

# Palladium-Catalyzed Cross Coupling Reaction of Benzyl Bromides with Diazoesters for Stereoselective Synthesis of (*E*)- $\alpha,\beta$ -Diarylacrylates

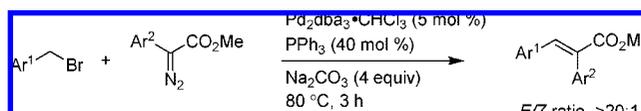
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## ABSTRACT



A Pd-catalyzed cross-coupling reaction of benzyl bromides with  $\alpha$ -aryldiazoesters is described, and *E*- $\alpha,\beta$ -diarylacrylates were obtained in good yields and excellent *E*-to-*Z* selectivity (>20:1).

$\alpha$ -Diazocarbonyl compounds are versatile reagents for organic synthesis.<sup>1</sup> With transition metal catalysts<sup>2a</sup> (e.g., Rh,<sup>2b,c</sup> Cu,<sup>3a–c</sup> Au,<sup>3b,e</sup> Ag,<sup>3d</sup> Ru<sup>3f,g,4</sup>),  $\alpha$ -diazocarbonyl compounds can be readily transformed to highly reactive metal–carbene complexes, which are known to functionalize C=C and C–H bonds for stereoselective C–C bond forma-

tion. Previously, we described that ruthenium complexes of porphyrins and  $\pi$ -aromatics can effect highly stereoselective heterocycle formation via a carbenoid C–H insertion reaction of  $\alpha$ -diazocarbonyl compounds.<sup>4</sup>

Coupling reaction of organopalladium complexes with carbon nucleophiles is a fundamental process that underlies many Pd-catalyzed C–C bond formation reactions.<sup>5</sup> The carbon nucleophiles include organometallic reagents (e.g., organoboron),<sup>6a</sup> alkenes,<sup>6b,c</sup> and arenes,<sup>6d,e</sup> etc. Apart from the conventional nucleophiles, we recently found that reactions of organopalladium complexes with nitrenes and carboradicals would bring about C–N and C–C bond formation.<sup>7</sup> In the light of these findings, we envisage the

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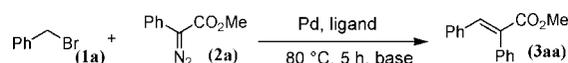
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**Table 1.** Optimization of Reaction Conditions<sup>a</sup>

entry	1a:2a	Pd source (5 mol %)	ligand (40 mol %)	base (4 equiv)	solvent %	convn <sup>b</sup> %	yield <sup>b,c</sup>
1	1:1.2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub> <sup>a</sup>	toluene	68	37
2	1:1.2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	<i>i</i> -Pr <sub>2</sub> NEt <sup>a</sup>	toluene	80	31
3	1:1.2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub> <sup>a</sup>	toluene	80	44
4	1:1.2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	AsPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	toluene	38	26
5	1:1.2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PCy <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	toluene	39	0
6	1:1.2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	dppb <sup>f</sup>	Na <sub>2</sub> CO <sub>3</sub>	toluene	53	0
7	1:2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	toluene	80	63
8	1:2	Pd(OAc) <sub>2</sub> <sup>d</sup>	PPh <sub>3</sub>	Na <sub>2</sub> CHO <sub>3</sub>	toluene	70	64
9	1:2	[pd(allylCl)] <sub>2</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	toluene	56	38
10 <sup>d</sup>	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	THF	100	87
11	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	dioxane	100	87
12	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	toluene	100	85
13	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	93	46
14	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	acetone	100	80
15	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	DCE	67	63
16	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	DMF	87	43
17	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	none	Na <sub>2</sub> CO <sub>3</sub>	THF	29	0
18	1:2	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub> <sup>g</sup>	Na <sub>2</sub> CO <sub>3</sub>	toluene	59	48
19	1:3	Pd <sub>2</sub> dba <sub>3</sub> ·CHCl <sub>3</sub>	PPh <sub>3</sub> <sup>h</sup>	Na <sub>2</sub> CO <sub>3</sub>	toluene	88	78
20	1:3	none	PPh <sub>3</sub>	Na <sub>2</sub> CO <sub>3</sub>	THF	55	0

<sup>a</sup> The reactions were carried out in a 0.2 mmol scale of **1a**. <sup>b</sup> Conversions and yields were determined by GC/FID using tetradecane as internal standard. <sup>c</sup> The percentage yield is based on **1a** conversion. <sup>d</sup> The reaction was run for 3 h. <sup>e</sup> 10 mol % of Pd(OAc)<sub>2</sub> was employed. <sup>f</sup> 2.5 mol % of Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub> was employed. <sup>g</sup> 30 mol % of ligand. <sup>h</sup> 20 mol % of ligand. <sup>i</sup> 2 equiv of base.

development of new C–C bond formation by exploiting the reaction of organopalladium with carbenes. By analogy to migratory CO insertion to the Pd–C bond, migratory insertion of carbene to organopalladium would create a new C–C bond as a stereogenic center.<sup>8</sup> Indeed, some reports on the Pd-catalyzed cross coupling reactions of aryl/vinyl halides with carbenes derived from  $\alpha$ -diazocarbonyls emerged recently in the literature.<sup>9</sup> In this work, we describe a stereoselective synthesis of *E*- $\alpha,\beta$ -diarylacrylates by the Pd-catalyzed reaction of benzyl bromides with  $\alpha$ -aryldiazoesters.  $\alpha,\beta$ -Diarylacrylates are common scaffolds in pharmaceutically active compounds, and Perkin aldol condensation is frequently employed for their synthesis.<sup>10</sup> However, the Perkin aldol reaction suffers from a rather limited substrate scope and low product yields.<sup>10a</sup> Here we showed that the Pd-catalyzed reaction of benzyl bromides with aryldiazoac-

etates is an effective approach for diarylacrylates synthesis; the desired alkenes can be obtained in good yield and excellent *E*-selectivity.

We started by examining the reaction of benzyl bromide (**1a**) with methyl  $\alpha$ -phenyldiazoacetate **2a** in the presence of Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub> (5 mol %), PPh<sub>3</sub> (40 mol %), and K<sub>2</sub>CO<sub>3</sub> (2 equiv) in toluene at 80 °C for 5 h, and *E*-acrylate **3aa** was produced in 37% yield based on 68% bromide conversion (Table 1, entry 1). By means of GC–MS techniques, the *E*-to-*Z* selectivity was determined to be >20:1. The *E*-configuration of the alkene was confirmed by <sup>1</sup>H NMR and X-ray crystallography (for acrylate **3ma**; see Supporting Information).

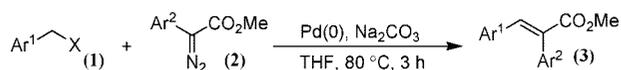
While the use of *i*-Pr<sub>2</sub>NEt as base for the Pd-catalyzed reaction gave **3aa** in 31% yield, a slightly better result (44% yield) was obtained with Na<sub>2</sub>CO<sub>3</sub> as base (entries 2 and 3). Prior to this work, Van Vranken and co-workers<sup>9f</sup> reported that a Pd-catalyzed reaction of **1a** and ethyldiazoacetate (EDA) would afford *trans*-cinnamate in moderate (25–74%) yields. According to Van Vranken's results,<sup>9f</sup> AsPh<sub>3</sub> was found to be the best ligand for the “**1a** + EDA” reaction. However, when AsPh<sub>3</sub> (40 mol %) was employed as ligand for our Pd-catalyzed reaction, **3aa** was formed in only 26% yield with 38% bromide conversion (entry 4). Notably, insignificant product formation resulted with PCy<sub>3</sub> and 1,4-bis(diphenylphosphino)butane (dppb) as ligands (entries 5 and 6).

During our optimization study, we found that better product yield (63%) can be obtained when the reaction was

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**Table 2.** Palladium-Catalyzed Cross Coupling Reactions of Benzyl Bromides with Diazoesters<sup>a</sup>

entry	Ar <sup>1</sup>	X	Ar <sup>2</sup>	product	% yield <sup>b,c</sup>
1		Br ( <b>1a</b> )		<b>3aa</b>	85
2		Cl ( <b>1b</b> )	<b>2a</b>	<b>3aa</b>	81 <sup>d</sup>
3		Br ( <b>1c</b> )	<b>2a</b>	<b>3ca</b>	66
4		Br ( <b>1d</b> )	<b>2a</b>	<b>3da</b>	74
5		Br ( <b>1e</b> )	<b>2a</b>	<b>3ea</b>	86
6		Br ( <b>1f</b> )	<b>2a</b>	<b>3fa</b>	75
7		Br ( <b>1g</b> )	<b>2a</b>	<b>3ga</b>	82
8		Br ( <b>1h</b> )	<b>2a</b>	<b>3ha</b>	88
9		Br ( <b>1i</b> )	<b>2a</b>	<b>3ia</b>	45
10		Br ( <b>1j</b> )	<b>2a</b>	<b>3ja</b>	52
11		Br ( <b>1k</b> )	<b>2a</b>	<b>3ka</b>	92
12		Br ( <b>1l</b> )	<b>2a</b>	<b>3la</b>	68
13		Br ( <b>1m</b> )	<b>2a</b>	<b>3ma</b>	75
14	<b>1a</b>	Br		<b>3ab</b>	89
15	<b>1a</b>	Br		<b>3ac</b>	48 <sup>e</sup>
16		Br ( <b>1n</b> )	<b>2a</b>	<b>3na</b>	<20 <sup>f</sup>
17		Br ( <b>1o</b> )	<b>2a</b>	<b>3oa</b>	20
18	<b>1a</b>	Br		<b>3ad</b>	8 <sup>g,h</sup>

<sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), Na<sub>2</sub>CO<sub>3</sub> (0.8 mmol), Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub> (5 mol %), PPh<sub>3</sub> (40 mol %), THF (2 mL), 80 °C for 3 h. <sup>b</sup> Isolated yield. <sup>c</sup> The percentage yield based on conversion. <sup>d</sup> The conversion of **1b** is 74%. <sup>e</sup> The conversion of **1a** is 67%. <sup>g</sup> NMR yield. <sup>h</sup> The conversion of **1a** is ca. 40%.

performed under the conditions: **1a** (1 equiv), **2a** (2 equiv), Na<sub>2</sub>CO<sub>3</sub> (4 equiv), Pd<sub>2</sub>dba<sub>3</sub>·CHCl<sub>3</sub> (5 mol %) in toluene at 80 °C for 5 h (entry 7). Employing other Pd precursors such as Pd(OAc)<sub>2</sub> and [Pd(allyl)Cl]<sub>2</sub> for the catalytic reaction did not afford better results (entries 8 and 9). However, when 3 equiv of **2a** was utilized for the coupling reaction with THF as solvent, **3aa** was furnished in 87% yield (entry 10). Solvents including THF, dioxane, and toluene were found to give comparable results; however, using MeCN, acetone, 1,2-dichloroethane, and DMF as solvent led to lower product yield and poor mass balance with respect to **1a** (entries

11–16). Apparently, PPh<sub>3</sub> (40 mol %) is essential for the acrylate formation. For example, in the absence of the PPh<sub>3</sub> ligand, no **3aa** formation was observed (entry 17). Yet, performing the “**1a** + **2a**” reaction using 30 mol % of PPh<sub>3</sub> gave **3aa** in 48% yield albeit with lower **1a** conversion (59%; entry 18). As expected, lowering the catalyst loading would diminish the product yield for the 5 h reaction (78% yield; 88% conversion, entry 19). In this work, when syringe pump addition of **2a** (addition rate = 0.5 mL h<sup>-1</sup>) was adopted for the coupling reaction, poor **3aa** formation (65%) and **1a** conversion (54%) were observed (see Supporting Information).

Table 2 demonstrates the scope of the Pd-catalyzed cross-coupling reaction. Benzyl bromide and chloride are both effective substrates, and **3aa** was obtained in ca. 80% yield despite slightly lower substrate conversion (74%) being observed for the chloride (entries 1 and 2). Facile transformations of bromides **1c**–**1h** containing electron-withdrawing and -releasing groups on the aromatic ring furnished the corresponding acrylates in 66–88% yields (entries 3–8). It is noteworthy that a bromo-substituent on the aromatic ring of either the benzyl bromide (e.g., **1c**) or the diazoacetate (e.g., **2c**) is tolerated under the Pd-catalyzed conditions (entries 3 and 15). We found that the reactions of bromide **1i** containing an *ortho*-OMe substituent afforded the product acrylate in 45% yield (entry 9). Nevertheless, the analogous reaction of diazoacetate **2b** bearing an *ortho*-OMe substituent on the aryl ring produced the desired alkene in 89% yield (entry 14).

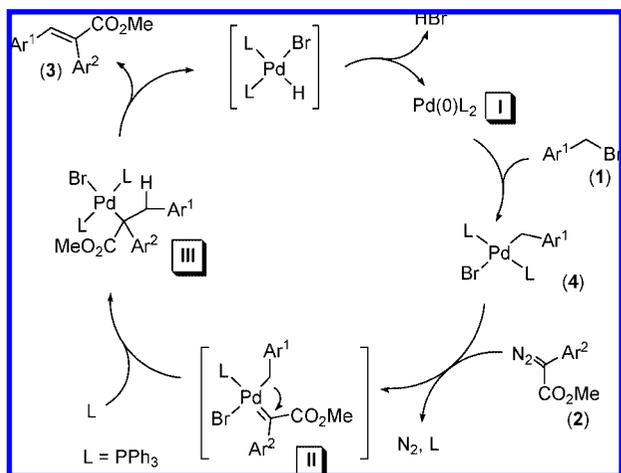
The Pd-catalyzed cross-coupling reactions of some polycyclic aromatic/heteroaromatic bromides (**1j**–**1l**) gave the expected acrylates in 52–92% yields with excellent *E*-stereoselectivity (Table 2, entries 10–12). Diarylacrylates bearing organosulfonyl groups as scaffolds were reported to exhibit biological activities, and they were prepared by Perkin aldol condensation in <40% yield.<sup>10a</sup> In this work, subjecting bromide **1m** containing an *N*-sulfonylmorpholino group and diazoester **2a** to our Pd-catalyzed protocol, **3ma** would be produced in 75% yield (entry 13).

A plausible mechanism for this coupling reaction may start with the oxidative addition of the benzyl bromide **1** to the Pd(0) catalyst **I** to give the organopalladium complex **4** (Scheme 1). Then, the diazoacetate **2** would react with **4** to form putatively a reactive palladium–carbene complex **II**, which would undergo migratory insertion of the benzyl group to produce the alkylpalladium complex **III**. Migratory insertion reactions for palladium carbenes are well predated in amino- and methoxycarbene palladium complexes.<sup>8a,b,d</sup> β-Elimination should provide the acrylate **3** and regenerate the Pd(0) catalyst. Consistent with this mechanism, a stoichiometric reaction of a well-characterized benzylpalladium complex **4a** (prepared by reacting **1a** with Pd(0) and PPh<sub>3</sub>)<sup>11</sup> and **2a** (3 equiv) in THF at 80 °C was found to afford **3aa** in 75% yield (Scheme 2).

As shown in Table 2, the reactions of **2a** with **1n** and **1o** proceeded in low product yields (ca. 20%, entries 16 and

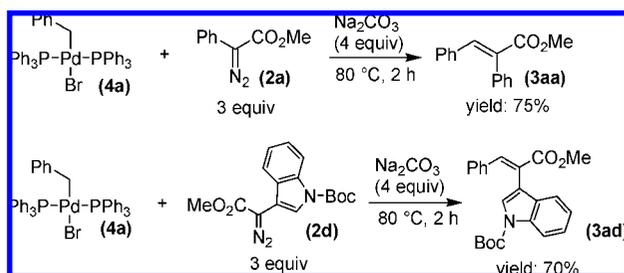
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**Scheme 1.** Proposed Catalytic Cycle



17). On the basis of TLC monitoring of the reaction mixtures, complete **1n** and **1o** consumption was achieved in 3 h.

**Scheme 2.** Coupling Reactions of Palladium Complex **4a** with **2a** and **2d**

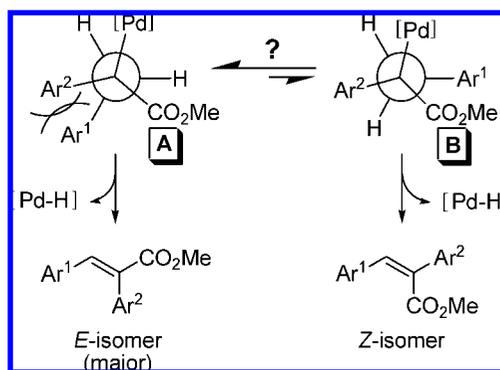


Pertinent to the poor results, the reactions of Pd(0)/PPh<sub>3</sub> with **1n** and **1o** failed to yield the corresponding organopalladium complexes. Therefore, the low product yields for **1n** and **1o** are probably associated with the difficulty in generating the key organopalladium intermediates. We also found that diazoacetate **2d** containing an indole moiety reacted with **1a** to afford **3ad** in ca. 8% yield (entry 18), along with significant dimer formation from the diazo reagent. Yet, a stoichiometric reaction of **4a** with **2d** afforded **3ad** in 70% yield (Scheme 2). Thus, the reactions with heterocyclic diazoesters may necessitate independent optimization.

In summary, a stereoselective synthesis of *E*- $\alpha,\beta$ -diarylacrylates was developed by the Pd-catalyzed coupling

reaction of benzyl bromides and  $\alpha$ -aryldiazoesters. Indeed, the observed *E*-selectivity of the coupling reaction appears intriguing. It is conceivable that the stereochemistry of the alkene product would be determined by the *syn*- $\beta$ -elimination step of complex **III**. By product inspection, transition state **A** (Scheme 3) for the formation of *E*-trisubstituted alkene

**Scheme 3.** Plausible Transition States for the  $\beta$ -Elimination Step



features two eclipsing aryl groups. According to a related work by Barluenga and co-workers,<sup>9c</sup> the transition state in the  $\beta$ -elimination for formation of trisubstituted alkenes should favor two bulky groups in a *trans*-arrangement, and a *Z*-alkene product is anticipated. However, the observed *E*-trisubstituted acrylate formation is incompatible with this notion.<sup>12</sup> At this juncture, the preference for the seemingly “less favored” transition state is not clear and is under separate investigation.

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**Supporting Information Available:** Detail experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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