

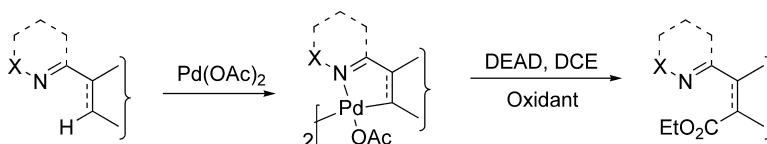
Communication

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Palladium-Catalyzed Oxidative Ethoxycarbonylation of Aromatic C–H Bond with Diethyl Azodicarboxylate

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Carboxylic acids and derivatives (e.g., esters) are valuable commodity chemicals and useful synthetic building blocks. A well established approach for carboxylic acids synthesis is the transition metal-catalyzed carbonylation of organic substrates containing C–halides and/or C=C bonds.¹ However, the catalytic carbonylation reaction is limited by (1) the necessity to handle hazardous gas often in high pressure and (2) the use of prefunctionalized substrates. From a standpoint of atom economy, direct functionalization of C–H bonds to C–CO₂R bonds is a highly desirable alternative.² To this end, Orito and co-workers previously reported Pd(OAc)₂-catalyzed direct carbonylation of aromatic amines for synthesis of five- and six-membered benzolactams.^{3,4} However, problems in regiocontrol of the carbonylation reaction remain to be addressed.

To achieve selective C–H bond functionalization, significant advances have been made by transition metal (Ru, Rh, Re, Pd)-mediated C–H bond cyclometallation assisted by directing functional groups.^{2d} Notably, Pd(OAc)₂-catalyzed regioselective *ortho*-C–H bond oxidation leading to C–C (aryl)^{2a,5} and C–heteroatom bond formations⁶ is attracting widespread attention. Although carbon monoxide insertion to palladacycles has been thoroughly investigated,⁷ developing catalytic protocols for *ortho*-selective C–H bond carbonylation based on this chemistry is exceedingly difficult because the depalladation process is often complicated by reduction of Pd(II) to Pd(0) under the CO atmosphere. Herein we disclose a Pd-catalyzed protocol for *ortho*-selective ethoxycarbonylation of aromatic C–H bonds using diethyl azodicarboxylate (DEAD) coupled with inexpensive oxidizing agents.⁸ This transformation is operated without the use of carbon monoxide and protection against air/moisture.

Initially we examined dialkyl azodicarboxylates as a potential reagent for C–H amination reactions.⁹ When palladacycle **5a** reacted with diethyl azodicarboxylate (DEAD, 1.5 equiv) in 1,2-dichloroethane (DCE) at 100 °C (Scheme 1), ester **2a** was formed in 83% yield accompanied with Pd black formation. Analogous reaction of **5b** with DEAD furnished **2b** in 80% yield. In both cases, the anticipated hydrazides were not formed. The structures of **2a** and **2b** have been confirmed by X-ray crystallography.¹⁰

Having established the stoichiometric reaction of the palladacycles with DEAD, we turned to develop a catalytic reaction of 2-arylpyridines with DEAD using appropriate oxidizing agents. To begin, treating **1a** with Pd(OAc)₂ (5 mol %), DEAD (2 equiv) and Cu(OAc)₂ (4 equiv) in DCE at 100 °C for 4 h afforded **2a** in 44% yield with 48% substrate conversion (Table 1, entry 1). After several trials, a protocol involving batchwise addition of DEAD (4 × 0.5 equiv) and 10 mol % of Cu(OAc)₂ was found to give better results; up to 82% substrate conversion with 88% product yield were achieved over 12 h (entry 2).¹¹ Yet, no further improvement in

Scheme 1. Reaction of Palladacycles with DEAD

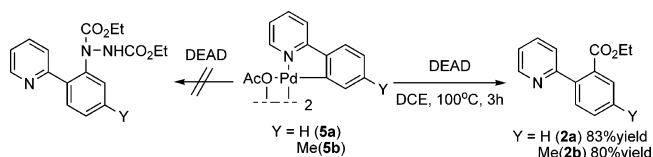


Table 1. Optimizing Reaction Conditions^a

entry	oxidant ^b	solvent	time/h	% conversion	% yield ^c
1	Cu(OAc) ₂ 4 equiv	DCE	4	48	44
2	Cu(OAc) ₂ 10 mol %	DCE	12	82	88
3	Oxone	DCE	6	100	91
4	K ₂ S ₂ O ₈	DCE	6	83	64
5	TBHP	DCE	6	88	88
6	CAN	DCE	6	72	n.d.
7	BQ	DCE	6	33	3
8 ^d	Oxone	DCE	6	33	48
9	Oxone	DMF	6	83	72
10	Oxone	1,4-dioxane	6	73	48
11	Oxone	MeOH	6	65	32
12	Oxone	acetone	6	51	22

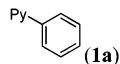
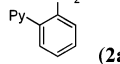
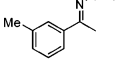
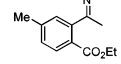
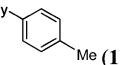
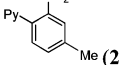
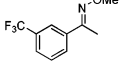
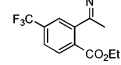
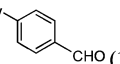
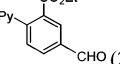
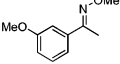
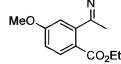
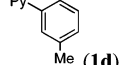
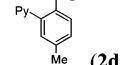
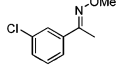
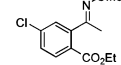
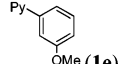
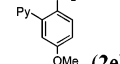
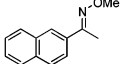
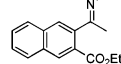
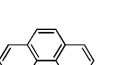
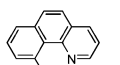
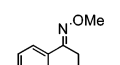
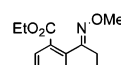
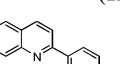
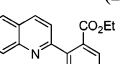
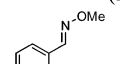
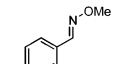
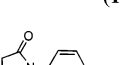
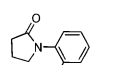
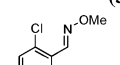
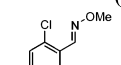
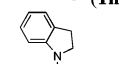
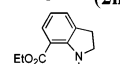
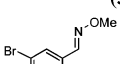
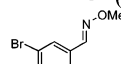
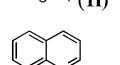
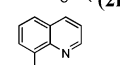
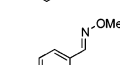
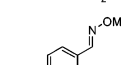
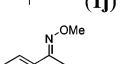
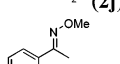
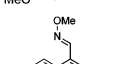
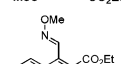
^a Reaction conditions: **1a** (0.5 mmol), DEAD (4 × 0.5 equiv/h for entries 3–12). ^b Batch-wise addition of oxidant (3 × 1 equiv/2h) for entries 3–12. ^c Conversion and product yield determined by GC/FID, the percentage yield based on conversion. ^d Reaction temperature: 60 °C.

product yield was obtained with Cu(OAc)₂ as the oxidant despite several protocol changes.

In a hope to achieve better substrate conversion and product yield, we examined other oxidants for the catalytic reaction. Gratifyingly, Oxone was found to be an effective oxidant for the Pd-catalyzed ethoxycarbonylation reaction. Treatment of **1a** (0.5 mmol) with Oxone (3 × 1 equiv), DEAD (4 × 0.5 equiv) and Pd(OAc)₂ (5 mol %) in DCE at 100 °C for 6 h, **2a** was obtained in 91% yield with complete substrate consumption (Table 1, entry 3). Employing ammonium cerium(IV) nitrate (CAN) and benzoquinone (BQ) as oxidants resulted in <5% product yield (entries 6–7). Other solvents such as DMF, 1,4-dioxane, MeOH, and acetone are less effective for this Pd-catalyzed reaction (entries 9–12).

The scope of the Pd-catalyzed ethoxycarbonylation reaction is depicted in Table 2. Pyrrolidinone **1h** and acetylindoline **1i** were converted to the corresponding esters in 84 and 80% yields under the Pd-catalyzed conditions (entries 8 and 9). For the direct carbonylation of the sp³ C–H bond, the reaction of 8-methylquino-

Table 2. Pd-Catalyzed Ethoxycarbonylation of Aromatic C–H Bonds

entry	substrate	product	%conv	%yield ^c	entry	substrate	product	%conv	%yield ^c
1 ^b	 (1a)	 (2a)	100	85	12 ^d	 (3b)	 (4b)	88	74
2 ^b	 (1b)	 (2b)	100	82	13 ^d	 (3c)	 (4c)	57	68
3 ^b	 (1c)	 (2c)	54	78	14 ^d	 (3d)	 (4d)	100	72
4 ^b	 (1d)	 (2d)	100	82	15 ^d	 (3e)	 (4e)	74	76
5 ^b	 (1e)	 (2e)	79	80	16 ^d	 (3f)	 (4f)	86	78
6 ^b	 (1f)	 (2f)	100	87	17 ^d	 (3g)	 (4g)	82	84
7 ^b	 (1g)	 (2g)	62	79	18 ^{d, h}	 (3h)	 (4h)	82	27
8 ^b	 (1h)	 (2h)	76	84	19 ^d	 (3j)	 (4j)	66	85
9 ^b	 (1i)	 (2i)	74	80	20 ^{d, i}	 (3k)	 (4k)	72	76
10 ^{c, f}	 (1j)	 (2j)	47	83	21 ^d	 (3l)	 (4l)	58	69
11 ^{d, g}	 (3a)	 (4a)	100	79	22 ^d	 (3m)	 (4m)	62	82

^a Reaction conditions: substrate (0.5 mmol), DEAD (4 × 0.5 equiv), Pd(OAc)₂ (5 mol %), DCE (1 mL), 100 °C for 6 h. ^b Oxidant: Oxone (3 × 1 equiv). ^c Oxidant: 10 mol % of Cu(OAc)₂. ^d Oxidant: K₂S₂O₈ (3 × 1 equiv). ^e The percentage yield based on conversion. ^f With 3 equiv of Oxone as oxidant: yield for **2j** = 23% based on 61% conversion. ^g With 3 equiv of Oxone as oxidant: yield of **4a** = 35%, *ortho*-hydroxylation product = 56%. ^h Diester formation = 52% yield. ⁱ DEAD (6 × 0.5 equiv), K₂S₂O₈ (5 × 1 equiv) for 10 h.

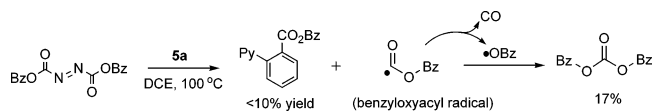
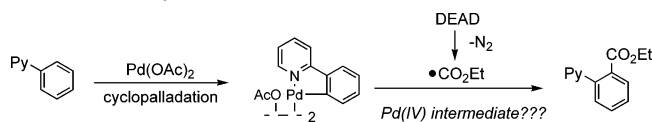
line (**1j**) with DEAD, Oxone, and Pd(OAc)₂ (5 mol %) gave **2j** in only 23% yield (61% conversion). However, when Cu(OAc)₂ (10 mol %) was employed as the oxidant, **2j** was obtained in 83% yield (47% conversion, entry 10). Yet, using more Cu(OAc)₂ (2 equiv) did not give higher yield and substrate conversion.

Facile transformation of *O*-methyl oximes of acetophenones to their *ortho*-esters was achieved using DEAD and K₂S₂O₈ (3 × 1 equiv) as oxidant (entries 11–22). In this reaction, functional groups such as Br, MeO, and CHO were all tolerated (entries 3, 5, 14, 20, 21). With meta-substituted substrates, the 2,4-regioisomers were obtained selectively (entries 4, 12–15, 20). The observed selectivity is linked to the regioselectivity of the cyclopladdation step¹² which is known to be steric sensitive.^{6c,7} By reacting Pd(OAc)₂ with 2-(3'-methoxyphenyl)pyridine (**1e**), we obtained palladacycle **5c** (X-ray structure characterized) as a single regioisomer in 90% yield. Other regioisomers were not detected by ¹H NMR analysis of the reaction mixture. As anticipated, **5c** reacted with DEAD to give **2e** exclusively in 85% yield.¹⁰

The Pd-catalyzed reaction of *O*-methyl oxime benzaldehyde (**3h**) with DEAD and K₂S₂O₈ furnished a mixture of mono- (27%) and diesters (52%; entry 18). Nevertheless, the reactions employing oximes of substituted benzaldehydes produced monoesters exclu-

sively in good yields (entries 19–22). Under this condition, ketones (e.g., acetophenone) and esters (e.g., ethyl benzoate) were ineffective substrates for the ethoxycarbonylation, whereas the reaction with *N*-(*p*-methoxyphenyl)benzylaldehyde imines gave <15% conversion and <50% product yield.¹⁰

We found that radical scavengers such as galvinoxyl would exert detrimental effect (<40% ester formation) to the “**5a** + DEAD” reaction,^{5h} indicative of the radical intermediates. Unlike DEAD, other azodicarboxylates [ROC(O)N=N(O)COR; R = benzyl, *tert*-butyl, trichloromethyl, dipiperidine] are poor reagents for converting **5a** to the product esters/amides (<13% yield).¹³ When **5a** reacted with an equimolar mixture of DEAD and dibenzyl azodicarboxylate, **2a** and the benzyl ester were formed in 62 and 9% yield, respectively. Whereas the DEAD was found to be completely consumed, ~25% dibenzyl azodicarboxylate was recovered unchanged.¹³ For the reaction of **5a** with dibenzyl azodicarboxylate, dibenzyl carbonate was obtained in 17% yield from a complicated reaction mixture.¹⁴ We believed that thermal decomposition of the azodicarboxylate would generate benzyloxyacyl radical,^{15,16} some of which would undergo decarbonylation to form benzyloxy

Scheme 2. Reaction of **5a** with Dibenzyl Azodicarboxylate**Scheme 3.** Proposed Mechanism

radical. As such, dibenzyl carbonate was produced by combining the benzyloxyacyl radicals with the benzyloxy radical (Scheme 2).

On the basis of the above findings, the catalytic reaction should be initiated by cyclopalladation of the *ortho*-C–H bond to form a palladacycle. The palladacycle subsequently reacts with the ethoxyacyl radicals, generated from thermal decomposition of DEAD, to afford the product esters (Scheme 3). At this stage, the mechanism for the radical insertion reaction to palladacycles remains unclear.¹⁷ Indeed, systemic mechanistic studies on radical addition to organometallic complexes are sparse in the literature.^{17,18} A plausible pathway for the radical insertion to Pd–C bond would be via formation of Pd(IV) species¹⁹ especially under oxidizing conditions,^{5h,g,6h} and that would be a subject for further investigation.

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

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