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Formation of C(sp^3)–C(sp^3) Bonds by Palladium Catalyzed Cross-Coupling of α-Diazoketones and Allylboronic Acids

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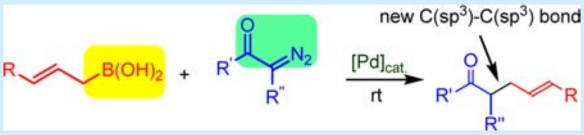
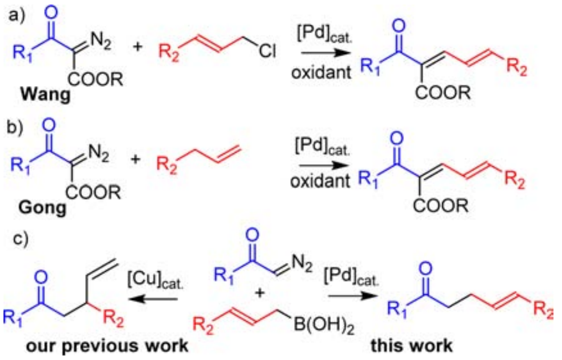
S Supporting Information

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.



Allylboronates have found many important applications in selective carbon–carbon bond formation reactions.[1] The most important selective transformations involve allylboration of carbonyl compounds[2] 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 Cu-catalyzed 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 Wang[5] and Gong[6] 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 Cu-catalyzed 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 acid[2i] **2a** (Table 1, entries 1–2). Pd(II) catalysts, such as Pd(TFA)$_2$ and Pd(OAc)$_2$, in CH$_2$Cl$_2$ gave promising yields (entries 3–5). Variation of the solvent (entries 6–7) led to lower yields than in the case of CH$_2$Cl$_2$. 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 *t*BuOH did not improve the yield either (entry 13). Addition of PPh$_3$, dppe, and 1,10-phenanthroline (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 Cu-catalyzed 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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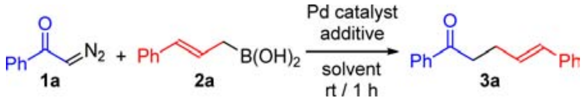
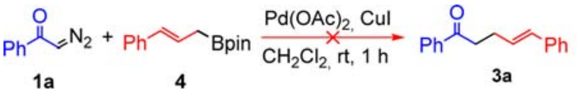
Table 1. Variation of the Reaction Conditions for Cross-Coupling of Allylboronic Acid 2a with α-Diazoketone 1a[a]



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[c]	$Pd(OAc)_2$	CH_2Cl_2	–	44
5	$Pd(OAc)_2$	CH_2Cl_2	–	51
6	$Pd(OAc)_2$	toluene	–	18
7	$Pd(OAc)_2$	CH_3CN	–	6
8	$Pd(OAc)_2$	CH_2Cl_2	CuI	60
9	$Pd(OAc)_2$	CH_2Cl_2	$CuI{\cdot}Me_2S$	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	*t*BuOH	47
14[e]	$Pd(OAc)_2$	CH_2Cl_2	CuI	70
15	–	CH_2Cl_2	CuI	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.



(1)

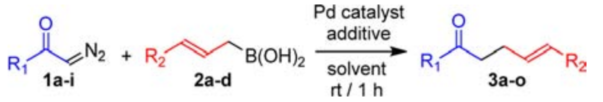
bond. The aromatic substituents of the α-diazoketone component had a relatively weak effect. α-Diazoketones with electron-withdrawing substituents (such as **1c–e**) reacted readily (Table 2, entries 2–6). In some cases, as for example for **1b** with a methoxy substituent (entry 2) and **1f** with a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

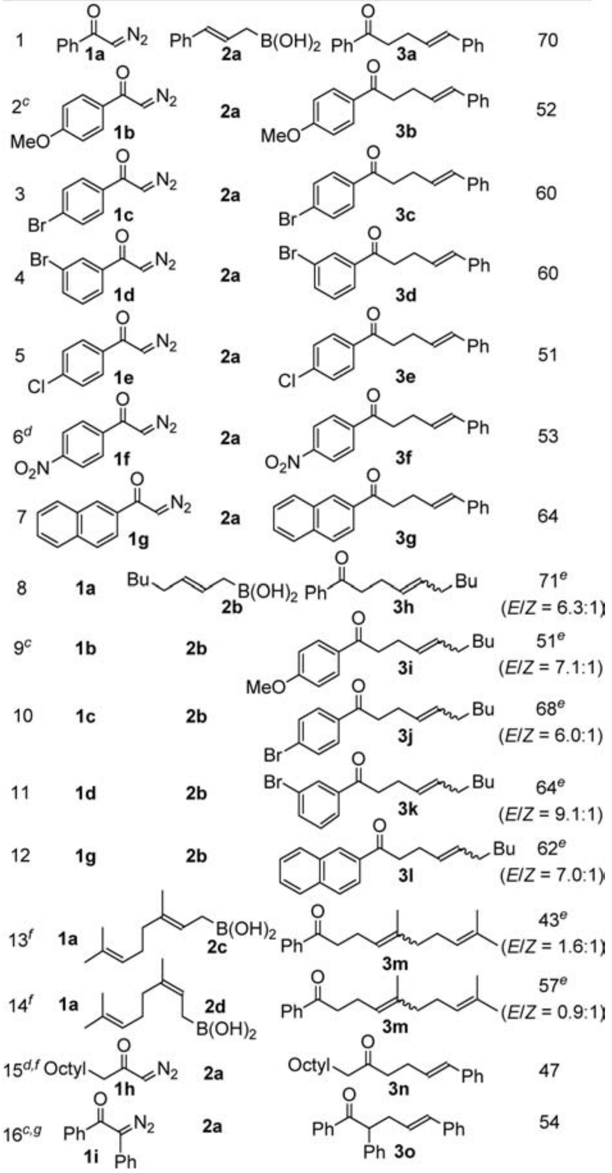
On the other hand **1g** with a naphthyl group reacted similarly to **1a** affording **3g** in 64% yield. The coupling of **2a** with **1a–g** gave a single diastereomer. Not only cinnamylboronic acid **2a** but also alkyl substituted allyl boronic acids **2b–2d** also proved to be useful cross-coupling 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 aliphatic (**2b–d**), especially using the disubstituted allyl boronic acids **2c–d**, suggests formation of η^3-allylpalladium complexes, which may undergo η^3-η^1-η^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

Table 2. Palladium Catalyzed Cross-Coupling of Allylboronic Acids with α-Diazoketones[a]

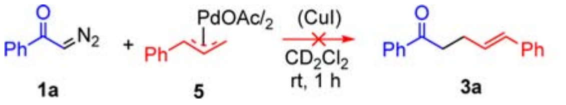




entry	diazoketone	boronic acid	product	yield (%)[b]
1	**1a**	**2a**	**3a**	70
2[c]	**1b**	**2a**	**3b**	52
3	**1c**	**2a**	**3c**	60
4	**1d**	**2a**	**3d**	60
5	**1e**	**2a**	**3e**	51
6[d]	**1f**	**2a**	**3f**	53
7	**1g**	**2a**	**3g**	64
8	**1a**	**2b**	**3h**	71[e] (*E*/*Z* = 6.3:1)
9[c]	**1b**	**2b**	**3i**	51[e] (*E*/*Z* = 7.1:1)
10	**1c**	**2b**	**3j**	68[e] (*E*/*Z* = 6.0:1)
11	**1d**	**2b**	**3k**	64[e] (*E*/*Z* = 9.1:1)
12	**1g**	**2b**	**3l**	62[e] (*E*/*Z* = 7.0:1)
13[f]	**1a**	**2c**	**3m**	43[e] (*E*/*Z* = 1.6:1)
14[f]	**1a**	**2d**	**3m**	57[e] (*E*/*Z* = 0.9:1)
15[d,f]	**1h**	**2a**	**3n**	47
16[c,g]	**1i**	**2a**	**3o**	54

[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 CH_2Cl_2 (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 CH_2Cl_2 was used. [g] 2 mL of CH_2Cl_2 were used.

formation of **3a** in any of these reactions (eq 2). This clearly indicates that **5** is not a kinetically competent intermediate of



(2)

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 Wang[5] and Gong[6] have shown that the reaction of α-diazocarbonyl compounds with allyl chlorides[5] and alkenes[6] 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 literature[9] and was invoked[7a,b] in many Pd-catalyzed transformations of α-diazocarbonyl compounds.

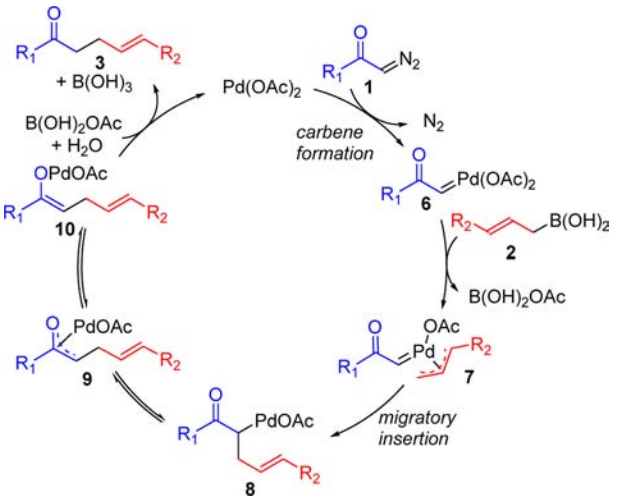


Figure 1. Proposed catalytic cycle for the cross-coupling of allylboronic acids with α-diazoketones.

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 transmetalation[10] 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 η^3-η^1-η^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 cross-coupling 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 Pd-carbene 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-η^3-intermediate **9**.[14] By a rapid **8** → **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 chlorides[5] or alkenes[6] (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(sp^3)–C(sp^3) bonds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.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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