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A Ligand Free and Room Temperature Protocol for Pd-Catalyzed Kumada−Corriu Couplings of Unactivated Alkenyl Phosphates

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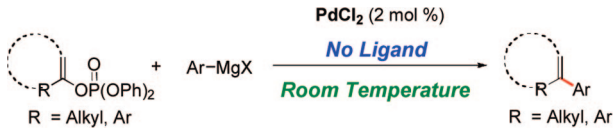

Kumada−Corriu cross-couplings of nonactivated cyclic and acyclic vinyl phosphates with aryl magnesium reagents afforded a series of 1,1-disubtituted alkenes in good yields for most cases when the reactions were performed at room temperature with the simple palladium salt, $PdCl_2$, without the presence of phosphine ligands.

Palladium-catalyzed coupling reactions have emerged as powerful tools in synthetic organic chemistry for the construction of carbon−carbon bonds.[1] Along side the traditional electrophiles,[1a,2] alkenyl phosphates have proved to be attractive and convenient coupling partners in such transformations.[3−7] Compared to the corresponding and more widely used triflates or nonaflates, phosphates and tosylates display a higher stability and a satisfactory reactivity in Pd-catalyzed coupling with the use of appropriate ligands. Even if the oxidative addition step to the catalyst is less favorable with these reagents, use of electron-rich tertiary phosphines can provide yields comparable to those obtained with the usual electrophiles.[4e,5f,8] The advantages in the use of phosphates compared to tosylates are their stability and their simple and inexpensive preparation from the reaction of phosphoryl chloride with an in situ generated enolate. The analogous vinyl tosylates require the use of the more expensive tosyl anhydride for effective derivatization.[5b]

In previous reports, we disclosed the application of unactivated alkenyl phosphates for the direct synthesis of unsymmetrical diaryl alkenes employing Ni-catalyzed Suzuki−Miyaura and the Pd-catalyzed Negishi couplings.[4a,j,k] Hartwig and co-workers revealed in 2005 the effective coupling of alkenyl tosylates with Grignard reagents using $Pd(dba)_2$ and JosiPhos ligands.[5b] Only few reports on the couplings of unactivated vinyl phosphates with Grignard reagents have previously been published.[4c,9] For example, Kumada et al. examined a Ni-catalyzed coupling of unactivated aryl phosphates with aryl Grignard reagents.[9c,10] More recently, Miller investigated a cross-coupling of an aryl Grignard reagent with in situ-derived enol phosphates using $PdCl_2(PPh_3)_2$ as catalyst.[9e] Iron catalysis proved also to be particularly efficient for the coupling of Grignard reagents with terminal dienol and trienol phosphates as reported by Cahiez et al.[11] Furthermore, previous reports have described that $NiBr_2$ can promote cross-coupling of enol phosphates with silylmethylmagnesium reagents without ligands.[7c,d]

From the point of view of experimental ease, the development of a palladium ligandless system for promoting Kumada−Corriu couplings would be of high interest. In this paper, we demon-

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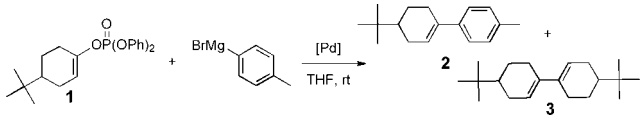
TABLE 1. Optimization Studies in the Kumada−Corriu Coupling of the *O*-Cyclohexenyl Phosphate 1[a]



entry	[Pd] (mol %)	[**1**] (M)	time (h)	**2** (%)[b]	**3** (%)[b]
1	$Pd(OAc)_2$ (5)	0.2	24	41	−[c]
2	$Pd(dba)_2$ (5)	0.2	3	80	4
3	$PdCl_2$(COD) (5)	0.2	3	91	3
4[d]	$PdCl_2$(COD) (5)	0.2	3	84	2
5	$PdCl_2$ (5)	0.2	3	74	2
6[d]	$PdCl_2$ (5)	0.2	4	83	−[c]
7	$PdCl_2$(COD) (2)	0.2	7	56	−[c]
8	$PdCl_2$(COD) (1)	0.2	7	46	2
9[e]	$PdCl_2$(COD) (2)	0.2	24	51	2
10[e,f]	$PdCl_2$(COD) (2)	0.3	6	82	2
11[f]	$PdCl_2$ (2)	0.3	3	85	−[c]
12[f,g]	$PdCl_2$ (2)	0.3	24	82	−[c]

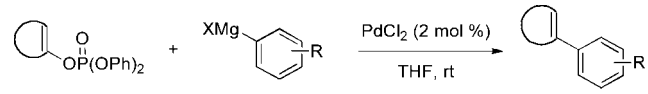
[a] Reaction conditions: **1** (0.50 mmol), *p*-tolyl magnesium bromide 1 M in THF (1.5 equiv, 0.75 mmol) added slowly over 2 h, catalyst (1.0−5.0 mol %), THF (V_{tot} = 2.75 mL), in sealed sample vials. [b] Isolated yield after column chromatrography. All reactions went to completion as determined by ^{1}H NMR. [c] **3** was not isolated (<1%). [d] The phosphate was diluted in toluene so as to obtain a mixture of THF/toluene (0.75:1, 1.75 mL). [e] The reaction was conducted at 40 °C. [f] The reaction was conducted with V_{tot} = 1.75 mL of THF. [g] The reaction was carried out with the direct addition of *o*-tolyl magnesium chloride.

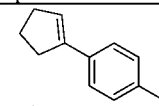
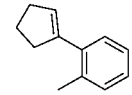
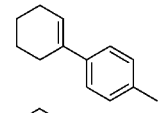
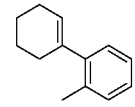
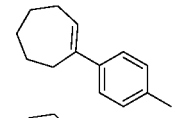
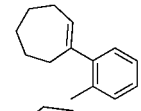
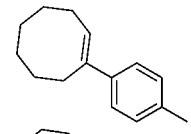
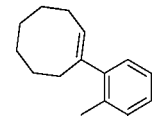
strate the use of $PdCl_2$ as a simple catalyst precursor without the requirement of phosphine ligands for the room temperature Kumada−Corriu cross-coupling of unactivated alkenyl phosphates. These conditions provide straightforward access to numerous 1,1-disubstituted alkenes in good yields.

An initial study was carried out on the cross-coupling reaction of the unactivated vinyl phosphate **1** with *p*-tolyl magnesium bromide testing a variety of reaction conditions (Table 1). The use of $PdCl_2$(COD) at room temperature in THF provided a satisfactory 91% isolated yield of the coupling product **2** (entry 3) and only 3% of the diene **3**, the formation of which was previously reported by Lipschutz.[12] To avoid the generation of the homocoupling byproduct **3**, the THF solution of the organomagnesium reagent was slowly added over a period of 2 h with a syringe pump. The efficiency of $PdCl_2$(COD) as a simple catalyst precursor is surprising considering the requirement of electron-rich diphosphines in the Pd-catalyzed Kumada−Corriu coupling of vinyl tosylates with arylmagnesium halides promoted by JosiPhos ligands.[5b] Both $Pd(dba)_2$ (entry 2) and even the less expensive catalyst $PdCl_2$ (entry 5) proved effective in this coupling leading to an 80% and 74% yield of **2**, respectively, whereas $Pd(OAc)_2$ (entry 1) proved less efficient. Adding toluene to the media revealed only a slight improvement in the yield with $PdCl_2$ as catalyst, whereas the opposite effect was noted for $PdCl_2$(COD) (entries 4 and 6).[13] However, by increasing the reagent concentrations from 0.2 to 0.3 M and lowering the catalyst loading from 5 to 2 mol %, $PdCl_2$ remained an effective catalyst for this reaction in contrast to $PdCl_2$(COD), furnishing **2** in an 85% yield (entry 11) with only traces of the dimer byproduct **3** (<1%).

In the case of the coupling of **1** with the sterically more encumbered Grignard reagent, *o*-tolyl magnesium chloride, a satisfactory 82% yield of the Kumada−Corriu product could also be secured with only 2 mol % of $PdCl_2$ (entry 12). Notably, *o*-tolyl magnesium chloride could be rapidly added without formation of the dimer product **3**.

TABLE 2. Kumada−Corriu Couplings of Cycloalkenyl Phosphates[a]



entry	R[b]	product	time (h)	yield (%)
1	*p*-Me		6	52
2	*o*-Me		24	72
3	*p*-Me		7	79
4	*o*-Me		7	79
5	*p*-Me		24	76
6	*o*-Me		16	68
7	*p*-Me		4	73
8	*o*-Me		18	26

[a] Reaction conditions: phosphate (0.50 mmol), Grignard reagent 1 M in THF (1.5 equiv, 0.75 mmol), $PdCl_2$ (2.0 mol %), THF (V_{tot} = 1.75 mL), rt. Isolated yield after column chromatrography. [b] The *p*-tolyl Grignard reagent was added over a period of 2 h with a syringe pump, whereas the *o*-tolyl reagent was added directly.

With this catalytic system in hand, we then examined the scope of the Kumada−Corriu coupling using a variety of alkenyl phosphates. The alkenyl phosphates were obtained by proton abstraction of the corresponding ketones with LiHMDS in THF at −78 °C followed by the addition of *o*,*o*-diphenyl phosphoryl chloride.[5a,8b]

As depicted in Table 2, several cycloalkenyl phosphates underwent successful coupling in moderate to good yields in the presence of the aryl Grignard reagents. The coupling with the more hindered *o*-tolyl magnesium chloride generally required longer reaction times (entries 2, 4, and 8). In all reactions, no vinyl phosphate homocoupling product was detected.

These ligandless conditions proved also applicable to the Kumada−Corriu coupling of alkyl- and arylvinyl phosphates. As illustrated in Table 3, vinyl phosphates possessing a secondary or tertiary C1-alkyl substituent were sufficiently reactive

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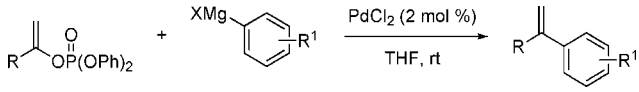
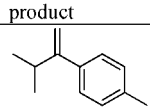
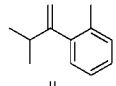
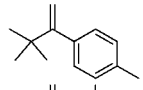
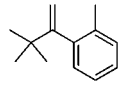
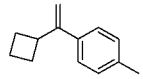
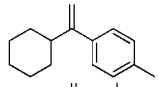
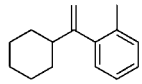
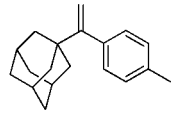
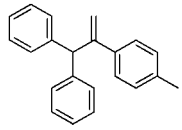
(13) Banno, T.; Hayakawa, Y.; Umeno, M. *J. Organomet. Chem.* **2002**, *653*, 288.

TABLE 3. Kumada−Corriu Couplings of Alkylvinyl Phosphates[a]



entry	R1[b]	product	time (h)	yield (%)
1	*p*-Me		6	64
2	*o*-Me		3	94
3	*p*-Me		3	50
4	*o*-Me		15	30
5	*p*-Me		6	46
6	*p*-Me		24	71
7	*o*-Me		24	70
8	*p*-Me		3	46
9	*p*-Me		7	79

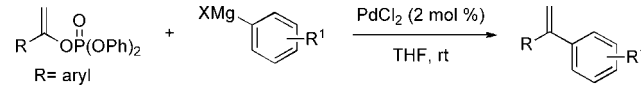
[a] Reaction conditions: phosphate (0.50 mmol), Grignard reagent 1 M in THF (1.5 equiv, 0.75 mmol), $PdCl_2$ (2.0 mol %), THF (V_{tot} = 1.75 mL), rt. Isolated yield after column chromatrography. [b] The *p*-tolyl Grignard reagent was added over 2 h with a syringe pump, whereas the *o*-tolyl reagent was added directly.

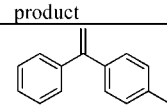
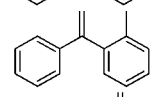
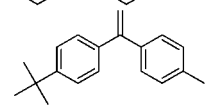
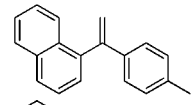
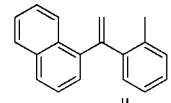
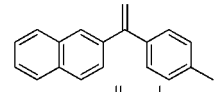
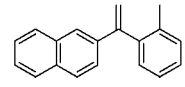
with the *o*-tolyl or *p*-tolyl magnesium reagents under these catalytic conditions producing the Kumada−Corriu product in moderate to good yields.

The results for the Kumada−Corriu coupling of C1-aryl-substituted vinyl phosphates under ligandless conditions are depicted in Table 4. Again, this simple coupling procedure proved to be useful with the four alkenyl phosphates tested providing coupling yields in the range of 44−74% with the *o*-tolyl and *p*-tolyl Grignard reagents. With the exception of entry 3, no vinyl phosphate homocoupling product was detected for these examples. We also briefly studied the Kumada−Corriu coupling of a (*Z*)-alkenyl phosphate bearing the reactive function in a terminal position to study the possible stereoselectivity of this protocol. The coupling of (*Z*)-butadienyl diethyl phosphate with *p*-tolyl magnesium bromide was not very productive, and from the ^{1}H NMR spectrum of the crude reaction mixture, both the *cis*- and *trans*-diene products could be detected. Hence, further work is required to optimize these reaction conditions.

Compared to the reactivity of the alkenyl tosylates, which were reported to require an electron-rich diphosphine ligand for promoting the Pd-catalyzed coupling with Grignard reagents, it is surprising that these ligandless conditions are effective for performing similar transformations with the vinyl phosphates.[5b]

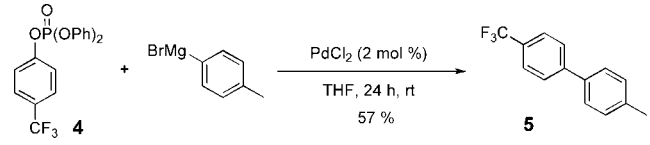
TABLE 4. Kumada−Corriu Couplings of Arylvinyl Phosphates[a]



entry	R1[b]	product	time (h)	yield (%)
1	*p*-Me		4	54
2	*o*-Me		8	74[c]
3	*p*-Me		4	52[d]
4	*p*-Me		6	44
5	*o*-Me		22	66
6	*p*-Me		24	46
7	*o*-Me		24	67

[a] Reaction conditions: phosphate (0.50 mmol), Grignard reagent 1 M in THF (1.5 equiv, 0.75 mmol), $PdCl_2$ (2.0 mol %), THF (V_{tot} = 1.75 mL), rt. Isolated yield after column chromatrography. [b] The *p*-tolyl Grignard reagent was added over 2 h with a syringe pump, whereas the *o*-tolyl reagent was added directly. [c] Yield determined by ^{1}H NMR of a mixture of the desired product and the Grignard homocoupling byproduct (1:0.25). [d] Yield determined by ^{1}H NMR of mixture of the desired product, the vinyl phosphate homocoupling byproduct and the Grignard homocoupling byproduct (8.7:1:0.3).

SCHEME 1. The Kumada−Corriu Coupling of the Arylphosphate 4 with *p*-Tolyl Magnesium Bromide



In an earlier report, Sekiya and Ishikawa suggested that Pd^{II}-salts in the presence of aryl magnesium halides form reactive nanopalladium particles.[14] Whether or not such nanopalladium particles are the reactive species under these conditions is currently under investigation.

Finally, in order to explore the scope of this catalytic protocol, we examined two aryl phosphates in their coupling with *p*-tolyl magnesium bromide. Whereas the more electron-rich diethyl 4-methoxyphenyl phosphate proved unreactive, diphenyl 4-(trifluoromethyl)phenyl phosphate **4** displayed higher reactivity and could be coupled furnishing the biaryl system **5** in a good 57% isolated yield after a reaction time of 24 h at room temperature (Scheme 1).

In conclusion, we have successfully developed a ligandless room temperature protocol for the Pd-catalyzed Kumada−Corriu coupling of unactivated C1-alkenyl phosphates with aryl magnesium

(14) Sekiya, A.; Ishikawa, N. *J. Organomet. Chem.* **1977**, *125*, 281.

reagents. These reactions were catalyzed by the simplest palladium salt, $PdCl_2$, at room temperature without the necessity of phosphine ligands. By avoiding expensive ligands and thermal energy, this work contributes to the challenge of developing economical protocols for the creation of carbon−carbon bonds. Further investigations are ongoing in an attempt to improve these coupling conditions with other aromatic phosphates.

Experimental Section

1-(4-*tert*-Butylcyclohex-1-enyl)-4-methylbenzene (2):[5b] General Procedure for the Kumada−Corriu Coupling of Vinyl Phosphates with *p*-Tolyl Magnesium Bromide. 4-*tert*-Butylcyclohex-1-enyl diphenyl phosphate (193 mg, 0.50 mmol) and $PdCl_2$ (1.8 mg, 0.01 mmol) were dissolved in THF (1 mL). The *p*-tolyl magnesium bromide (0.75 mL of a 1.0 M solution in THF, 1.5 equiv) was added slowly over 2 h at room temperature. The sample vial was then fitted with a Teflon sealed screwcap and removed from the glovebox. After an additional 3 h of stirring, the reaction mixture was quenched with methanol (0.5 mL), concentrated in vacuo, and purified by flash chromatography on silica gel with pentane as the eluant. This afforded 97.1 mg of the title compound (85% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.30 (d, $J = 8.0$ Hz, 2H), 7.13 (d, $J = 8.0$ Hz, 2H), 6.12−6.10 (m, 1H), 2.56−2.50 (m, 2H), 2.47−2.37 (m, 1H), 2.35 (s, 3H), 2.30−2.22 (m, 2H), 1.43−1.27 (m, 2H), 0.94 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 139.5, 136.3, 136.2, 129.6 (2C), 124.9 (2C), 124.2, 44.0, 32.4, 29.0, 27.6, 27.4 (3C), 24.6, 21.2. GCMS $C_{17}H_{24}$ [M] calcd 228, found 228. Spectroscopic data were in accordance with those reported in the literature.

1-(4-*tert*-Butylcyclohex-1-enyl)-2-methylbenzene (Table 1, entry 12):[15] General Procedure for the Kumada−Corriu Coupling of Vinyl Phosphates with *o*-Tolyl Magnesium Chloride. 4-*tert*-Butylcyclohex-1-enyl diphenyl phosphate (193 mg, 0.50 mmol) and $PdCl_2$ (1.8 mg, 0.01 mmol) were dissolved in THF (1 mL). *o*-Tolyl magnesium chloride (0.75 mL of a 1.0 M solution in THF, 1.5 equiv) was added at room temperature. The sample vial was then fitted with a Teflon sealed screwcap and removed from the glovebox. After 24 h of stirring, the reaction mixture was quenched with methanol (0.5 mL), concentrated in vacuo, and purified by flash chromatography on silica gel with 10% CH_2Cl_2 in pentane as the eluant. This afforded 94.2 mg of the title compound (82% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20−7.08 (m, 4H), 5.61−5.58 (m, 1H), 2.40−2.19 (m, 3H), 2.32 (s, 3H), 2.03−1.94 (m, 2H), 1.47−1.31 (m, 2H), 0.96 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.5, 138.8, 135.2, 130.1, 128.4, 126.5, 126.0, 125.6, 44.1, 32.4, 31.8, 27.4 (3C), 27.3, 24.7, 20.0. GCMS $C_{17}H_{24}$ [M] calcd 228, found 228. Spectroscopic data were in accordance with those reported in the literature.

4-Methyl-4′-(trifluoromethyl)biphenyl (5).[5a] Diphenyl 4-(trifluoromethyl)phenyl phosphate (197 mg, 0.50 mmol) and $PdCl_2$ (1.8 mg, 0.01 mmol) were dissolved in THF (1 mL). *p*-Tolyl magnesium bromide (0.75 mL of a 1.0 M solution in THF, 1.5 equiv) was added slowly over 2 h at room temperature. The sample vial was then fitted with a Teflon sealed screwcap and removed from the glovebox. After an additional 22 h of stirring, the reaction mixture was quenched with methanol (0.5 mL), concentrated in vacuo, and purified by flash chromatography on silica gel with pentane as the eluant. This afforded 67.6 mg of the title compound (57% yield) as a colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.68 (m, 4H), 7.51 (d, $J = 8.0$ Hz, 2H), 7.27 (d, $J = 8.0$ Hz, 2H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.8, 138.3, 137.0, 129.8 (2C), 129.2 (q, $J = 32.3$ Hz), 127.3 (2C), 127.2 (2C), 125.8 (q, $J = 3.8$ Hz, 2C), 124.5 (q, $J = 271.7$ Hz), 21.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ (ppm) −62.75. GCMS $C_{14}H_{11}F_3$ [M] calcd 236, found 236. Mp 121−122 °C. Spectroscopic data were in accordance with those reported in the literature.

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Supporting Information Available: Experimental details for all compounds including copies of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.