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Superior Effect of a π-Acceptor Ligand (Phosphine–Electron-Deficient Olefin Ligand) in the Negishi Coupling Involving Alkylzinc Reagents

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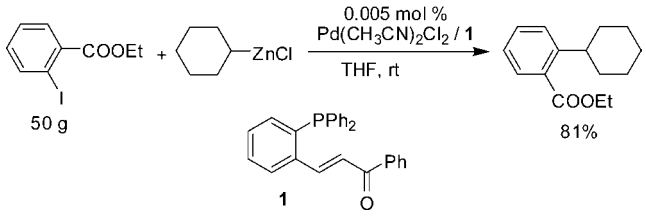
ABSTRACT



Palladium-catalyzed Negishi cross-coupling involving primary and secondary alkyls, even in the presence of β-H, can be achieved at ambient temperature using chelating ligands containing a phosphine and an electron-deficient olefin. The superior effects of the ligands were shown not only in the desired cross-coupling product yields but also in the fast reaction at mild conditions. This reaction has been also scaled up to 50 g in 0.005 mol % catalyst (20,000 TONs) at room temperature.

Since their discovery 3 decades ago, transition-metal-catalyzed cross-coupling reactions have been widely applied in the syntheses of biaryls and aralkyls via the substitution of aryl halides (ArX) by organometallic agents (Ar′M/RM).[1] The emergence of a large number of drug candidates containing biaryls in recent years speaks for the utility and impact of this powerful technology. It is generally considered a well-established fact that palladium-catalyzed cross-coupling reactions proceed via the following sequence of three elementary steps: (1) oxidative addition of a Pd(0) species to an aryl electrophile (ArX), (2) transmetallation of the resultant Pd(II) moiety with the nucleophile (RM), and (3) reductive elimination of the ArPd(II)R to afford the coupled product (Ar-R) with regeneration of the Pd(0) catalyst.[2] Facilitating oxidative addition has been a focal point and has proven fruitful in recent years.[3,4] Major breakthroughs in this aspect were made by employing sterically hindered and/or electronically rich ligands to render previously unattainable reactions possible or effective under much milder conditions.[5−18]

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However, much less attention has been given to investigating possibilities of accelerating the rate of the reductive elimination step, one that is generally considered slower and more critical to the overall reaction rate, except leveraging the steric bulk of the phosphine ligand to elevate the ground state energy. Problems caused by slow reductive elimination are especially acute for coupling reactions involving alkyl (Csp^3 center) nucleophiles, where the presence of β-hydrogens often leads to the deleterious β-elimination pathway,[19] especially in the cases of secondary Csp3 centers.[20,21] It is known that non-phosphine, π-acceptor ligands such as maleic anhydride, fumaronitrile, *p*-fluorostyrene, as well as other olefins,[22−26] are known to accelerate the reductive elimination. However, these ligands are known to stabilize Pd(0) species so much that their tendency toward oxidative addition is much attenuated. To address this dilemma, we designed and synthesized two hybrid ligands, which include the phosphine and electron-deficient olefins shown in Figure 1,

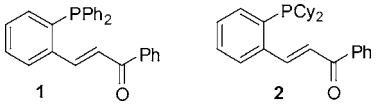

Figure 1. Phosphine electron-deficient olefin ligands.

and we demonstrate that they are effective in palladium-catalyzed Negishi Csp^2-Csp^3 coupling that can occur at room temperature and that involves a secondary sp^3-carbon in the presence of a β-H.

Cross-coupling reactions on sp^3-carbons are more difficult than those on sp- and sp^2-carbons as a result of a slower rate of reductive elimination and a facile process of β-H elimination if available.[7,27−29] In the oxidative cross-coupling of organometals, we attributed the success of the transformation to the unexpected rate enhancement of Csp-Pd-Csp^3 reductive elimination to using dba as the ligand, which is a good π-acceptor.[30] It was reported that oxidative addition and transmetallation of the Csp^2-Csp^3 Negishi coupling are faster than reductive elimination when PPh_3 is used as the ligand.[19,31] However, with in situ reaction monitoring by IR (ReactIR), we found that the reaction of ArI (**3a**) and RZnCl (**4a**) at room temperature using ligand **1** is complete in less than 2 min (Figure 2).

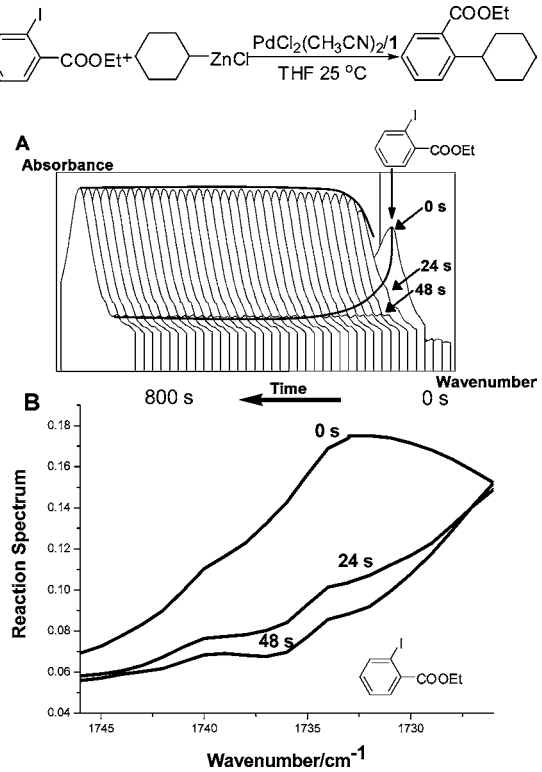

Figure 2. (A) 3D spectrum of ReactIR experiment. (B) Selected 2D spectrum of **3a** during the reaction period. Reaction conditions: 2 mmol **4a**, 1 mmol **3a**, 0.005 mmol $PdCl_2(CH_3CN)_2$/**1** in total 4 mL THF, 25 °C.

We then further studied the Negishi coupling of **3a** with diethylzinc by employing different ligands.[32] The results are listed in Table 1. The reactions using PPh_3 gave only low to moderate yields (Table 1, entries 1−3). Formation of the hydridodehalogenated product **13** is an indication of the

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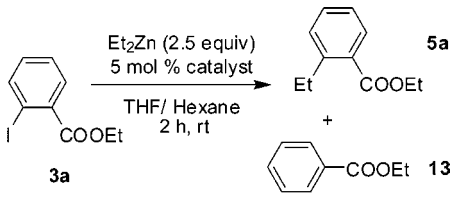
(32) We try to clarify the capability of ligand **1** in the formation of Csp^2(Ar)-Csp^3 bond, in which the possible problem might be the reductive elimination and β-H elimination. ArI **3a**, an electronic-deficient ArI, could be a good substrate for the oxidative addition. If the oxidative addition is fast enough and it is not the rate-determining step, we will have a chance to see the differences between ligand **1** and the others.

Table 1. Effect of Ligands on Csp^3-Involved Negishi Coupling[a]



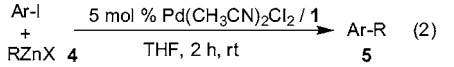
entry	catalyst	selectivity(%)[b] 5a	13	yield of 5a (%)[b]
1	$PdCl_2(PPh_3)_2$	39.1	60.9	38
2	$PdCl_2(MeCN)_2/PPh_3$ (1:1)	12.0	88.0	11
3	$Pd(PPh_3)_4$	56.2	43.8	54
4	$PdCl_2(MeCN)_2$/**1** (1:1)	**93.9**	6.1	91[c]
5	$PdCl_2$(dppf)	60.5	39.5	59
6	$PdCl_2(MeCN)_2/{}^tBu_3P{\cdot}HBF_4$ (1:1)	70.2	29.8	68
7	$PdCl_2(MeCN)_2/{}^tBu_3P{\cdot}HBF_4$ (1:2)	39.8	60.2	39
8[d]	$PdCl_2(MeCN)_2$/**1** (1:1) (open to air)	**94.0**	6.0	91
9	$Pd(dba)_2$	45.2	39.7	44
10	$PdCl_2(meCN)_2$/DPPBz[e](1:1)	0	0	0

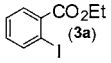
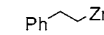
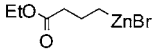
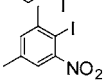
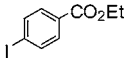
[a] For the procedure refer to Supporting Information. [b] GC yield. [c] Isolated yield. [d] Carried out under air. [e] DPPBz: 1,2-bis(diphenylphosphino)benzene.

extent of the undesired β-H elimination. Good selectivities and yields toward the desired cross-coupling product were obtained by employing the new synthesized ligand **1** (Table 1, entry 4). When *t*-Bu_3P was used as a ligand at a ratio of 1:1, 70% selectivity and 68% isolated yield were obtained (Table 1, entry 6), while lower selectivity and yield (40% and 39%, respectively) were observed when the ratio of *t*-Bu_3P/Pd was changed to 2:1, (Table 1, entry 7). A 59% yield was achieved with this substrate using dppf as the ligand. Interestingly, reactions under the influence of ligand **1** are able to tolerate oxygen well. When the reaction was carried out under aerobic conditions at ambient temperature, similarly high yield and selectivity were observed as that obtained under strict oxygen-free conditions (Table 1, entry 8 vs entry 4).

A combination of the ligand **1** with $PdCl_2(MeCN)_2$ displayed excellent activity toward promoting the Negishi coupling as displayed in Table 2. Yields higher than 84% were achieved when primary alkylzinc reagents were employed (Table 2, entries 1−4). A substrate containing an ester group also afforded the desired product in 86% yield (Table 2, entry 5). Secondary alkylzinc reagents could also be used in this catalytic system at ambient temperature. Reaction of cyclohexylzinc chloride and cyclopentylzinc chloride with substrate **3a** gave the desired cross-coupling product in 86% and 76% yield, respectively. However, for acyclic secondary and tertiary alkylzincs, substantial isomerization, presumably through β-H elimination and hydropalladation, was observed when 2-propylzinc chloride, 2-butylzinc chloride, and *tert*-butylzinc chloride were employed as the nucleophiles (Table 2, entries 7−9), but the cross-coupling yields for 2-propylzinc chloride and 2-butylzinc chloride are 93% and 99%, respectively (Table 2, entries 7 and 8). It is noteworthy that all

Table 2. Negishi Coupling Promoted by **1**



entry	Ar-I	RZnX[a]	yield of 5 (%)[b]	
1	 (3a)	^nBuZnCl	93	(**5b**)
2	**3a**	$^nC_8H_{17}ZnCl$	84	(**5c**)
3	**3a**	$^nC_{12}H_{25}ZnCl$	86	(**5d**)
4	**3a**		96	(**5e**)
5	**3a**		86	(**5f**)
6	**3a**		76	(**5g**)
7	**3a**		93[c]	(**5h**)
8	**3a**		99[d]	(**5i**)
9	**3a**		50[e]	(**5j**)
10	**3a**	 (**4a**)	86	(**5k**)
11		**4a**	81	(**5l**)
12		**4a**	74	(**5m**)
13		**4a**	64	(**5n**)
14		**4a**	71	(**5o**)

[a] RZnX was prepared in situ via RMgX and $ZnCl_2$. [b] Isolated yield. [c] 61/29 mixture of *i*-Pr and *n*-Pr isomers. [d] 55/45 mixture of *s*-Bu and *n*-Bu isomers. [e] 100% isobutyl isomer product.

reactions shown in Table 2 were carried out under ambient temperature. The reaction of phenyl iodide gave the desired coupling product (**5l**) in 81% isolated yield (Table 2, entry 11). When a nitro group is present at the *ortho* position of phenyl iodide, the product **5m** was obtained in 74% yield (Table 2, entry 12). Gratifyingly, a sterically hindered substrate was able to be employed, forming the desired coupling product (**5n**) in moderate yield (Table 2, entry 13).[33]

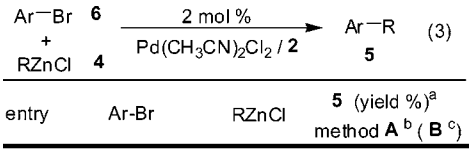
Ligand **2**, containing an electronically rich phosphine, was further investigated for the Negishi coupling of ArBr (**6**) with alkylzinc chloride, and the results are listed in Table 3. Good to excellent yields were obtained in the coupling of primary alkylzinc nucleophiles with ArBr (Table 3). The reactions of secondary alkylzinc reagents with ArBr produced the desired products in moderate to good yields (Table 3, entries 6−8). The reaction can occur at room temperature in 16 h, whereas it can take place at 60 °C within 3 h.[34]

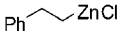
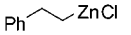
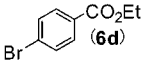
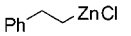
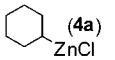
The transformation was also examined on a larger scale. Under aerobic conditions at ambient temperature (25 °C),

(33) The reactions of cyclohexylzinc chloride and 2-iodoanisole or 4-iodoanisole produced the desired cross-coupling products in 34% and 48% isolated yields, respectively.

(34) ArCl (electronic-deficient or electronic-rich) were not effective substrates at room temperature or 60 °C.

Table 3. Negishi Coupling of ArBr Promoted by **2**



entry	Ar-Br	RZnCl	**5** (yield %)[a] method **A**[b] (**B**[c])
1	 (**6a**)	^{n}BuZnCl	(96) (**5p**)
2	**6a**	$^{n}C_8H_{17}ZnCl$	94 (96) (**5q**)
3	**6a**		96 (98) (**5r**)
4	 (**6c**)		85 (88) (**5s**)
5	 (**6d**)		88 (94) (**5t**)
6	**6a**	 (**4a**)	78[d] (85) (**5u**)
7	**6c**	**4a**	88 (90[d]) (**5l**)
8	**6d**	**4a**	78 (74[d]) (**5o**)

[a] Isolated yield. [b] Method **A**: in toluene at rt for 16 h. [c] Method **B**: in toluene at 60 °C for 3 h. [d] Determined by GC.

the reaction of cyclohexylzinc chloride and ArI (**3**) was carried out on a 50 g scale (0.18 mol) with 0.005 mol % catalyst, which was generated from the ligand **1** and $PdCl_2$-$(MeCN)_2$ (20,000 TONs). A selectivity of 90% (GC) and an isolated yield of 81% were obtained after a reaction time of 48 h.

In conclusion, we have designed and synthesized a new phosphine−electron-deficient olefin chelating ligand, which has been successfully employed in a palladium-catalyzed coupling reaction of aryl halides with alkylzinc reagents (including primary and secondary alkyl nucleophiles with β-H). High selectivities and yields were achieved under ambient temperature. Further mechanistic studies along with the scope of different reactions are currently being investigated and will be reported in due course.

Acknowledgment. This work was support by National Natural Science Foundation of China (20502020) and the startup fund from Wuhan University. We thank Prof. Xinquan Hu (College of Chemical Engineering and Materials Science, Zhejiang University of Technology, PR China) for helpful discussion and generously providing the ArI compounds.

Supporting Information Available: The syntheses of ligand **1** and **2**, kinetic studies, spectroscopic data, and experiments details. This material is available free of charge via the Internet at http://pubs.acs.org.

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