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Palladium-catalyzed carbene insertion into benzyl bromides

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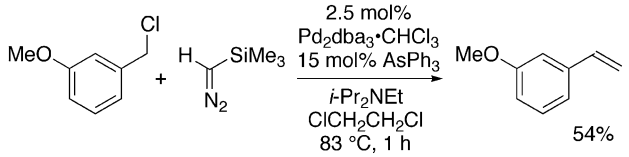
Abstract—Palladium can catalyze the insertion of ethyl diazoacetate into benzyl bromides. The key step in the catalytic cycle is the migratory insertion of a carbene, derived from ethyl diazoacetate, into a Pd–C bond.

1. Introduction

Palladium-catalyzed CO insertion offers a precise and powerful method for introduction of one carbon units. In contrast, the analogous palladium-catalyzed insertion of carbenes has received little attention. In published crystal structures of alkylpalladium–carbene complexes, the Pd-alkyl bond is generally aligned with the empty p-orbital of the carbene ligand,[1] suggesting that migratory insertion of the carbene ligand could be facile when the carbene is not stabilized by donor groups. The first reported examples of palladium-catalyzed carbene insertion using trimethylsilyldiazomethane[2] (TMSD) suffered from low turnover and palladium-catalyzed protodesilylation[3] (Scheme 1). Since that time, Ihara and co-workers showed that Pd(II) can catalyze the polymerization of ethyl diazoacetate in the presence of amines.[4] In addition, several elegant examples of non-catalytic carbene insertion have been documented for palladium carbene complexes. Albéniz and co-workers showed that a Fischer carbene ligand could insert into a Pd–C_6F_5 bond, although the reaction was not catalytic.[5] Two more recent examples of stoichiometric insertion of Fischer carbenes into Pd–C bonds have been reported.[6,7] Solé and co-workers showed that dichlorocarbene, ethyl diazoacetate, and TMSD can insert into the Pd–C bond of a 4-membered palladacycle, again a non-catalytic reaction.[8] In a recent advance, Montgomery and Ni demonstrated that TMSD can participate in a nickel-catalyzed [4+2+1] reaction.[9]

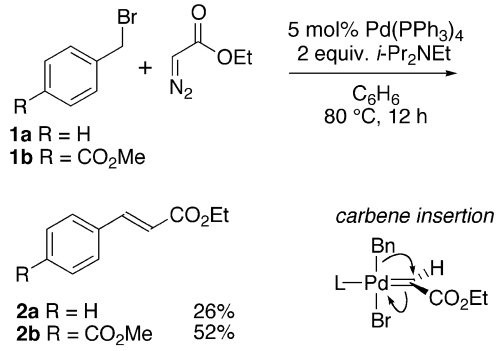


Scheme 1. Precedented insertion of TMSD.

This communication describes the first example of palladium-catalyzed carbene insertion leading to homologation without loss of the carbene functional group. The deceptively simple one-step transformation of benzyl bromides to cinnamates has previously been achieved using a tandem alkylation/sulfenate elimination reaction under phase transfer conditions.[10] This work reveals the broader potential for migratory insertion of carbenes in metal-catalyzed synthetic transformations.

2. Results and discussion

In theory, α-diazoesters could react with benzyl halides without the aid of a catalyst. However, when 1.5 equiv ethyl diazoacetate was added slowly to benzyl bromide at 83 °C over 12 h with Hünig's base in the absence of a palladium catalyst, no reaction was observed. In contrast, when



Scheme 2. Initial homologation experiments.

Keywords: Palladium; Carbene; Stoichiometric insertion.
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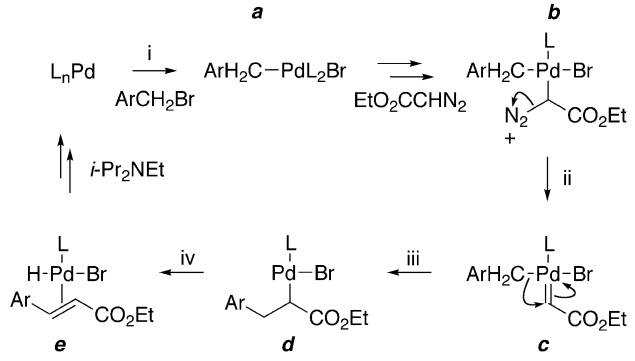
5 mol% $(Ph_3P)_4Pd$ was included the corresponding α,β-unsaturated ester was isolated in 26% yield (Scheme 2). At the end of the reaction, the ethyl diazoacetate was depleted, but unreacted benzyl bromide was still present. Using excess ethyl diazoacetate did not improve the yield, implying that the yield was limited by catalyst turnover.

When the reaction was carried out on bromide **1b** a more gratifying 52% yield of the homologation product was obtained. A series of experiments was carried out with $Pd_2dba_3 \cdot CHCl_3$ in order to identify the best ligand and the best ratio of ligand to palladium (Table 1). With triphenylphosphine, the best results were obtained with a 2:1 ratio of phosphine to palladium. A hindered, strongly donating ligand did not improve the results with a ligand to palladium ratio of 1:1. Since phosphines are known to react with ethyl diazoacetate[11] and benzyl bromide,[12] triphenylarsine was tested as a ligand. At a ligand to palladium ratio of 4:1 triphenylarsine gave much better results than triphenylphosphine. A control reaction with triphenylarsine alone generated no homologation product. Using 2.5 mol% $Pd_2dba_3 \cdot CHCl_3$ and 20 mol% Ph_3As, benzene proved to be the best solvent for the reaction. Other typical solvents such as MeCN, DME, THF, and 1,2-dichloroethane gave yields between 50 and 60%.

Table 1. Ligand effect on insertion of ethyl diazoacetate into bromide **1b** using 2.5 mol% $Pd_2dba_3 \cdot CHCl_3$

Ligand	Yield
20 mol% Ph_3P	28%
10 mol% Ph_3P	55%
5 mol% Ph_3P	32%
5 mol% Cy_2P(*o*-biphenyl)	25%
20 mol% Ph_3As	74%
10 mol% Ph_3As	28%
5 mol% Ph_3As	27%

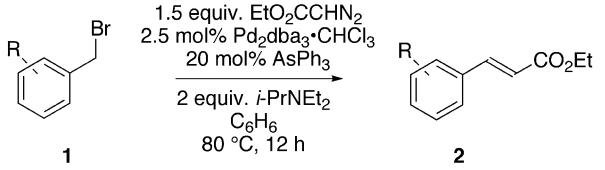
Since the migratory insertion of carbene ligands into palladium–carbon bonds is now well precedented, it is reasonable to propose a mechanism involving the steps shown in Scheme 3: (i) oxidative addition to benzyl bromide,[13] (ii) carbene formation,[14] (iii) migratory carbene insertion,[8] and (iv) beta-hydride elimination. There is literature precedent for each of these processes at or below room temperature; however, no product was formed unless the reaction was heated. The slow steps may involve isomerization between *trans*-L_2BnPdX to *cis*-L_2BnPdX.



Scheme 3. Proposed catalytic cycle.

A series of substituted benzylic bromide starting materials was examined in order to better understand the scope and limitations of the reaction (Table 2). When the reaction was applied to 3-methoxybenzyl bromide **1c** the starting materials remained virtually un-reacted, suggesting that there was no catalyst turnover. In general, electron-rich benzyl bromides gave low yields and low conversion. For substrates **1a**, **1d**, **1e**, and **1f** the mass balance was poor, even when starting material was observed in the final reaction mixture (Table 2). The best yields were obtained when the benzyl bromide was substituted by carboethoxy groups (substrates **1b** and **1h**). No starting material remained at the end of these reactions.

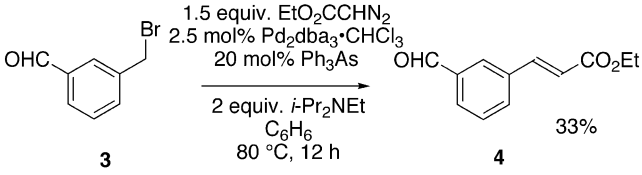
Table 2. Arene substituent effects



	R	Yield	S.M.?
1a	H	25%	Yes
1b	4-MeO_2C	74%	No
1c	3-MeO	0%	Yes
1d	2,4,6-Me_3	27%	Yes
1e	3,5-F_2	51%	Yes
1f	3-Cl	50%	Yes
1 g	3-O_2N	52%	No
1 h	3-MeO_2C	68%	No

When ethyl cinnamate **2a** was added to the reaction of substrate **1b**, 93% of the ethyl cinnamate was recovered at the end of the reaction. Thus, product decomposition does not account for low yields. Since the starting material **1b** and ethyl diazoacetate were shown to be stable to the reaction conditions in the absence of catalyst, the mass deficit is probably due to a competitive catalytic process. The only additional products visible by TLC appeared at the baseline. When eluted from silica gel, these low-mobility by-products gave a ^1H NMR spectrum that did not integrate to enough protons in the aromatic region to account for the fate of the benzyl bromide that was not converted to ethyl cinnamate.

As a test of functional group compatibility, the homologation reaction was carried out on 3-formylbenzyl bromide **3**. Even though the yield for this homologation reaction was lower than that for the analogous ester substrate **1h**, the selectivity was extraordinary for a one step transformation (Scheme 4).



Scheme 4. Selectivity of Pd-catalyzed insertion in the presence of an aldehyde.

3. Conclusion

In summary, we have shown that palladium can catalyze the homologation of alkyl halides to α,β-unsaturated carbonyls. This report describes the first practical application of palladium-catalyzed reaction involving insertion of a carbene ligand into a Pd–C bond. The reaction works best with electron deficient benzyl halide substrates, apparently because they resist decomposition under the reaction conditions. Ultimately, related migratory palladium-catalyzed insertion of carbene ligands could be used to install chiral centers in a manner analogous to CO insertion.

4. Experimental

4.1. General procedure

A flame dried round bottom flask, equipped with a reflux condenser and a magnetic stir bar, was charged with $Pd_2(dba)_3 \cdot CHCl_3$ (13 mg, 0.013 mmol) and triphenylarsine (32 mg, 0.104 mmol). The flask was evacuated and backfilled with an atmosphere of argon three times. Anhydrous benzene (5.0 mL) was added, and the solution was heated to reflux. After 5 min, the resulting clear yellow solution was cooled to room temperature. *N*,*N*-diisopropylethylamine (175 μL, 1.00 mmol) and a solution of the appropriate benzylic bromide (0.5 mmol) in anhydrous benzene (5.0 mL) were added. The solution was returned to reflux. Ethyl diazoacetate (0.11 mL, 0.76 mmol) in anhydrous benzene (1.0 mL) was added via syringe pump over 12 h, after which time the mixture was cooled to room temperature. EtOAc (50 mL) was added, and the organic phase was washed with water (3×10 mL) and dried (Na_2SO_4). Concentration in vacuo afforded a brown residue, which was purified by flash chromatography

4.1.1. (*E*)-Ethyl cinnamate (2a). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[15] **2a** in 25% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J=16.0 Hz, 1H), 7.51–7.53 (m, 2H), 7.37–7.39 (m, 3H), 6.44 (d, J=16.0 Hz, 1H), 4.25 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H).

4.1.2. Methyl 4-((*E*)-2-(ethoxycarbonyl)vinyl)benzoate (2b). Following the general procedure, purification by flash chromatography (93:7 hexanes/EtOAc) afforded the previously described[16] **2b** in 74% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J=8.3 Hz, 2H), 7.70 (d, J=16.0 Hz, 1H), 7.59 (d, J=8.3 Hz, 2H), 6.52 (d, J=16.0 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.93 (s, 3H), 1.35 (t, J=7.1 Hz, 3H).

4.1.3. (*E*)-Ethyl 3-mesitylacrylate (2d). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[17] **2d** in 27% yield: ^{1}H NMR δ 7.84 (d, J=16.4 Hz, 1H), 6.89 (s, 2H), 6.05 (d, J=16.4 Hz, 1H), 4.27 (q, J=7.1 Hz, 2H), 2.32 (s, 6H), 2,28 (s, 3H), 1.34 (t, J=7.1 Hz, 3H).

4.1.4. (*E*)-Ethyl 3-(3,5-difluorophenyl)acrylate (2e). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[18] **2e** in 51% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, J=16.1 Hz, 1H), 7.01-7.05 (m, 2H), 6.83 (tt, J=8.7, 2.3 Hz, 1H), 6.42 (d, J=16.1 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H).

4.1.5. (*E*)-Ethyl 3-(3-chlorophenyl)acrylate (2f). Following the general procedure, purification by flash chromatography (95:5 hexanes/EtOAc) afforded the previously described[19] **2f** in 50% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, J=16.0 Hz, 1H), 7.51 (t, J=1.6 Hz, 1H), 7.30-7.40 (m, 3H), 6.44 (d, J=16.0 Hz, 1H), 4.27 (q, J=7.1 Hz, 2H), 1.34 (t, J=7.1 Hz, 3H).

4.1.6. (*E*)-Ethyl 3-(3-nitrophenyl)acrylate (2g). Following the general procedure, purification by flash chromatography (90:10 hexanes/EtOAc) afforded the previously described[20] **2g** in 52% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.39 (t, J=1.8 Hz, 1H), 8.24 (dd, J=8.1, 2.1 Hz, 1H), 7.81-7.85 (m, 1H), 7.72 (d, J=16.0 Hz, 1H), 7.59 (t, J=8.1 Hz, 1H), 6.57 (d, J=16.0 Hz, 1H), 4.30 (q, J=7.1 Hz, 2H), 1.36 (t, J=7.1 Hz, 3H).

4.1.7. Methyl 3-((*E*)-2-(ethoxycarbonyl)vinyl)benzoate (2h). Following the general procedure, purification by flash chromatography (93:7 hexanes/EtOAc) afforded the previously described[21] **2h** in 68% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (t, J=1.5 Hz, 1H), 8.05 (dt, J=7.8, 1.5 Hz, 1H), 7.69-7.71 (m, 1H and d, J=16.0 Hz, 1H), 7.47 (t, J=7.8 Hz, 1H), 6.52 (d, J=16.0 Hz, 1H), 4.28 (q, J=7.1 Hz, 2H), 3.94 (s, 3H), 1.35 (t, J=7.1 Hz, 3H).

4.1.8. (*E*)-Ethyl-3-(3-formylphenyl)acrylate (4). Following the general procedure, purification by flash chromatography (93:7 hexanes/EtOAc) afforded **4** in 33% yield: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.03 (t, J=1.7 Hz, 1H), 7.90 (dt, J=7.5, 1.4 Hz, 1H), 7.77-7.79 (m, 1H), 7.74 (d, J=16.0 Hz, 1H), 6.54 (d, J=16.0 Hz, 1H), 4.29 (q, J=7.1 Hz, 2H), 1.35 (t, J=7.1 Hz, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 191.7, 166.6, 142.9, 137.0, 135.6, 133.6, 131.1, 129.8, 128.9, 120.3, 60.8, 14.4; FT-IR (thin-film) 2980, 2925, 2846, 1705, 1640 cm^{-1}; GC-MS (EI) *m*/*z* 204(17), 175(20), 159(41), 131(52), 103(86), 77(100).

Acknowledgements

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