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# Palladium-Catalyzed Cross Coupling Reaction of Benzyl Bromides with Diazoesters for Stereoselective Synthesis of (*E*)-α,*β*-Diarylacrylates

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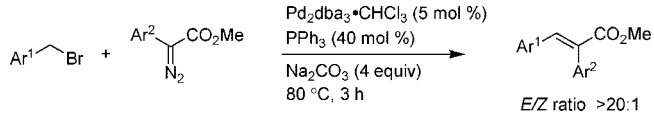
## ABSTRACT




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

α-Diazocarbonyl compounds are versatile reagents for organic synthesis.[1] With transition metal catalysts[2a] (e.g., Rh,[2b,c] Cu,[3a−c] Au,[3b,e] Ag,[3d] Ru[3f,g,4]), α-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 formation. Previously, we described that ruthenium complexes of porphyrins and π-aromatics can effect highly stereoselective heterocycle formation via a carbenoid C−H insertion reaction of α-diazocarbonyl compounds.[4]

Coupling reaction of organopalladium complexes with carbon nucleophiles is a fundamental process that underlies many Pd-catalyzed C−C bond formation reactions.[5] The carbon nucleophiles include organometallic reagents (e.g., organoboron),[6a] alkenes,[6b,c] and arenes,[6d,e] 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.[7] In the light of these findings, we envisage the

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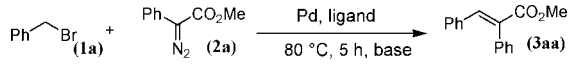
**Table 1.** Optimization of Reaction Conditions[a]




| entry | 1a:2a | Pd source (5 mol %) | ligand (40 mol %) | base (4 equiv) | solvent % | convn[b] % | yield[b,c] |
|---|---|---|---|---|---|---|---|
| 1 | 1:1.2 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $K_2CO_3$[a] | toluene | 68 | 37 |
| 2 | 1:1.2 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | *i*-$Pr_2NEt$[a] | toluene | 80 | 31 |
| 3 | 1:1.2 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$[a] | toluene | 80 | 44 |
| 4 | 1:1.2 | $Pd_2dba_3$·$CHCl_3$ | $AsPh_3$ | $Na_2CO_3$ | toluene | 38 | 26 |
| 5 | 1:1.2 | $Pd_2dba_3$·$CHCl_3$ | $PCy_3$ | $Na_2CO_3$ | toluene | 39 | 0 |
| 6 | 1:1.2 | $Pd_2dba_3$·$CHCl_3$ | dppb[f] | $Na_2CO_3$ | toluene | 53 | 0 |
| 7 | 1:2 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | toluene | 80 | 63 |
| 8 | 1:2 | $Pd(OAc)_2$[d] | $PPh_3$ | $Na_2CHO_3$ | toluene | 70 | 64 |
| 9 | 1:2 | $[pd(allylCl)]_2$ | $PPh_3$ | $Na_2CO_3$ | toluene | 56 | 38 |
| 10[d] | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | THF | 100 | 87 |
| 11 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | dioxane | 100 | 87 |
| 12 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | toluene | 100 | 85 |
| 13 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | $CH_3CN$ | 93 | 46 |
| 14 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | acetone | 100 | 80 |
| 15 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | DCE | 67 | 63 |
| 16 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$ | $Na_2CO_3$ | DMF | 87 | 43 |
| 17 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | none | $Na_2CO_3$ | THF | 29 | 0 |
| 18 | 1:2 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$[g] | $Na_2CO_3$ | toluene | 59 | 48 |
| 19 | 1:3 | $Pd_2dba_3$·$CHCl_3$ | $PPh_3$[h] | $Na_2CO_3$ | toluene | 88 | 78 |
| 20 | 1:3 | none | $PPh_3$ | $Na_2CO_3$ | THF | 55 | 0 |

[a] The reactions were carried out in a 0.2 mmol scale of **1a**. [b] Conversions and yields were determined by GC/FID using tetradecane as internal standard. [c] The percentage yield is based on **1a** conversion. [d] The reaction was run for 3 h. [e] 10 mol % of $Pd(OAc)_2$ was employed. [f] 2.5 mol % of $Pd2dba_3$·$CHCl_3$ was employed. [g] 30 mol % of ligand. [h] 20 mol % of ligand. [i] 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.[8] Indeed, some reports on the Pd-catalyzed cross coupling reactions of aryl/vinyl halides with carbenes derived from α-diazocarbonyls emerged recently in the literature.[9] In this work, we describe a stereoselective synthesis of *E*-α,*β*-diarylacrylates by the Pd-catalyzed reaction of benzyl bromides with α-aryldiazoesters. α,*β*-Diarylacrylates are common scaffolds in pharmaceutically active compounds, and Perkin aldol condensation is frequently employed for their synthesis.[10] However, the Perkin aldol reaction suffers from a rather limited substrate scope and low product yields.[10a] Here we showed that the Pd-catalyzed reaction of benzyl bromides with aryldiazoacetates 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 α-phenyldiazoacetate **2a** in the presence of $Pd_2dba_3$·$CHCl_3$ (5 mol %), $PPh_3$ (40 mol %), and $K_2CO_3$ (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 $^1H$ NMR and X-ray crystallography (for acrylate **3ma**; see Supporting Information).

While the use of *i*-$Pr_2NEt$ as base for the Pd-catalyzed reaction gave **3aa** in 31% yield, a slightly better result (44% yield) was obtained with $Na_2CO_3$ as base (entries 2 and 3). Prior to this work, Van Vranken and co-workers[9f] 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,[9f] $AsPh_3$ was found to be the best ligand for the "**1a** + EDA" reaction. However, when $AsPh_3$ (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 $PCy_3$ 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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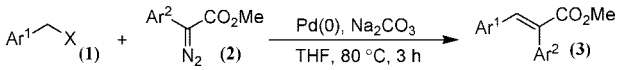
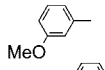
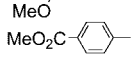
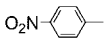
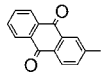
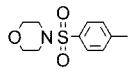
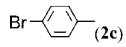
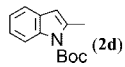
**Table 2.** Palladium-Catalyzed Cross Croupling Reactions of Benzyl Bromides with Diazoesters[a]




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

[a] Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $Na_2CO_3$ (0.8 mmol), $Pd_2dba_3$·$CHCl_3$ (5 mol %), $PPh_3$ (40 mol %), THF (2 mL), 80 °C for 3 h. [b] Isolated yield. [c] The percentage yield based on conversion. [d] The conversion of **1b** is 74%. [e] The conversion of **1a** is 67%. [g] NMR yield. [h] The conversion of **1a** is ca. 40%.

performed under the conditions: **1a** (1 equiv), **2a** (2 equiv), $Na_2CO_3$ (4 equiv), $Pd_2dba_3$·$CHCl_3$ (5 mol %) in toluene at 80 °C for 5 h (entry 7). Employing other Pd precursors such as $Pd(OAc)_2$ and $[Pd(allyl)Cl]_2$ 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, $PPh_3$ (40 mol %) is essential for the acrylate formation. For example, in the absence of the $PPh_3$ ligand, no **3aa** formation was observed (entry 17). Yet, performing the "**1a** + **2a**" reaction using 30 mol % of $PPh_3$ 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 $h^{-1}$) 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 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 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.[10a] 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 precedented in amino- and methoxycarbene palladium complexes.[8a,b,d] $\beta$-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 $PPh_3$)[11] 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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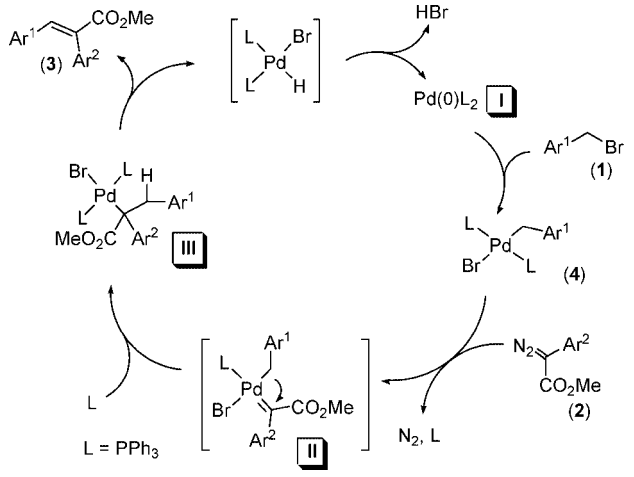
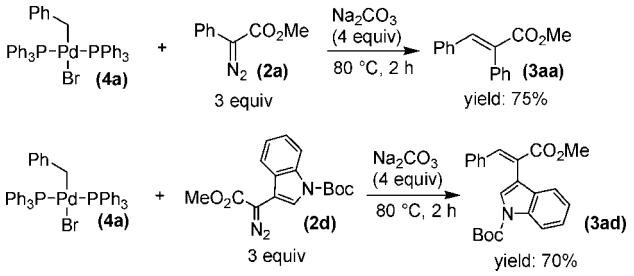
**Scheme 1.** Proposed Catalytic Cycle




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

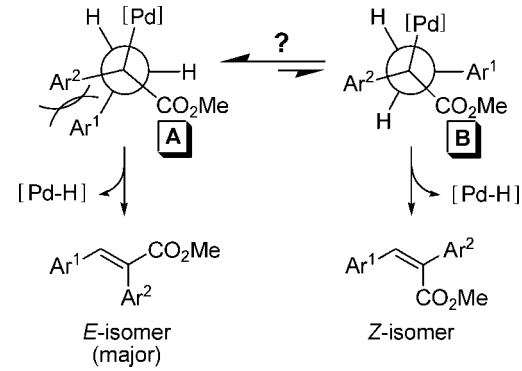
**Scheme 2.** Coupling Reactions of Palladium Complex **4a** with **2a** and **2d**




Pertinent to the poor results, the reactions of Pd(0)/$PPh_3$ 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*-α,*β*-diarylacrylates was developed by the Pd-catalyzed coupling reaction of benzyl bromides and α-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*-*β*-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 *β*-Elimination Step




features two eclipsing aryl groups. According to a related work by Barluenga and co-workers,[9e] the transition state in the *β*-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.[12] 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.

OL8026076

(12) (*E*)-Trisubstituted acrylates formation was also observed for the Perkin aldol condensation, and we thank one of the reviewers for bringing these references to our attention: (a) Zimmermann, H.; Ahramjian, L. *J. Am. Chem. Soc.* **1959**, *81*, 2086. (b) Pálinkó, I.; Török, B.; Tasi, G.; Körtvélyesi, T. *Experimental and Computational Tools for Mechanistic Study: A Modified Perkin Condensation leading to Alpha-Phenylcinnamic Acid Isomers*; Electronic Conference on Trends in Organic Chemistry-1, June 12−July 7, 1995.