3	2	*n*-octylMgBr	dppe	8	81
4	2	*n*-octylMgBr	dppp	8	82
5	1	PhMgBr	dppe	9	68[d]
6[e]	1		dppe	10	58
7	3	PhMgBr	dppe	11	92
8[e]	4	PhMgBr	dppe	12	89
9[e]	5	PhMgBr	dppe	13	40
10	6	MeMgBr	dppp	14	63[f]
11	1	2-octylMgBr	dppp	15	–[g]
12	6	2-butylMgBr	dppe	16	45[h]

[a] Unless otherwise stated the reactions were carried out in ether according to the procedure in the Experimental Section. [b] Isolated yield of 2-substituted diene after flash chromatography (or distillation for aryl-substituted cyclohexadienes). [c] GLC yield, *n*-decane as internal standard. [d] Reaction was run on a 120 mmol scale. [e] TBS = *tert*-butyldimethylsilyl. [f] Reaction was run in refluxing ether. [g] Incomplete conversion after 20 h. [h] Reaction was carried out in THF at 40 °C.

**Table 2. Cross-Coupling of Acyclic Dienyl Phosphate 17
with Grignard Reagents**[a]
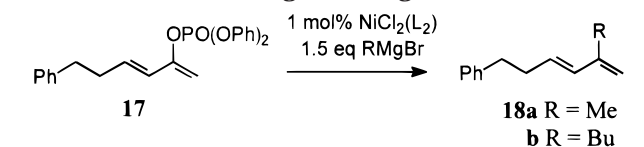
entry	RMgBr	L$_2$	solvent / temp	reactn time (h)	yield of 18[b] (%)
1	BuMgBr	dppe	Et$_2$O/rt	0.5	77
2	MeMgBr	dppe	Et$_2$O/rt	20	<50 convn
3	MeMgBr	dppp	Et$_2$O/rt	7	76
4	2-BuMgBr	dppp	THF/reflux	2	c

[a] Experimental procedure as stated in Experimental Section.
[b] Isolated yield after column chromatography. [c] No cross-coupling product could be isolated.

Reaction between **1** and 2-octylMgBr with NiCl$_2$(dppp) (1 mol %) as catalyst in ether at room temperature resulted in low conversion even at prolonged reaction times (Table 1, entry 11). On the other hand, the reaction between **6** and 2-butylMgBr with NiCl$_2$(dppe) as catalyst in THF at 40 °C was complete within 2 h and 5,5-diphenyl-2-(2-butyl)-1,3-cyclohexadiene (**16**)[2] was isolated in 45% yield (Table 1, entry 12).

The nickel-catalyzed cross-coupling was also studied for acyclic dienyl phosphates. Dienyl phosphate **17** (Table 2) was obtained from (E)-6-phenyl-3-hexen-2-one[11,12] in 75% yield after chromatography. Reaction of **17** with n-BuMgBr using NiCl$_2$(dppe) as catalyst yielded the desired cross-coupling product **18b** in 77% yield within 30 min (Table 2, entry 1). On the other hand, reaction between **17** and MeMgBr was very slow with NiCl$_2$(dppe) as catalyst (50% conversion after 20 h at room temperature) (Table 2, entry 2). Change of catalyst to NiCl$_2$-(dppp) gave a significant increase in reaction rate. The reaction was complete within 7 h, and (3E)-2-methyl-6-phenyl-1,3-hexadiene (**18a**)[13] was isolated in 76% yield (Table 2, entry 3). Attempted cross-coupling with 2-BuMgBr failed (Table 2, entry 4).

To study the stereoselectivity of the nickel-catalyzed cross-coupling, dienyl phosphate **19** (Table 3) was employed as substrate. Phosphate **19** was obtained in 60% yield from (E)-8-phenyl-5-octen-4-one[11] as a 55:45 mixture of (Z)- and (E)-isomers, which was separated by column chromatography. Cross-coupling of purified (Z)-**19** with MeMgBr using NiCl$_2$(dppp) as catalyst in ether at room temperature produced a 50:50 mixture of stereoisomeric cross-coupling products **20a** (Table 3, entry 1). The E:Z ratio could be slightly improved to 57:43 in refluxing THF, with the major isomer being that with retained stereochemistry (Table 3, entry 2). Reaction of (E)-**19** with MeMgBr also showed poor stereoselectivity (Table 3, entry 3). However, reaction of (E)-**19** with BuMgBr with NiCl$_2$(dppe) as catalyst at room temperature resulted in stereoselective formation of the cross-coupling product **20b** with retention of double-bond geometry (95% reten-

tion) in 62% isolated yield after a 2 h reaction time (Table 3, entry 4). NiCl$_2$(dppp) gave a similar result but with a slight decrease in yield and stereoselectivity (Table 3, entry 5). On the other hand, reaction between (Z)-**19** and BuMgBr was very slow at room temperature with NiCl$_2$-(dppe) as catalyst (Table 3, entry 6), showing how sensitive this reaction is to steric effects. A catalyst change to NiCl$_2$(dppp) increased the reaction rate and afforded a 78% isolated yield of **20b** after 5 h at room temperature (Table 3, entry 7). However, conservation of double-bond configuration was not observed and the product with Z-configuration dominated (E:Z ratio 30:70). By performing the reaction in refluxing THF, the trend previously observed (faster conversion, slightly lower yield, and improved conservation of stereochemistry) was followed, and **20b** with an E:Z ratio of 55:45 was obtained (Table 3, entry 8).

For simple alkenyl halides, reaction with Grignard reagents under nickel catalysis generally results in a stereospecific reaction with retention of configuration of the double bond in the cross-coupling product.[14] 1,2-Dihaloethylenes on the other hand react nonstereospecifically with Grignard reagents to yield disubstituted olefins.[14,15] However, by using 1 equiv of Grignard reagent, 1-chloroalkenes can be stereospecifically synthesized from dichloroethylene.[16] The cross-coupling between dienyl halides and Grignard reagents under nickel catalysis has, to our knowledge, not been studied. (E)- and (Z)-dienyl sulfides, however, were found to react stereospecifically with retention of configuration with MeMgI under nickel catalysis to yield 1,3-dienes.[17] Regardless of the double-bond configuration in dienyl phosphate **19**, a mixture of E and Z cross-coupling products was obtained in reaction with MeMgBr or BuMgBr under nickel catalysis. An explanation of the low stereoselectivity observed is that the dienyl−nickel complex obtained from oxidative addition is in equilibrium with an allenyl−nickel intermediate (Scheme 1).

Conclusion

For the synthesis of 2-substituted dienes, nickel-catalyzed cross-coupling of dienyl phosphates with Grignard reagents is a good complement to our previously reported copper-catalyzed cross-coupling of dienyl triflates with Grignard reagents. The nickel-catalyzed coupling has the advantage that it works with dienyl phosphates and gives good results for aryl and n-alkyl Grignard reagents. The copper-catalyzed reaction, which requires dienyl triflates, is advantageous for methyl and s-alkyl Grignard reagents, but the low stability of acyclic dienyl triflates makes this reaction unsuitable for the synthesis of acyclic dienes. The nickel-catalyzed reaction works for acyclic dienyl phosphates, but the reaction shows low stereoselectivity. The nickel-catalyzed reaction is sensitive to changes in substrate and Grignard reagent

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Table 3. Cross-Coupling of Acyclic Dienyl Phosphate 19 with Grignard Reagents[a]
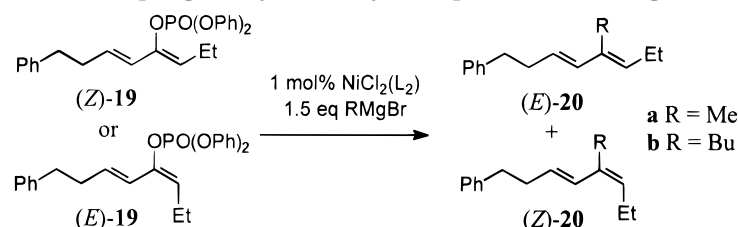
entry	substrate	R	L₂	solvent/temp	reactn time (h)	yield[b] (%)	E:Z ratio of **20**
1	(Z)-**19**	Me	dppp	Et₂O/rt	48	68	50:50
2	(Z)-**19**	Me	dppp	THF/reflux	2	53	57:43
3	(E)-**19**	Me	dppp	THF/reflux	2	55	40:60
4	(E)-**19**	Bu	dppe	Et₂O/rt	2	62	5:95
5	(E)-**19**	Bu	dppp	Et₂O/rt	3	56	10:90
6	(Z)-**19**	Bu	dppe	Et₂O/rt	20	43[c]	35:65
7	(Z)-**19**	Bu	dppp	Et₂O/rt	5	78	30:70
8	(Z)-**19**	Bu	dppp	THF/reflux	1	54	55:45

[a] Procedure as stated in the Experimental Section. [b] Isolated yield after column chromatography. [c] 60% conversion after 20 h, unreacted (Z)-**19** recovered.

Scheme 1
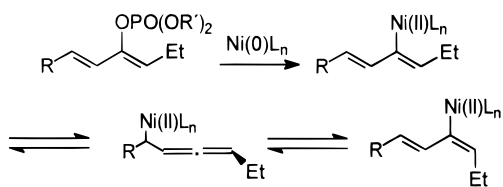
structure. The catalyst and other reaction conditions have to be varied accordingly.

Experimental Section

NMR spectra were recorded for CDCl₃ solutions (^{1}H at 400 MHz, ^{13}C at 100.5 MHz, and ^{31}P at 161.8 MHz) using tetramethylsilane (0.0 ppm) or residual CHCl₃ (7.26 ppm) as internal standards in ^{1}H NMR, and CDCl₃ (77.0 ppm) in ^{13}C NMR. Phosphoric acid was used as external standard (0.0 ppm) in ^{31}P NMR. Ether and THF were dried over Na−benzophenone prior to use. Diisopropylamine was dried over CaH₂ and distilled immediately before use. Grignard reagents were made according to standard procedures and titrated before use.[18] All reactions were run under a dry nitrogen atmosphere.

Preparation of 1,3-Cyclohexadien-2-yl Diphenyl Phosphate (1). General Procedure for Preparation of Dienyl Phosphates.[4b] A solution of LDA (5.7 mmol) in THF (10 mL), prepared from diisopropylamine (0.75 mL, 5.7 mmol) and *n*-butyllithium (1.6M in hexane, 3.6 mL, 5.7 mmol) at 0 °C under N₂, was cooled to −78 °C by means of a dry ice/acetone bath. 2-Cyclohexenone (500 mg, 5.2 mmol) in THF (10 mL) was added dropwise, and the reaction mixture was stirred for 30 min at −78 °C. Diphenyl chlorophosphate (1.19 mL, 5.7 mmol) was added in one portion, and the reaction mixture was allowed to warm to 0 °C and stirred at this temperature until the reaction was judged complete according to TLC. The solvent was evaporated, the crude material was dissolved in ether, and the organic phase was washed twice with water. The organic layer was dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified by column chromatography (pentane:Et₂O 75:25) to yield 1.61 g (94%) of **1** as a white solid. Spectral data were in agreement with those previously reported.[8]

1,3-Cyclohexadien-2-yl Diethyl Phosphate (2). Yield: 56% as a pale oil. Spectral data are consistent with those previously reported.[9]

(3E)-1-Phenyl-3,5-octadien-5-yl Diphenyl Phosphate (19). Yield: 60% as a 55:45 mixture of *Z*- and *E*-isomers that were separated by column chromatography (eluent pentane:Et₂O 90:

10), (Z)-**19**, R_f 0.26, (E)-**19** R_f 0.21 (TLC, pentane:Et₂O 80:20). Stereochemistry was determined by NOE experiments. (Z)-**19**: ^{1}H NMR δ 7.37−7.30 (m, 4H), 7.28−7.11 (m, 11H), 5.92 (m, 2H), 5.10 (dt, J = 2.1, 7.5 Hz, 1H), 2.61 (m, 2H), 2.34 (m, 2H), 2.20 (dqvintet, J = 2.5, 7.5 Hz, 2H), 0.95 (t, J = 7.5 Hz); ^{13}C NMR δ 150.6 (d, J(^{13}C,^{31}P) = 7.6 Hz), 144.6, 141.6, 130.5, 129.7, 128.3 (d, J(^{13}C,^{31}P) = 5.3 Hz), 125.8, 125.3, 124.9, 121.2 (d, J(^{13}C,^{31}P) = 6.1 Hz), 120.2 (d, J(^{13}C,^{31}P) = 5.3 Hz), 35.4, 34.3, 19.3, 13.6; ^{31}P NMR δ 55.3. (E)-**19**: ^{1}H NMR δ 7.38−7.30 (m, 4H), 7.28−7.12 (m, 11H), 6.12 (dq, J = 15.3, 1.7 Hz, 1H), 5.89 (dt, J = 15.3, 7.1 Hz), 5.46 (dt, J = 2.6, 7.9 Hz, 1H), 2.63 (m, 2H), 2.37 (q, J = 7.6 Hz, 2H), 2.12 (dqvintet, J = 2.1, 7.6 Hz, 2H), 0.98 (t, J = 7.6 Hz); ^{13}C NMR δ 150.6 (d, J(^{13}C,^{31}P) = 7.6 Hz), 144.2 (d, J(^{13}C,^{31}P) = 8.6 Hz), 141.5, 132.3, 129.7, 128.3 (d, J(^{13}C,^{31}P) = 4.7 Hz), 125.9, 125.4, 120.2 (d, J(^{13}C,^{31}P) = 4.6 Hz), 119.9 (d, J(^{13}C,^{31}P) = 6.0 Hz), 118.5 (d, J(^{13}C,^{31}P) = 4.0 Hz), 35.4, 34.5, 19.6, 14.2; ^{31}P NMR δ 55.5.

General Procedure for Nickel-Catalyzed Cross-Coupling Reactions. NiCl₂(L₂) (0.01 mmol) and the dienyl phosphate (1 mmol) were mixed in Et₂O (10 mL) at 0 °C under a dry nitrogen atmosphere. The Grignard reagent (1.5 mmol of a 0.5 M solution in ether) was then added via syringe. The reaction mixture was stirred at room temperature until judged complete according to TLC. The initially yellow solution gradually became cloudy as the reaction proceeded. The reaction was quenched by addition of a 0.1 M aqueous HCl solution. The organic phase was collected, and the water phase was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine, dried (MgSO₄), and evaporated *in vacuo*. The resulting crude products were purified by column chromatography except for aryl-substituted cyclohexadienes that were purified by distillation.

Spectral data for 2-butyl-1,3-cyclohexadiene (**7**),[2] 2-octyl-1,3-cyclohexadiene (**8**),[2] 2-phenyl-1,3-cyclohexadiene (**9**),[19] 2-phenyl-1,3-cycloheptadiene (**11**),[2] 5,5-diphenyl-2-methyl-1,3-cyclohexadiene (**14**),[2] 5,5-diphenyl-2-but-2-yl-1,3-cyclohexa-diene (**16**),[2] and (E)-2-methyl-6-phenyl-1,3-hexadiene (**18a**)[13] were consistent with data reported in the literature.

(3E)-5-Methyl-1-phenyl-3,5-octadiene (20a) was isolated as an inseparable mixture of *Z*- and *E*-isomers after column chromatography (pentane). Stereochemistry was determined via NOE experiments. **20a**: ^{1}H NMR δ 7.32−7.16 (m, 10H), 6.46 (dm, J = 15.6 Hz, 1H, (Z)), 6.10 (d, J = 15.6 Hz, 1H, (E)), 5.70 (dt, J = 15.6, 6.7 Hz, 1H, (Z)), 5.60 (dt, J = 15.6, 6.7 Hz, 1H, (E)), 5.38 (t, J = 7.5 Hz, 1H, (E)), 5.26 (t, J = 7.5 Hz, 1H, (Z)), 2.71 (q, J = 7.5 Hz, 4H), 2.43 (m, 4H), 2.13 (m, 4H), 1.78 (q, J = 1.2 Hz, 3H, (Z)), 1.71 (q, J = 0.6 Hz, 3H, (E)), 0.98 (t, J = 7.5 Hz, 3H).

(3E)-5-Butyl-1-phenyl-3,5-octadiene (20b) was isolated as an inseparable mixture of *Z*- and *E*-isomers after column

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chromatography (pentane). Stereochemistry was determined via NOE experiments. (*Z*)-**20b**: ^{1}H NMR δ 7.32−7.27 (m, 2H), 7.23−7.17 (m, 3H). 6.34 (dq, *J* = 15.8, 1.3 Hz, 1H) 5.72 (dt, *J* = 15.8, 7.0 Hz, 1H), 5.25 (t, *J* = 7.4 Hz, 1H), 2.74 (m, 2H), 2.45 (q, *J* = 7.6 Hz, 2H), 2.14 (quintet, *J* = 7.2 Hz 4H), 1.45−1.25 (m, 4H), 0.97 (t, *J* = 7.5 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR δ 142.0, 135.5, 130.2, 128.8, 128.5, 128.2, 126.6, 125.7, 36.2, 35.3, 33.8, 31.2, 22.7, 20.6, 14.5, 14.1. (*E*)-**20b**: ^{1}H NMR δ 5.99 (m, 1H), 5.63 (m, 1H), 5.34 (t, *J* = 7.4, 1H).

Supporting Information Available: Characterization data (^{1}H, ^{13}C NMR) for compounds **3**−**6**, **10**, **12**, **13**, **17**, and **18b** and copies of ^{1}H and ^{13}C NMR spectra of compounds **3**−**6**, **10**, **12**, **13**, **17**, **18b**, (*E*)-**19**, (*Z*)-**19**, **20a**, **20b**, and (*Z*)-**20b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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