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Organic LETTERS

Letter

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Stereoretentive Pd-Catalyzed Kumada–Corriu Couplings of Alkenyl Halides at Room Temperature

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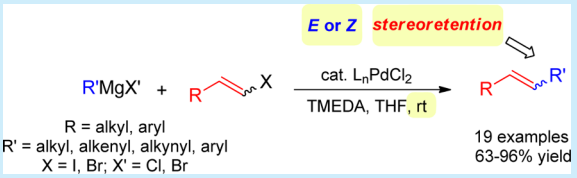
Supporting Information

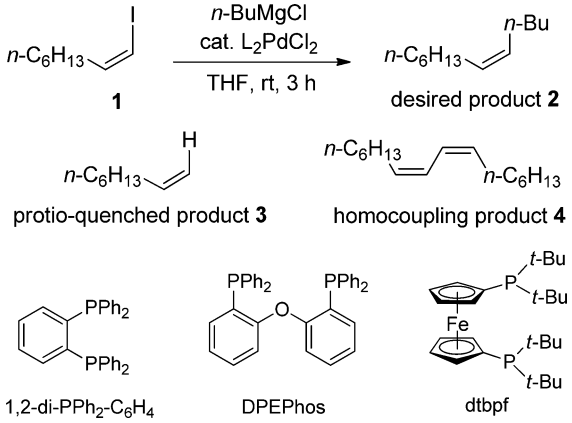
ABSTRACT: Stereoselective palladium-catalyzed Kumada–Corriu reactions of functionalized alkenyl halides and a variety of Grignard reagents, *including those bearing β-hydrogen atoms and sensitive functional groups*, can be carried out at room temperature using a new combination of reagents.



Kumada–Corriu cross-couplings are among the earliest transition-metal-catalyzed reactions introduced as a means of forming carbon–carbon bonds.[1] Initially reported as nickel-catalyzed processes between Grignard reagents and aryl or alkenyl halides, subsequent developments in palladium-catalyzed couplings have led to variations based on this less toxic and more functional group tolerant process, as first reported by Murahashi.[2] While these Pd-catalyzed couplings are highly effective for biaryl formation, those involving alkenyl halides together with alkyl Grignard reagents bearing *β*-hydrogens are notoriously problematic, owing to the considerable potential for competing *β*-hydride elimination.[3] Although great progress has been made toward minimizing this undesired pathway through careful tuning of phosphine-based ligands,[4,5] room for further optimization and improvements remain, especially regarding functionalized Grignard reagents.[6] We now describe Pd-catalyzed Kumada–Corriu cross-couplings with *alkenyl* halides that take place relatively rapidly under ambient conditions and that minimize side-product formation. Notably, mild reaction conditions allow for the synthesis of alkenes bearing sensitive functionality, such as cyano and ester groups.[7]

Early work by Kumada revealed that careful selection of the phosphine ligand could prove highly effective at controlling the pathways that can lead to undesired byproducts.[8] Indeed, in the absence of a coordinating ligand or additive, reactions catalyzed by $PdCl_2$ strongly favor *β*-hydride elimination to ultimately afford product **3** (Table 1, entry 1). The addition of bidentate amine ligand TMEDA dramatically increased the relative amounts of the desired cross-coupled product **2** (compare entries 1, 2, 6, and 7). By replacing monodentate-phosphine ligands (entries 4, 5) with bidentate analogs derived from diphenyl ether or ferrocene, the relative yield of cross-coupled product **2** was increased significantly (entries 6, 10). Bidentate 1,2-bis(diphenylphosphino)benzene (entry 8) was ineffective at catalyzing the desired cross-coupling reaction. Eventually it was found that a mixed catalyst system involving both TMEDA and the sterically demanding bidentate phosphine ligands DPEPhos or dtbpf led to efficient formation of the desired product (entries 7, 11).[9] We hypothesized that the effects might be additive, although not necessarily of equal impact, since the bidentate phosphine ligand likely coordinates strongly to the palladium, while the amine ligand should show a preference for

Table 1. Screening of Representative Catalyst Systems[a]



entry	ligand (L)	2	3	4[b]
1	none	3	85	12
2	TMEDA (1.1 equiv)	83	8	9
3	TMEDA (0.1 equiv)	11	76	13
4	PPh_3	16	82	2
5	P(*o*-Tol)$_3$	10	90	0
6	DPEPhos	65	25	10
7	**DPEPhos/TMEDA**	**90**	**8**	**2**
8	1,2-di-PPh_2-C_6H_4	0	79	21
9	1,2-di-PPh_2-C_6H_4/TMEDA	50	50	0
10	dtbpf	91	7	2
11	**dtbpf/TMEDA**	**94**	**6**	**0**

[a]Conditions: 0.3 mmol of alkenyl halide substrate (0.25 M in THF). Palladium catalyst (2 mol %), Grignard reagent (1.75 equiv), TMEDA (1.85 equiv). [b]GC ratio.

Received: May 28, 2014
Published: August 7, 2014

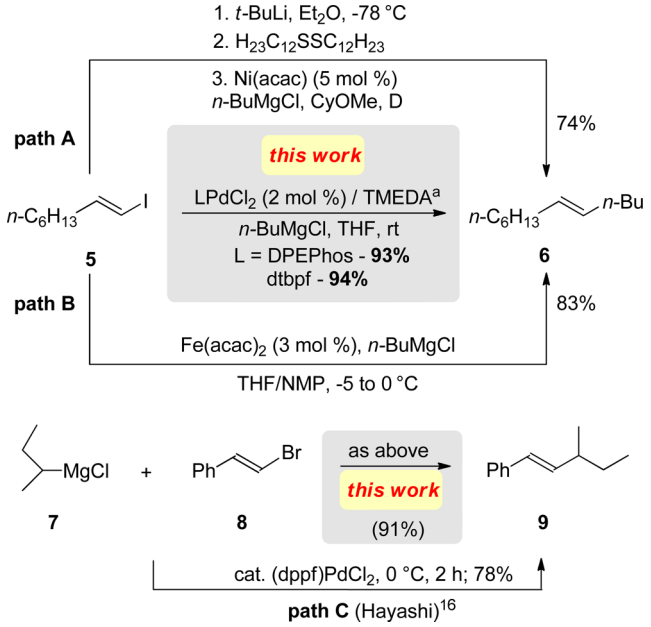
 © 2014 American Chemical Society dx.doi.org/10.1021/ol501535w | *Org. Lett.* 2014, 16, 4066–4069

coordination to magnesium.[10] Support for this hypothesis can be found in the significant erosion in selectivity observed when the diamine ligand was reduced to less than 1 equiv relative to the Grignard reagent (entry 2 vs 3).

The vastly improved selectivity upon addition of the dtbpf ligand to palladium was attributed to the bulky di-*tert*-butylphosphine residues appended to the ferrocene rings that may distort the expected square planar geometry of the transition state in a manner similar to that proposed by Espinet.[11] In this way the group derived from the Grignard is forced into closer proximity to the alkenyl moiety, and a more rapid reductive elimination ensues favoring the cross-coupled product. Moreover, this ligand seems well suited to minimize homodimerization of the alkenyl halide, presumably by generating a steric environment around palladium that effectively discourages ligand exchange between palladium centers. The role of TMEDA, that likely coordinates to the Grignard as described by Nakamura,[9] may hasten transmetalation, as is commonly seen with organozinc reagents.[12] The combination of these two ligands leads to the desired cross-couplings in less than 3 h (0.25 M in THF) at room temperature in most cases with excellent selectivity.[13] Additional screening of the reaction conditions for the cross-coupling of β-bromostyrene with PhMgBr, along with the effect of different amines (e,g., TEEDA), confirmed our initial findings (see Supporting Information).

This methodology compares favorably with the procedures and results reported by Oshima[14] (Scheme 1, **path A**; CyOMe = cyclopentyl methyl ether) and Cahiez[15] (Scheme 1, **path B**).

Scheme 1. Comparison to Literature Work[a]

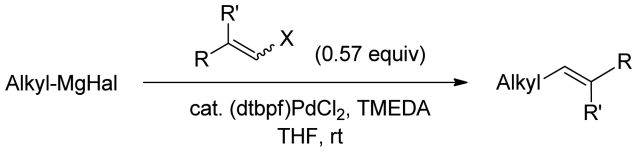


[a]Conditions: palladium catalyst (2 mol %), Grignard reagent (1.75 equiv), TMEDA (1.85 equiv).

Interestingly, in this case once again both DPEPhos and dtbpf ligands afforded desired product **6** with very similar conversions and isolated yields. Likewise, direct comparison with the classical work of Hayashi,[16] e.g., conversion of Grignard **7** and alkenyl halide **8** to product **9** (**path C**), is again indicative of the positive effect of both the change in ligand, as well as the use of TMEDA.

With this new catalyst system in place, an investigation of the scope and limitations of the reaction of alkyl-Grignard reagents was undertaken (Table 2). Both primary and secondary sp^3-magnesium reagents were shown to be excellent cross-coupling partners. The acetal in Grignard reagent **15** (entry 4) did not impede coupling. The example involving phenethyl Grignard **17** (entry 5) is noteworthy in that although the β-hydrogens present are also benzylic, β-hydride elimination was not a major pathway. Cross-coupling of alkenyl halide with a secondary alkyl Grignard reagent **20** (entry 6) afforded the trisubstituted olefinic product **22** in good yield. Attempts to affect the same reaction using *t*-BuMgCl, however, led to only trace amounts of the desired adduct, with the corresponding reduced styrene being formed efficiently (ca. 97%). Use of the more hindered α-bromostyrene, together with a primary alkyl Grignard reagent, increased the β-hydride elimination pathway (ca. 30%). Tetrahydropyranyl (THP; entries 1 and 2) as well as benzyl ethers (entry 5) present in the alkenyl coupling partner are well tolerated and afforded the desired products in good to excellent yields.

Table 2. Pd-Catalyzed Couplings of Alkenyl Halides with sp^3-Grignard Reagents[a]



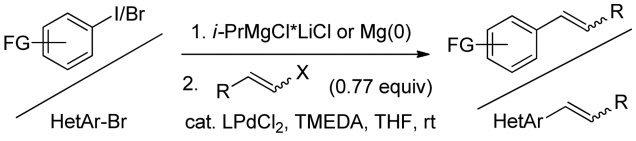
entry	Grignard	alkenyl halide	product[b]
1	MeMgBr **10**	THPO, I **11**	THPO **12**, 93%
2	MgCl **13**	THPO, I **11**	THPO **14**, 95%
3	MgCl **13**	n-C6H13, I **1**	n-C6H13 **2**, 94%
4	O, O, MgBr **15**	n-C6H13, I **1**	n-C6H13, O, O **16**, 96%
5	Ph, MgBr **17**	BnO, 3, Br **18**	BnO, 3, Ph **19**, 85%
6	MgCl **20**	Ph, Br **21**	Ph **22**, 89%

[a]Conditions: 0.3 mmol of alkenyl halide (0.25 M in THF), Pd catalyst (2 mol %), Grignard reagent (1.75 equiv), TMEDA (1.85 equiv), 3 h. [b]Isolated yield.

Aromatic and heteroaromatic Grignard reagents were also investigated (Table 3). Cross-coupling of room temperature

dx.doi.org/10.1021/ol501535w | Org. Lett. 2014, 16, 4066−4069

Table 3. Pd-Catalyzed Couplings of Alkenyl Halides with Aryl- and Heteroaryl Grignard Reagents[a]



entry	Grignard	alkenyl halide	product[b]
1	Ph-MgCl	*n*-C_6H_{13}, I	*n*-C_6H_{13}, Ph
	23	**1**	**24**, 96%[c]
2	MgBr, O, O	OTIPS$_2$, Br	OTIPS$_2$, O, O
	25	**26**	**27**, 92%[c]
3	S, MgBr	OBn$_3$, Br	S, OBn$_3$
	28	**29**	**30**, 63%[c,d]
4	MgBr, N, TIPS	*n*-C_6H_{13}, I	*n*-C_6H_{13}, N, TIPS
	31	**32**	**33**, 84%[c,d]
5	Br, MgCl*LiCl	Br, Ph	Br, Ph
	34	**35**	**36**, 85%
6	Br, MgCl*LiCl	Ph, Br	Br, Ph
	34	**37**	**38**, 81%
7	CN, F, MgCl*LiCl	Br, Ph	CN, F, Ph
	39	**35**	**40**, 87%
8	MgCl*LiCl, EtO_2C	Br, Ph	Ph, EtO_2C
	41	**35**	**42**, 85%
9	MgBr	Cl, N, Ph	N, Ph
	43	E/Z - 1/1 **44**	E/Z - 1/1 **45**, 77%[e]

[a]Conditions: 0.3 mmol of alkenyl halide, DPEPhosPdCl$_2$ (5 mol %), Grignard reagent (1.3 equiv), TMEDA (1.5 equiv), 8 h. [b]Isolated yield. [c](dtbpf)PdCl$_2$ (2 mol %) was used. [d]Reaction time is 16 h. [e]Run for 4 h at 60 °C.

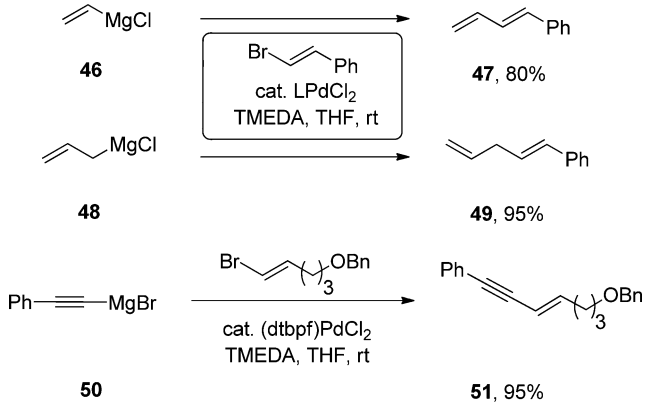
stable phenylmagnesium chloride **23** (entry 1) and dimethoxyphenylmagnesium bromide **25** (entry 2) led to the desired products in high yields. Thiophene-derived Grignard reagent **28** gave the desired product in modest yield, as expected for the more slowly reacting *Z*-alkenyl bromides (entry 3).[16] The TIPS protected pyrrole **31** served as an excellent partner leading to an efficient coupling with the *E*-trisubstituted vinyl iodide **32** (entry 4).

Under these standard conditions ((dtbpf)PdCl$_2$/TMEDA), reactions of Grignard reagents bearing sensitive functionalities[17] were complicated with unidentified byproducts and, thus, required tedious purification. Fortunately, these competing pathways could be averted using our modified conditions (DPEPhosPdCl$_2$/TMEDA). Moreover, with 5 mol % of DPEPhos as ligand, only 1.3 equiv of the corresponding Grignard reagent were needed to achieve full conversion (entries 5−8). Grignard reagents such as *ortho*-bromophenylmagnesium chloride (**34**) are known to be unstable at room temperature,[17,18] serving as precursors to benzyne via elimination of MgBr$_2$. Under our conditions, however, this reagent was successfully cross-coupled at room temperature with both *E*- and *Z*-alkenyl halides (**35** and **37**) affording the corresponding alkenes with complete retention of stereochemistry and high yields.

Interestingly, both cyano- (entry 7) and ester functions (entry 8) are fully tolerated,[7] while these groups are normally incompatible with the presence of Grignard reagents at room temperature. We did not observe any byproducts that can be explained by nucleophilic attack of these aryl Grignard reagents (**39**, **41**) to the cyano or ester residues, suggesting that ligation of magnesium by TMEDA may afford additional stabilization of functionalized Grignards, thereby reducing their nucleophilicity. At 60 °C, an alkenyl chloride could be successfully introduced using this cross-coupling reaction under our standard conditions (entry 9).

The prospects for use of vinyl-, allyl-, and alkynyl Grignard reagents were also briefly ascertained (Scheme 2). Both conjugated

Scheme 2. Synthesis of Dienes and Enynes[a]



[a]Conditions: Palladium catalyst (2−5 mol %), Grignard reagent (1.3 equiv), TMEDA (1.5 equiv), 3 h.

47 and skipped dienes **49** were prepared in good yields, starting from commercially available Grignard reagents. Here again, we observed greater efficiency employing DPEPhosPdCl$_2$. Likewise, an acetylenic Grignard reagent **50** led to the desired enyne **51** in high isolated yield.

In summary, the sterically hindered bidentate diphosphine ligands dtbpf and DPEPhos, in the presence of TMEDA, form an effective combination leading to efficient Pd-catalyzed Kumada−Corriu coupling reactions of alkenyl halides in THF at room temperature. In the case of cross-coupling of the Grignard reagents

dx.doi.org/10.1021/ol501535w | Org. Lett. 2014, 16, 4066−4069

bearing reactive functionalities, DPEPhos/TMEDA proved to be a better system leading to the desired products in higher yields. Importantly, electrophilic functionality within the Grignard reagent can be tolerated. Both in situ derived catalyst systems minimize β-hydride elimination commonly associated with the use of Grignard reagents for such reactions, thereby affording cross-coupled products usually in high yields.

■ ASSOCIATED CONTENT

Supporting Information

Contains experimental procedures and copies of NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from the NIH (GM 86485). We also thank Johnson Matthey for providing (dtbpf) $PdCl_2$ and Boulder Scientific for Cp_2ZrCl_2.

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