Palladium-Phenylpyrazolylphosphine-Catalyzed Cross-Coupling of Alkenyl Pivalates

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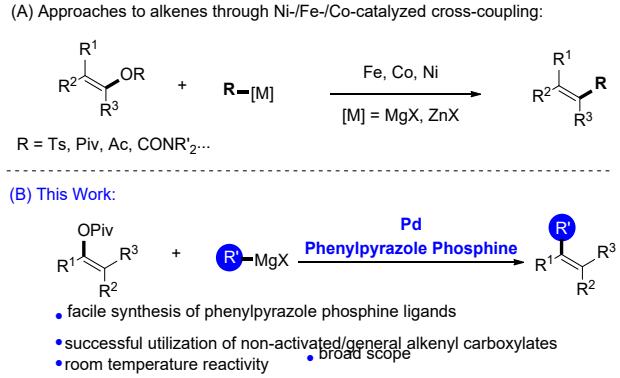
Abstract: Palladium-catalyzed cross-coupling reactions are indispensable tools for C−C bond formation, and new catalyst development remains a powerful driving force in this field. In this study, a new type of easily accessible phenylpyrazole phosphine ligand is developed. The catalyst generated from $Pd(OAc)_2$ and **PP-Phos** (**L15**) is highly effective in the palladium-catalyzed cross-coupling of alkenyl pivalates with organomagnesium reagents. The reaction accommodates a broad scope of alkenyl carboxylates under mild conditions, providing an alternative but practical way to the synthesis of multi-substituted alkenes in value.

Transition-metal-catalyzed cross-coupling reactions represent one of the most efficient approaches for C−C bond construction.[1] Substantial growth in this area has taken place during the last decades, with a wide range of valuable investigations emerging.[2] Classical coupling partners, such as aryl halides, have been widely employed in the synthetic practice of academic and industrial communities.[3] Recent advancements were spotted on expanding the scope of electrophiles beyond aryl halides from easily obtainable feedstocks.[4] The exploration of new catalytic systems to achieve the usage of novel substrates has also received considerable attention.[5]

Alkenyl electrophiles are useful building blocks complementary to aryl coupling partners derived from phenolic compounds. Alkenyl electrophiles are readily prepared from the corresponding carbonyl compounds, and they are considered promising substrates for introducing alkenyl motifs into the skeleton.[6] Since alkenyl pivalates were found to be applicable in Ni-catalyzed cross-coupling reaction,[7] O-based alkenyl electrophiles, including alkenyl sulfonates, carboxylates, and carbamates, have captured significant interest.[8] They have recognized advantages compared to alkenyl halides: (1) multi-substituted alkenyl halides are not broadly available, and their synthesis requires harsh conditions;[9] (2) O-based alkenyl electrophiles are easily synthesized from the corresponding carbonyl compounds with a variety of substitution patterns. Alkenyl sulfonates, such as alkenyl triflates, are important complements to alkenyl halides; however, the triflyl reagents are relatively expensive. Alkenyl triflates are less stable upon storage and easily subjected to hydrolysis in the reaction. Alkenyl tosylates are more stable during preparation and storage and are commonly used in catalysis.[10] Nevertheless, the higher molecular weight leaving group (OTs) renders the cross-coupling reactions less atom-efficient. Alkenyl carboxylates are considered promising coupling partners in future investigations due to their higher atom utilization. Among these alkenyl carboxylates, alkenyl pivalates possess attractive qualities and are thus selected as substrates in our study.

Despite the easy preparation of alkenyl electrophiles, their utilization could be challenging. Appropriate catalytic systems are required to convert alkenyl electrophiles into final products.[8] Catalysts of the first-row transition metals (iron, cobalt, and nickel) are favored in cross-coupling reactions mainly because of the smoother oxidation addition processes.[11] Shi and co-workers demonstrated the cross-coupling of aryl/alkenyl pivalates by nickel catalysis.[7] The scope of inexpensive metal-catalyzed coupling was further expanded by their followed Fe-catalyzed system.[11a] The advantages of Co-catalysis are also demonstrated.[11b, c] However, the first-row-transition-metal catalysis still suffers from certain limitations, for instance, the cross-coupling reactions of sterically hindered substrates were seldom reported. Yet, the advantages of Pd catalysis have been proven by practical findings in Pd-catalyzed reactions for demanding cross-coupling combinations.[12c, d] Related mechanistic studies also offer possible catalytic pathways.[12b, e, f]



Scheme 1. Cross-coupling of alkenyl electrophiles

Although notable findings showed a great achievement in cross-coupling by using alkenyl electrophiles,[10b, 12] sporadic

investigations focused on palladium-catalyzed cross-coupling of alkenyl carboxylate, especially non-activated alkenyl electrophiles. Considering the value of those structures,[13] new catalytic systems need to be explored to tackle the inert reactivities of these electrophiles. Herein, we report a palladium-catalyzed cross-coupling reaction of alkenyl pivalates with organomagnesium or organozinc reagents. A catalytic system based on a new type of phenylpyrazole phosphine ligand was established to achieve this transformation.

The design and synthesis of structurally tunable heterocyclic phosphines have become a common pursuit in palladium-catalyzed cross-coupling reactions since Beller and his co-workers reported the PAP-type ligands.[14] The use of heterocycle moieties as ligand skeletons has several obvious advantages: (1) Numerous established methods support the synthesis of heterocycles.[15] (2) The acidities[16] of the protons attaching to heterocycles allow further installation of substituents through direct deprotonation. Moreover, heterocycle-based phosphines are found to be efficient supporting ligands in various reactions,[17] such as Suzuki-Miyaura coupling, Buchwald-Hartwig amination, Heck reaction, and other functionalization.

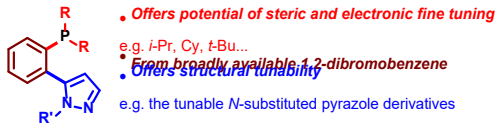
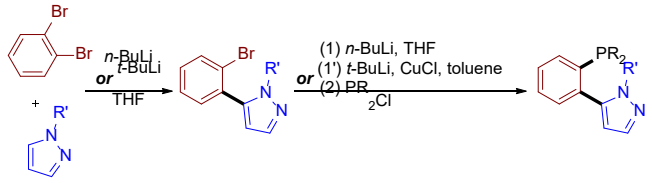


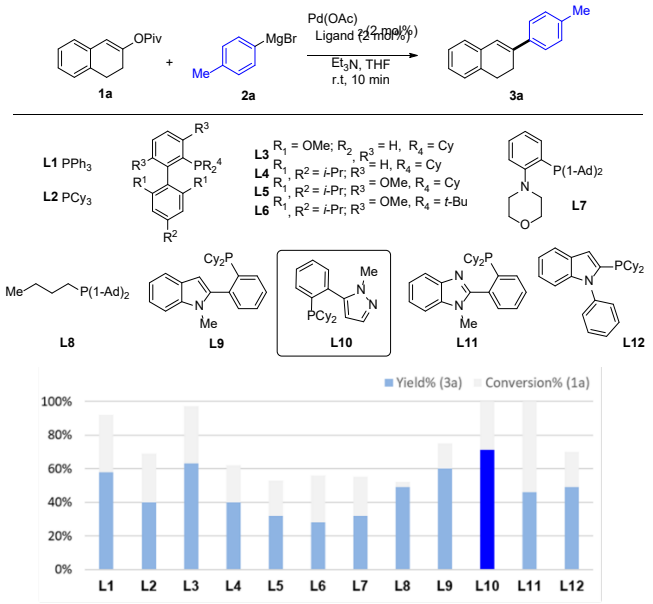
Figure 1. Proposed ligand design

In this study, the key consideration of the supporting ligand design is their high synthetic accessibility and modular modification: (1) the *ortho*-heterocyclic substituents are easily installed; (2) the ligand skeletons are easily tunable by different *N*-substituted pyrazole derivatives. Considering these advantages, a set of novel phosphine ligands based on phenylpyrazolyl scaffolds were synthesized and further investigated. This type of ligand embodies an easily accessible and main pyrazolyl skeleton with electronic bias, offering the possibility of stepwise, regiospecific, and unsymmetrical modification. This ligand backbone could be obtained by the deprotonation of *N*-substituted pyrazole (which can be accessed from the nucleophilic substitution at the *N*-position) by *n*-BuLi or *t*-BuLi, and reacting the intermediate by 1,2-dibromobenzene. With the *N*-substituted pyrazolyl precursor, the phenylpyrazolyl phosphines could be afforded by lithiation using *n*-BuLi or *t*-BuLi and CuCl, and subsequent trapping with $ClPR_2$ (Scheme 2).



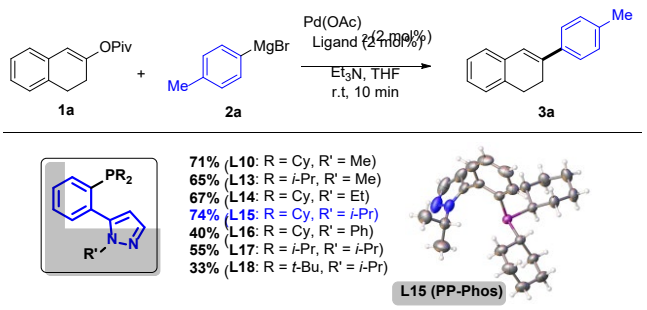
Scheme 2. Synthetic protocol for phenylpyrazole phosphine ligands

To probe the feasibility of the Kumada coupling of alkenyl pivalate, we commenced the ligand screening at room temperature in a short reaction time using alkenyl pivalate **1a** and *p*-tolylmagnesium bromide **2a** as the benchmarking substrates. The coupling product was detected when using monodentate ligands, PPh_3, and PCy_3 (Scheme 3, **L1** and **L2**). Buchwald-type ligands were also evaluated (Scheme 3, **L3**–**L6**). SPhos afforded the corresponding product with moderate yield, while the product yield decreased when more electron-rich and steric hindered ligands were employed, such as *t*-BuBrettPhos (Scheme 3, **L6**). CataCXium®A and CataCXium®PInCy bear different scaffolds but gave similarly low yields (Scheme 3, **L8**, and **L12**).



Scheme 3. Comparison of the reactivities of ligands. Reaction conditions: alkenyl pivalate **1a** (0.2 mmol), Grignard reagent **2a** (0.4 mmol), $Pd(OAc)_2$ (2 mol%), Ligand (2 mol%), Et_3N (0.05 mL), THF (totally around 1.0 mL), r.t., under N_2. Calibrated GC yields were reported using dodecane as an internal standard.

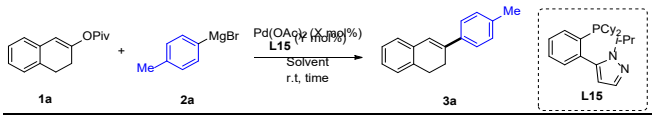
In our previous study, MorDalPhos showed its efficacy in inert C−O bond activation;[18] however, it offered the product with an unsatisfactory yield in this scenario (Scheme 3, **L7**). To our delight, the new phenylpyrazole-type phosphine ligand **L10** was found to be most effective in this transformation, affording the product a good yield compared with other heterocyclic based phosphine ligand such as CM-Phos[19] and PhMezole-Phos[20] (Scheme 3, **L9**–**L11**).



Scheme 4. Ligand derivation and effect on the model reaction. The structural model of **L15** is experimentally determined by X-ray crystallography.

As 5-phenylpyrazole was found to be a promising skeleton in this transformation, we set out to synthesize a type of new phosphines with different substituents and evaluate their catalytic efficiency in the cross-coupling reaction (Scheme 4). Since the reactivity of **L10** was superior to the commercially available ligands examined, its P-isopropyl version was synthesized (Scheme 4, **L13**). However, Pd/**L13** catalyst provided a lower reactivity, which indicated that $-PCy_2$ could be important to the ligand reactivity. We next focused on *N*-substitution modification in the pyrazole ring (Scheme 4, **L14**–**L16**). Moderate yields were obtained using **L14** (*N*-Et) and **L16** (*N*-Ph) as ligands. Yet Pd/**L15** (*N*-*i*Pr) catalyst provided a higher reactivity and offered the alkenyl product with a promising yield (Scheme 4, **L15**). P-isopropyl and P-*tert*-butyl versions of **L15** were also synthesized to study the steric effect of the phosphine moiety (Scheme 4, **L16** and **L17**). However, they failed to give a higher product yield. According to these results, the congested environment provided by the P-*tert*-butyl group was retarding the reaction, while the P-cyclohexyl group was the suitable substituent compared with the P-isopropyl group. A single crystal of **L15** was grown by liquid-liquid diffusion of hexane into a DCM solution, and was fully characterized by X-ray crystallographic analysis.[21]

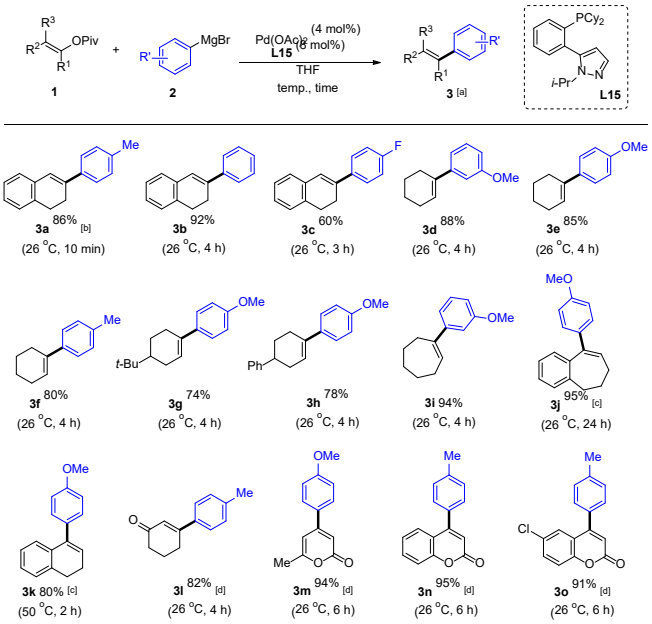
Table 1. Condition screening



Entry	$Pd(OAc)_2$/L15 (mol%)	Solvent	Time	Yield[a, b]
1[c]	2 / 2	THF	10 min	74% (69%[d])
2[e]	2 / 2	THF	10 min	90%
3	4 / 4	THF	10 min	90% (86%[d])
4	1 / 1	THF	10 min	65%
5	1 / 2	THF	10 min	76%
6	1 / 2	THF	1 h	84%
7	0.5 / 1	THF	1 h	83%
8	0.5 / 1	toluene/THF	1 h	77%
9	0.5 / 1	dioxane/THF	1 h	65%
10	0.5 / 1	CPME/THF	1 h	81%

[a] Reaction conditions: alkenyl pivalate **1a** (0.2 mmol), Grignard reagent **2a** (0.4 mmol), $Pd(OAc)_2$ (loading as indicated), **L15** (loading as indicated), solvent (totally around 1.0 mL) were stirred at room temperature under N_2. [b] Calibrated GC yields were reported using dodecane as an internal standard. [c] Et_3N (0.05 mL) was used for catalyst pre-generation. [d] Isolated yields. [e] Catalyst pre-generation without Et_3N.

Based on the ligand screening results, **L15** was selected further to optimize the reaction condition (Table 1). The addition of Et_3N in catalyst pre-generation was found to be unnecessary and excellent the yield was obtained in a short-time reaction (Table 1, entries 1 and 2). When the ligand ratio was increased from 1:1 to 1:2 under 1 mol% Pd catalyst loading, the product yield was improved from 65% to 76% (Table 1, entries 4 and 5). The catalyst loading down to 0.5 mol% Pd could also be achieved and provided a good yield (Table 1, entry 7). Other solvents for substrate dissolution were also investigated (Table 1, entries 8–10). Replacing THF with other solvents was not beneficial to this reaction, although the CPME/THF system gave an acceptable yield.

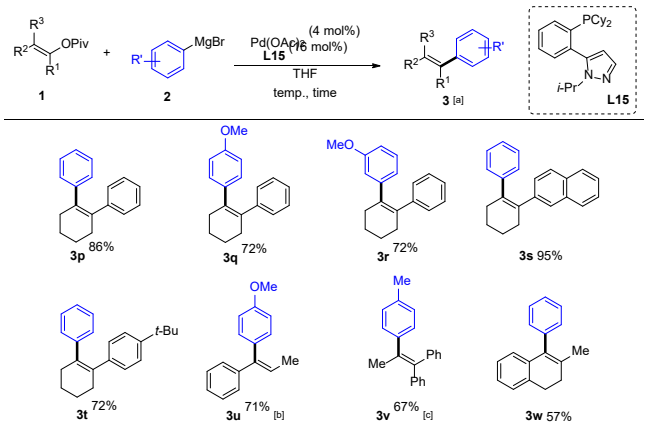


Scheme 5. Cross-coupling of non-activated/activated alkenyl pivalates with Grignard reagents. [a] $Pd(OAc)_2$ (4 mol%), **L15** (8 mol%), alkenyl pivalate (0.2 mmol), Grignard reagent (0.4 mmol). Isolated yields were reported. [b] Pd/L = 1:1. [c] Pd/L = 1:4. [d] Pd/L = 1:1, $ZnAr_2$ (0.4 mmol) was used.

Following the condition optimization, we set out to explore the scope. A wide range of non-activated alkenyl pivalates were first evaluated (Scheme 5, **3a**–**3i**). To accommodate substrates with different skeletons, a more general catalyst loading was used (4 mol% Pd). These alkenyl carboxylates with saturated alkyl substituents were seldom reported in Pd-catalyzed reactions due to their lower reactivities. However, under our catalytic condition, the corresponding products were obtained with excellent-to-good yields at room temperature. Alkenyl pivalate with benzene-fused skeletons may hinder the coupling process, yet the reactions also produced the coupling products at an elevated temperature or extended time (Scheme 5, **3j** and **3k**). In addition, activated alkenyl substrates were found to be feasible cross-coupling partners (Scheme 5, **3l**–**3o**). The cross-coupling of these activated substrates with organomagnesium reagents didn't give the products with satisfactory yields due to possible side-reactions when organomagnesium reagents served as nucleophiles. However, the reactions proceeded smoothly when Grignard reagents were replaced by milder organozinc reagents. Decreasing the metal-to-ligand ratio remarkably increases the yields regarding this reaction conditions. The selective arylation of the cyclic enone-type alkenyl acetate occurs in the presence of aryl halides, which may be because the cyclic enone-type alkenyl acetate can undergo the C−O activation via a more facile β-carboxyl elimination pathway (Scheme 5, **3o**).[12e]

The cross-coupling reactions toward sterically congested alkenes are considered more difficult to achieve through Pd-

catalysis, and examples were rarely reported in the first-row transition-metal-catalyzed coupling reactions.[11] Sterically hindered alkenyl pivalates were also tested under our reaction condition (Scheme 6). A type of diaryl-substituted alkenes were obtained with good yields (Scheme 6, **3p**–**3t**). Multi-substituted alkenes with different scaffolds were also synthesized (Scheme 6, **3u**–**3w**). In general, the cross-coupling of sterically hindered substrates was more challenging and required higher temperature to complete the reactions within acceptable reaction time. In some cases, the reduced metal-to-ligand ratio (Scheme 6, **3u**) as well as the elevated temperature (Scheme 6, **3v**) experimentally promoted the yields of products.



Scheme 6. Cross-coupling of sterically hindered alkenyl pivalates with Grignard reagents. [a] $Pd(OAc)_2$ (4 mol%), **L15** (16 mol%), alkenyl pivalate (0.2 mmol), Grignard reagent (0.4 mmol), 50 °C, 24 h, under N_2. Isolated yields were reported. [b] Pd/L = 1:2. [c] Condition: 110 °C, 24 h.

In conclusion, we have developed a type of novel phenylpyrazole phosphine ligand. The catalyst system comprising of $Pd(OAc)_2$ and the newly developed **PP-Phos** (**L15**) showed excellent efficiency toward this palladium-catalyzed cross-coupling of alkenyl pivalates with organomagnesium reagents. These reactions were carried out under mild reaction conditions and accommodated a broad scope, including activated, non-activated, and sterically hindered alkenyl carboxylates. In view of the simplicity of the ligand synthesis, as well as the easy modification of the ligand skeleton, we anticipate that further enhancements in the reactivity and versatility of this novel ligand type Pd-catalyzed cross-coupling reactions will be attainable.

Acknowledgements

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Keywords: palladium-catalyzed • cross-coupling • heterocyclic phosphine • alkenyl pivalate • alkene

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[21] CCDC 2055780 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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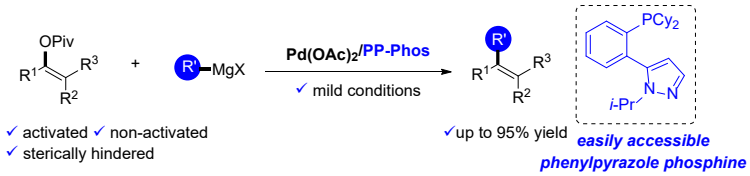

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