<u>LETTERS</u>

Formation of C(sp³)–C(sp³) Bonds by Palladium Catalyzed Cross-Coupling of α -Diazoketones and Allylboronic Acids

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(5) Supporting Information

ABSTRACT: Palladium catalyzed cross-coupling of allylboronic acids with α -diazoketones was studied. The reaction selectively affords the linear allylic product. The reaction proceeds with formation of a new $C(sp^3)-C(sp^3)$ bond. The reaction was performed without an external oxidant, likely without the Pd-catalyst undergoing redox reactions.



A llylboronates have found many important applications in selective carbon–carbon bond formation reactions.¹ The most important selective transformations involve allylboration of carbonyl compounds² and imines,³ but recently an increasing number of metal-catalyzed cross-coupling reactions involving allylboronates have also been appeared.⁴ A particularly interesting feature is the regiochemistry of the cross-coupling. The Pd-catalyzed cross-coupling of allyl boron compounds with aryl halides inherently results in the branched allylic product.^{4b,c,e,f} However, the ligand effects and the applied substrates can alter this regioselectivity affording a linear cross-coupling product.^{4e,f} Very recently, we reported^{4d} a Cucatalyzed cross-coupling of allylboronic acids and α -diazoketones, which also resulted in a branched allylic product (Scheme 1c).

Scheme 1. Cross-Coupling of α -Diazocarbonyl Compounds with Allyl Substrates by the Groups of Wang,⁵ Gong,⁶ and Our Group^{4d}



Applications involving α -diazocarbonyl compounds with organoboronates represent a very interesting concept for new selective cross-coupling reactions. The typical organoboronate components in previously reported examples of Pd-catalyzed coupling reactions included aryl and vinyl boron species.⁷ Allyl boron species have never been used in these types of transformations. On the other hand, the groups of Wang⁵

and Gong⁶ applied allylic chlorides (Scheme 1a) and terminal alkenes (Scheme 1b) as coupling components. These processes required the use of an oxidant (benzoquinone) affording linear butadiene products. Considering these^{5,6} (Scheme 1a-b) and our recent results^{4d} (Scheme 1c), it was appealing to study the Pd-catalyzed reactions of α -diazocarbonyl compounds and allylboronic acids (Scheme 1c). Indeed, we have found that α diazocarbonyl compounds and allylboronic acids underwent Pd-catalyzed cross-coupling. Surprisingly, this cross-coupling reaction did not require use of an oxidant and the reaction occurred with formation of a new $C(sp^3)-C(sp^3)$ bond (cf. Scheme 1c with 1a-b). Furthermore, in contrast to the Cucatalyzed procedure^{4d} the Pd-catalyzed process gave the linear allylic product (Scheme 1c). Optimization of the reaction conditions showed that Pd(0) catalysts are not efficient for cross-coupling of α -diazoketone **1a** and cinnamylboronic acid²ⁱ 2a (Table 1, entries 1-2). Pd(II) catalysts, such as Pd(TFA)₂ and $Pd(OAc)_{2}$, in CH_2Cl_2 gave promising yields (entries 3–5). Variation of the solvent (entries 6-7) led to lower yields than in the case of CH₂Cl₂. We have found that addition of catalytic amounts (20 mol %) of CuI substantially improved the yield (entry 8). However, other Cu-salts were not as efficient as CuI (entries 9-12). Addition of tBuOH did not improve the yield either (entry 13). Addition of PPh₃, dppe, and 1,10phenanthroline (potential ligands to Pd) also led to lowering of the yield. We have found that the yield can be slightly improved (70%), when α -diazoketone 1a was added in two portions (in 15 min) to the reaction mixture (entry 14).

When the reaction was conducted without a Pd-catalyst, we did not observe formation of 3a (entry 15). Similarly to Cucatalyzed cross-coupling,^{4d} product 3a did not form, when 2a was replaced by its Bpin analog 4 (eq 1).

With the optimal conditions in hand, we studied the synthetic scope of the reaction. All reactions are completed in about 1 h under mild neutral conditions at rt selectively affording the linear allylic product with a new $C(sp^3)-C(sp^3)$

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Table 1. Variation of the Reaction Conditions for Cross-Coupling of Allylboronic Acid 2a with α -Diazoketone 1a^{*a*}

Ph 1a	_⊱ N ₂ + Ph 2 ;	Pd B(OH) ₂ a	catalyst dditive olvent t / 1 h	3a Ph
entry	Pd catalyst	solvent	additive	yield (%) ^b
1 ^c	$Pd(PPh_3)_4$	CH_2Cl_2	-	0
2 ^c	$Pd(dba)_2$	CH_2Cl_2	-	21
3 ^c	$Pd(TFA)_2$	CH_2Cl_2	-	36
4 ^{<i>c</i>}	$Pd(OAc)_2$	CH_2Cl_2	-	44
5	$Pd(OAc)_2$	CH_2Cl_2	-	51
6	$Pd(OAc)_2$	toluene	-	18
7	$Pd(OAc)_2$	CH ₃ CN	-	6
8	$Pd(OAc)_2$	CH_2Cl_2	Cul	60
9	$Pd(OAc)_2$	CH_2Cl_2	Cul·Me ₂ S	0
10	$Pd(OAc)_2$	CH_2Cl_2	CuOAc	0
11	$Pd(OAc)_2$	CH_2Cl_2	CuBr	50
12	$Pd(OAc)_2$	CH_2Cl_2	CuCl	41
13 ^d	$Pd(OAc)_2$	CH_2Cl_2	<i>t</i> BuOH	47
l4 ^e	$Pd(OAc)_2$	CH_2Cl_2	Cul	70
15	_	CH_2Cl_2	Cul	0

^{*a*}Unless otherwise stated a mixture of **1a** (0.12 mmol), **2a** (0.10 mmol), Pd catalyst (10 mol %), and the additive (20 mol %) in CH_2Cl_2 (0.5 mL) was stirred for 1 h at rt. ^{*b*}Isolated yield. ^{*c*}**1a** (0.10 mmol), **2a** (0.12 mmol), and Pd catalyst (10 mol %) were used. ^{*d*}The reaction was performed with 10 equiv of *t*BuOH. ^{*e*}**1a** was added in two portions.

$$Ph \xrightarrow{O} N_2 + Ph \xrightarrow{Ph} Bpin \xrightarrow{Pd(OAc)_2, Cul} Ph \xrightarrow{O} Ph (1)$$
1a 4

bond. The aromatic substituents of the α -diazoketone component had a relatively weak effect. α -Diazoketones with electron-withdrawing substituents (such as 1c-e) reacted readily (Table 2, entries 2–6). In some cases, as for example for 1b with a methoxy substituent (entry 2) and 1f with a nitro group, an excess of α -diazoketone substrate was employed to improve the yield.

On the other hand 1g with a naphthyl group reacted similarly to 1a affording 3g in 64% yield. The coupling of 2a with 1a-ggave a single diastereomer. Not only cinnamylboronic acid 2a but also alkyl substituted allyl boronic acids 2b-2d also proved to be useful cross-coupling partners (entries 8–15). In the case of monosubstituted allylboronic acid 2b, the E/Z ratio of the product varied between 6.0 and 9.0 to 1.

When γ -disubstituted boronic acids, such as geranyl (2c) and neryl (2d) boronic acids, were used the E/Z ratio was poor (1.6–0.9 to 1) indicating that substantial isomerization of the allylic *E* and *Z* double bond occurs (entries 13–14). We tried to improve the E/Z ratio by conducting the reaction at low temperature (0 °C and -20 °C) or by dilution of the reaction mixture. However, these attempts remained fruitless. In these reactions (entries 8–14) we observed a formation of traces (<5%) of the branched allylic product as well. We were able to perform cross-coupling of aliphatic α -diazoketone **1h** with **2a** affording **3n** (entry 15). Disubstituted α -diazoketone **1i** was also reacted readily giving a linear allylic product **3o** (entry 16).

Probably the most interesting feature of the cross-coupling reaction of α -diazoketones and allylboronic acids is the opposite regioselectivity in Cu- and Pd-catalyzed reactions (Scheme 1c). A decrease in the diastereoselectivity for the

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Table 2. Palladium Catalyzed Cross-Coupling of

^{*a*}Unless otherwise stated a mixture of 1 (0.12 mmol, added in two portions), 2 (0.10 mmol), Pd(OAc)₂ (10 mol %), and CuI (20 mol %) in CH₂Cl₂ (0.5 mL) were stirred at rt for 1 h. ^{*b*}Isolated yields. ^{*c*}The reaction was performed with 0.15 mmol of 1. ^{*d*}The reaction was performed with 0.20 mmol of 1. ^{*e*}The product contains less than 5% of the branched product. ^{*f*}The reaction was performed without CuI, and 1 mL of CH₂Cl₂ was used. ^{*g*}2 mL of CH₂Cl₂ were used.

aliphatic (**2b**-**d**), especially using the disubstituted allyl boronic acids **2c**-**d**, suggests formation of η^3 -allylpalladium complexes, which may undergo $\eta^3 - \eta^1 - \eta^3$ isomerization.⁸ Thus, a conceivable initial step of the reaction is transmetalation of the allylboronic acid component with the Pd(II) catalyst to give η^3 allylpalladium complex **5**. In order to test this hypothesis, we prepared complex **5** and reacted it with α -diazoketone **1a** in the presence and in the absence of CuI. We could not observe formation of 3a in any of these reactions (eq 2). This clearly indicates that 5 is not a kinetically competent intermediate of



the Pd-catalyzed cross-coupling reaction of α -diazoketones (such as 1a) and allylboronic acids (such 2a). This is a very surprising finding in view of the fact that Wang⁵ and Gong⁶ have shown that the reaction of α -diazocarbonyl compounds with allyl chlorides⁵ and alkenes⁶ do proceed via η^3 -allyl palladium complexes, such as 5.

Considering the above-mentioned results (including eq 2), we propose a catalytic cycle initiated by formation of Pd-carbenoid **6** from **1** and Pd(OAc)₂ (Figure 1). A similar type of Pd-carbenoid formation has been reported in the literature⁹ and was invoked^{7a,b} in many Pd-catalyzed transformations of α -diazocarbonyl compounds.



Figure 1. Proposed catalytic cycle for the cross-coupling of allylboronic acids with α -diazoketones.

Subsequently, Pd-carbenoid 6 may undergo transmetalation with allylboronic acid 2 affording η^3 -allylpalladium carbenoid complex 7. As mentioned above (Table 1, entries 8), addition of CuI improved the yield of the reaction. A possible explanation is that the Cu-salt facilitates the transmetalation¹⁰ of allylboronic acid 2 with the palladium atom of 6. In this process CuI was more efficient than CuCl and CuBr (Table 1, entries 11-12), possibly because of the better solubility in the reaction media. Formation of η^3 -allylpalladium carbenoid complexes, such as 7, has been suggested in the coupling of α -diazocarbonyl compounds with allylic substrates.^{5,6} Complex 7 may undergo $\eta^3 - \eta^1 - \eta^3$ isomerization. An indication of the η^3 - η^1 - η^3 isomerization is the formation of the E/Z isomers of **3m** using geranyl 2c and neryl boronic acids 2d in the crosscoupling with 1a (Table 2, entries 13-14). The η^3 - η^1 - η^3 isomerization involves formation of various syn-anti isomers of the η^3 -allylpalladium complexes.^{8,11} The final E/Z ratio is mainly determined by the steric effects of the substituents.^{8,11} The η^1 -form of 7 with the least substituted allylic terminus is probably more stable than the other η^1 -allylic isomer. The η^1 allyl group may undergo migratory insertion into the Pdcarbene to give 8. Formation of η^1 -alkylpalladium complex 8

would also explain the regioselective formation of the linear allylic product 3. Migratory insertion of vinyl and aryl groups to Pd-carbene was previously suggested by the groups of Van Vranken,¹² Barluenga,¹³ and Wang.^{7c,d} The last step of the reaction is probably formation of Pd-enolate 10 via $oxa-\eta^3$ intermediate 9.¹⁴ By a rapid $8 \rightarrow 10$ tautomerization, the β hydride elimination in 8 can be avoided, and therefore formation of a diene product, such as in the reaction of α diazocarbonyl compounds with allylic chlorides⁵ or alkenes⁶ (Scheme 1a-b), can be avoided. The Pd(II) catalyst is recovered by formation of product 3 and boric acid from 10. Water necessary for this process was probably formed by dehydration of $B(OH)_n$ (n = 2, 3) species by formation of boroxines.²ⁱ A very interesting feature of the above-mentioned reaction is that palladium does not undergo redox reactions but it is kept in oxidation state +2. Therefore, we did not need to use oxidants (such as BQ), as in the analogous allylation reactions of α -diazocarbonyl compounds (Schemes 1a-b).

In summary we have shown that Pd-catalyzed cross-coupling of α -diazoketones and allylboronic acids can be performed. The reaction selectively provides a linear allylic product. Thus, the presented Pd-catalyzed coupling and the previously reported Cu-catalyzed reaction have the opposite regiopreference. The reaction was performed without using oxidants. The Pd-catalyst probably preserves its oxidation state during the entire reaction. The presented process widens the synthetic scope of the transition metal catalyzed cross-coupling reactions,¹⁵ which are suitable for formation of C(sp³)-C(sp³) bonds.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.6b01132.

Detailed experimental procedures and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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