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Palladium Catalyzed Intermolecular Aminoacetoxylation of Alkenes and the Influence of PhI(OAc)₂ on Aminopalladation Stereoselectivity

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Abstract

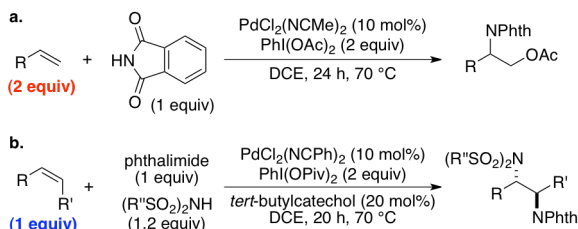
A modified protocol has been identified for Pd-catalyzed intermolecular aminoacetoxylation of terminal and internal alkenes that enables the alkene to be used as the limiting reagent. The results prompt a reassessment of the stereochemical course of these reactions. X-ray crystallographic characterization of two of the products, together with isotopic labeling studies, show that the amidopalladation step switches

from a *cis*-selective process under aerobic conditions to a *trans*-selective process in the presence of diacetoxyiodobenzene.

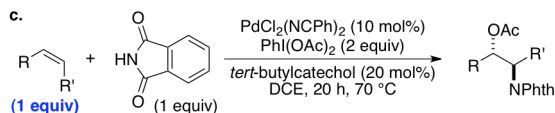
In recent years, a number of palladium-catalyzed methods have been reported for aminoacetoxylation¹ and diamination² of alkenes with diacetoxyiodobenzene [PhI(OAc)₂] as the stoichiometric oxidant. These difunctionalization reactions are initiated by nucleopalladation of the alkene,³ followed by PhI(OAc)₂-induced oxidative cleavage of the Pd–C bond, presumably via Pd^{III} or Pd^{IV} intermediates.⁴ In 2006, Liu and Stahl reported a method for intermolecular aminoacetoxylation of terminal alkenes that employs two equivalents of alkene with respect to the nitrogen nucleophile (Scheme 1a).^{1b} Recently, Martínez and Muñiz identified modified conditions that enabled regio- and diastereoselective intermolecular diamination of internal alkenes with the alkene as the limiting reagent (Scheme 1b).^{2c} Here, we show that similar modified conditions are effective in intermolecular aminoacetoxylation reactions (Scheme 1c). In the course of this work, we obtained new mechanistic insights into the stereochemical course of these reactions, which prompted a reassessment of the originally proposed mechanistic pathway. The data show that PhI(OAc)₂ can alter the stereochemical course of the aminopalladation pathway relative to aerobic oxidative amination reactions.

Scheme 1. 1,2-Difunctionalization of Alkenes

Previous work:



This work:



The catalyst conditions recently reported for diamination of alkenes (Scheme 1b^{2c}) were used as a starting point to explore improved aminoacetoxylation conditions. Switching from PhI(OPiv)₂ to

PhI(OAc)₂ as the oxidant enabled selectivity for aminoacetoxylation products (Scheme 1c). The scope of this reaction is similar to that observed for the diamination chemistry (Table 1). Representative terminal allyl ethers undergo the aminoacetoxylation in good yields (entries 1-4), as expected based on the earlier precedents. In addition, three allyl benzenes are successful (entries 5-7). These compounds are commonly difficult substrates in palladium catalysis, as they can undergo isomerization to the internal alkene in the presence of the palladium catalyst. Nevertheless, moderate yields could be obtained in the aminoacetoxylation reaction. Internal alkenes, such as (*Z*)- β -methylstyrene and (*Z*)-cinnamyl methyl ether, also undergo aminoacetoxylation without the formation of side products (entries 8-9). Only one diastereomer of the product is obtained.

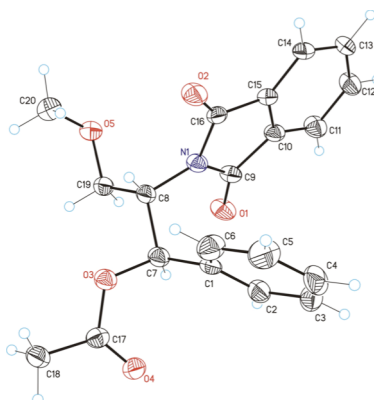
Table 1. Aminoacetoxylation of Alkenes

entry	alkene	product	yield (%) ^a
1			72
2			66
3			71
4			40
5			56
6			50
7			51
8			81
9			61

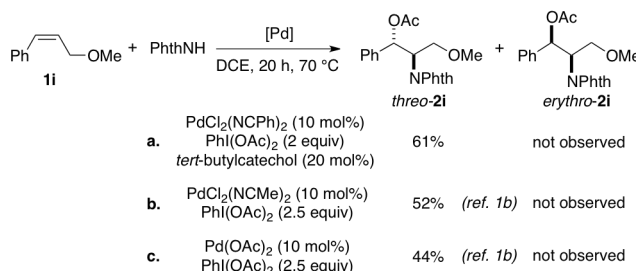
^a Isolated yield after chromatography

The relative stereochemistry of compound **2i** was established by single-crystal X-ray diffraction analysis to be the *threo* isomer, and this product is formed exclusively under the optimized reaction conditions (Figure 1).⁵ This stereochemical assignment is opposite to that proposed in the aminoacetoxylation reactions reported previously.^{1b} The latter study proposed formation of *erythro-2i* on the basis of previously reported NMR characterization data for this compound.⁶ The single-crystal X-ray diffraction data reported here reveal that the NMR characterization data were inaccurate. Control experiments, summarized in Scheme 2, show that *threo-2i* is the sole aminoacetoxylation product obtained under several different catalytic conditions, including those from the original report by Liu and Stahl.^{1b} The stereochemical course of these aminoacetoxylation reactions match that of the diamination reaction in Scheme 1b, which was similarly supported by X-ray crystallography.^{2c}

Figure 1. X-Ray Crystal Structure of *threo-2i*.



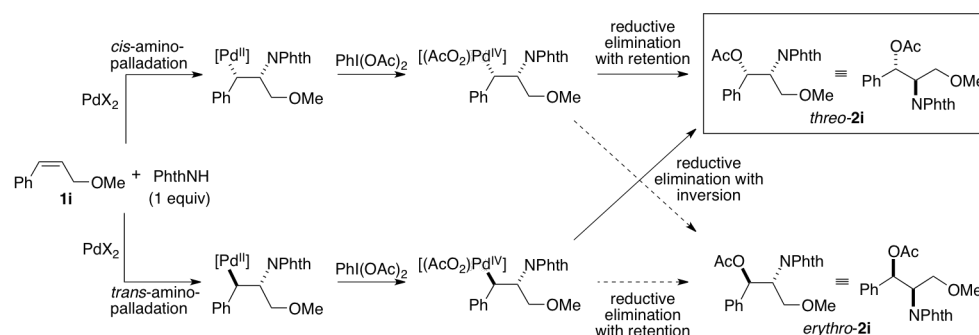
Scheme 2. Exclusive formation *threo-2i* across related catalyst systems.



The relative stereochemistry of product **2i** is controlled by the stereochemical course of the individual steps in the mechanism (Scheme 3). Following *cis*- or *trans*-aminopalladation of the alkene, oxidation of

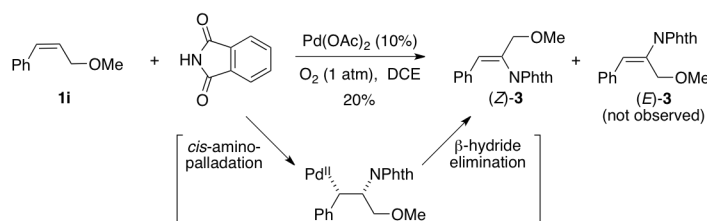
the Pd-alkyl species in the presence of $\text{PhI}(\text{OAc})_2$ is expected to generate a high-valent Pd-alkyl species that undergoes facile reductive elimination (for simplicity, the high-valent intermediate is illustrated as a Pd^{IV} species). This intermediate could undergo reductive elimination of the aminoacetoxylated product either by an $\text{S}_{\text{N}}2$ -type transition state with inversion of stereochemistry,⁷ or by a concerted three-centered transition state with retention of stereochemistry.^{8, 9} Thus, *threo*-**2i** could be generated via *cis*-aminopalladation of the alkene and acetoxylation with retention of stereochemistry or *trans*-aminopalladation of the alkene and acetoxylation with inversion of stereochemistry.

Scheme 3. Stereochemical Pathways for the Aminoacetoxylation of Substrate **1i**.



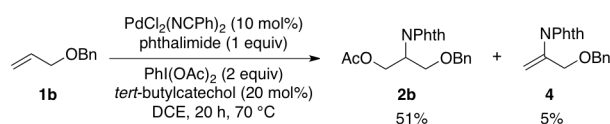
Liu and Stahl previously tested the reactivity of substrate **1i** under aerobic oxidation conditions [i.e., in the absence of $\text{PhI}(\text{OAc})_2$], and found that a $\text{Pd}(\text{OAc})_2/\text{O}_2$ catalyst system converts **1i** into Wacker-type amination product (*Z*)-**3** in 20% yield (Scheme 4).^{1b} The conversion of **1i** to (*Z*)-**3** rather than (*E*)-**3** is indicative of a *cis*-aminopalladation pathway. No Wacker-type amination products are observed with **1i** under the aminoacetoxylation conditions. Formation of product *threo*-**2i** via *cis*-aminopalladation implies that C–O reductive elimination proceeds with retention of stereochemistry, which has limited precedent.¹⁰

Scheme 4. Oxidative Amination of Substrate **1i** Under Aerobic Conditions (ref. 1b).

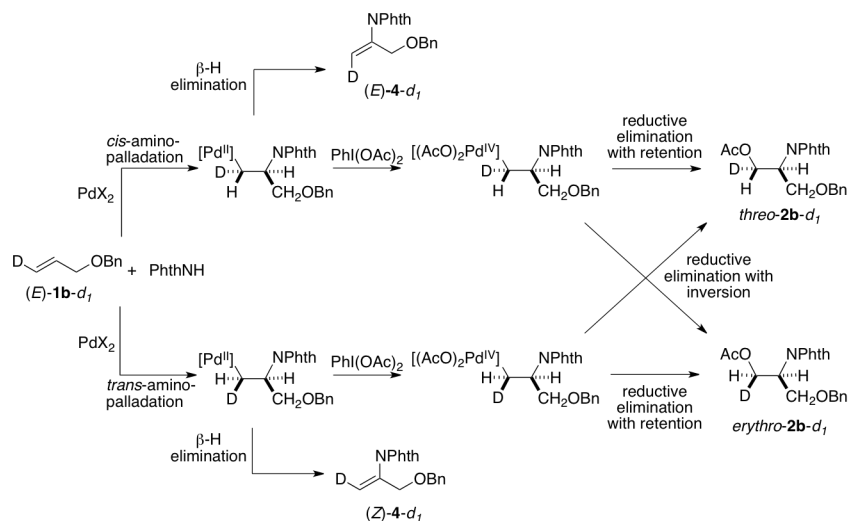


The identity of the oxidant [O_2 vs. $\text{PhI}(\text{OAc})_2$] could influence the stereochemistry of the reactions, and we sought a substrate probe that could be used to assess the aminopalladation stereochemistry under aerobic vs. aminoacetoxylation reactions conditions. Fortuitously, substrate **1b** yields a small amount of the Wacker-type amination product **4** under aminoacetoxylation conditions (Scheme 5). This result enables the use of deuterated substrate (*E*)-**1b-d₁ as a probe for the stereoselectivity of the aminopalladation step. Wacker-type oxidative amination could afford products (*E*)-**4-d₁ or (*Z*)-**4-d₁, and aminoacetoxylation could afford *threo*-**2b-d₁ or *erythro*-**2b-d₁,¹¹ and the product identity can be used to gain insight into the stereochemical course of the reactions (Scheme 6).**********

Scheme 5. Aminoacetoxylation of **1b** Yields Wacker-Type Amination Byproduct **4**.



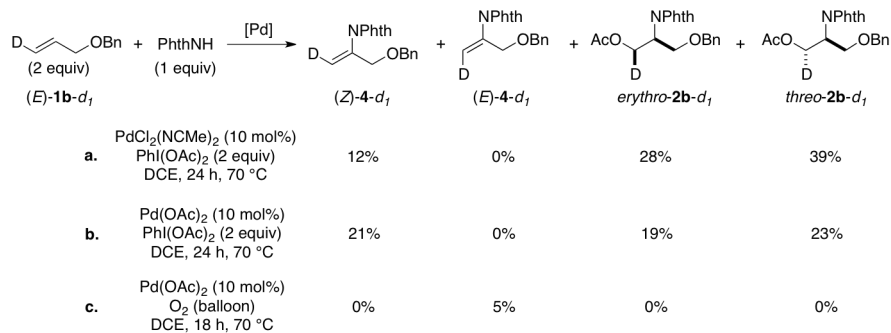
Scheme 6. Stereochemical Pathways for the Reaction of Deuterated Substrate (*E*)-**1b-d₁.**



Use of substrate (*E*)-**1b-d₁ under aminoacetoxylation conditions yielded Wacker-type oxidative amination product (*Z*)-**4-d₁** and a diastereomeric mixture of aminoacetoxylation products *threo*-**2b-d₁** and *erythro*-**2b-d₁** (Scheme 7a-b). Formation of enamide (*Z*)-**4-d₁** is the product expected from *trans*-aminopalladation of the alkene. Since none of the *cis*-aminopalladation product (*E*)-**4-d₁** is detected, the mixture of aminoacetoxylation products is believed to arise from poor stereoselectivity in the reductive**

elimination of the primary alkyl-Pd^{IV} intermediate. The origin of this poor selectivity is not presently understood.¹² When substrate (*E*)-**1b-d₁** was subjected to aerobic conditions analogous to the aminoacetoxylation conditions (Scheme 7b vs. 7c), the oxidative amination product (*E*)-**4-d₁** was observed as the sole product [5% yield; 70% recovered (*E*)-**1b-d₁**]. In spite of the poor yield, this product arises from a *cis*-aminopalladation pathway (cf. Scheme 6), consistent with the conclusion reached from the reaction of substrate **1i** under aerobic conditions in the previous study (cf. Scheme 4).^{1b,13}

Scheme 7. Reaction of Deuterated Substrate **4-d₁** Under Aminoacetoxylation and Aerobic Amidation Conditions.



Collectively, these results indicate that PhI(OAc)₂ alters the stereochemical course of the aminopalladation step. Prior studies have shown that ligands play a critical role in modulating of nucleopalladation stereoselectivity.¹⁴ Most germane to the reactivity described here, Weinstein and Stahl recently demonstrated that Pd(TFA)₂ exhibits greater proclivity for *trans*-aminopalladation relative to Pd(OAc)₂ in Wacker-type oxidative amidation reactions.^{14d} This trend can be rationalized by recognizing that substitution of an anionic ligand by an alkene in the *trans*-aminopalladation pathway will be more facile with less basic (i.e., less strongly coordinating) anionic ligands. Basic anionic ligands facilitate deprotonation of the amide nucleophile to afford a Pd–amidate intermediate that undergoes *cis*-aminopalladation of the alkene.¹⁵ In light of these considerations, we speculate that the Lewis acidic character of PhI(OAc)₂ facilitates displacement of acetate from Pd(OAc)₂ by the alkene and favors a *trans*-aminopalladation pathway.^{16,17}

Conclusions

We have identified reaction conditions that enable the alkene substrate to be used as the limiting reagent in the aminoacetoxylation of terminal and internal alkenes. Furthermore, we have obtained evidence that $\text{PhI}(\text{OAc})_2$ influences the stereochemical course of $\text{Pd}(\text{OAc})_2$ -mediated aminopalladation of alkenes, shifting the reaction from a *cis*- to a *trans*-selective process.

Experimental Section

General considerations: MS (ESI-LCMS) experiments were performed using a C8 (5 cm x 4.6 mm, 5 μm particles) column with a linear elution gradient from 100% H_2O (0.5% HCO_2H) to 100% MeCN in 13 min at a flow rate of 0.5 mL/min.

General procedure for the aminoacetoxylation reaction (Table 1): A Pyrex tube equipped with a stirrer bar is charged with 59 mg phthalimide (0.4 mmol, 1.0 eq) and 15 mg bis(benzonitrile)palladiumdichloride (0.04 mmol, 0.1 eq). Then, 0.6 mL of absolute dichloroethane are added via syringe and the solution is stirred at 70 °C for 1h. At this point, 260 mg iodosobenzene diacetate (0.80 mmol, 2.0 eq) and a previously prepared solution of 0.40 mmol of alkene with 14 mg of 4-*tert*-butylcatechol (0.08 mmol, 20%) are added. The resulting solution is sealed and stirred at 70 °C for 12h. After cooling to room temperature, the solution is washed with a 2%-solution of KOH (5 mL) and extracted with CH_2Cl_2 (4 x 10 mL). The organic phases were combined, dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by chromatography (silica gel, neutralized with *n*-hexane/ Et_3N (3%) and then *n*-hexane/ethyl acetate, 3/1, v/v) to give the pure product.

3-Butoxy-2-(1,3-dioxoisindolin-2-yl)propyl acetate (2a). Obtained as colorless oil; 92 mg, 72% of yield. ^1H NMR (400 MHz, CDCl_3): δ = 0.84 (t, J = 7.4 Hz, 3H), 1.36–1.16 (m, 2H), 1.54–1.42 (m, 2H), 2.00 (s, 3H), 3.41 (dt, J = 9.3, 6.5 Hz, 1H), 3.48 (dt, J = 9.3, 6.5 Hz, 1H), 3.83 (dd, J = 10.0, 6.7 Hz, 1H), 3.91 (dd, J = 10.0, 8.1 Hz, 1H), 4.62–4.44 (m, 2H), 4.73 (tdd, J = 8.2, 6.6, 5.1 Hz, 1H), 7.74 (dd, J = 5.5, 3.1 Hz, 2H), 7.86 (dd, J = 5.4, 3.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ = 13.8, 19.1, 20.7, 31.6, 50.2, 61.7, 67.3, 70.9, 123.3, 131.8, 134.0, 168.3, 170.6. IR $\nu(\text{cm}^{-1})$: 2958, 2932, 2871, 1743, 1709. HRMS: calcd for $\text{C}_{17}\text{H}_{21}\text{NO}_5\text{Na}$: 342.1317, found: 342.1304.

3-(Benzyloxy)-2-(1,3-dioxoisindolin-2-yl)propyl acetate (2b). Obtained as colorless oil; 93 mg, 66% of yield. ^1H NMR (400 MHz, CDCl_3): δ = 2.00 (s, 3H), 3.89 (dd, J = 9.9, 6.4 Hz, 1H), 3.98 (dd, J = 9.9, 8.1 Hz, 1H), 4.64–4.44 (m, 4H), 4.86–4.73 (m, 1H), 7.42–7.13 (m, 5H), 7.74 (dd, J = 5.5, 3.0 Hz, 2H), 7.86 (dd, J = 5.4, 3.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ = 20.7, 50.2, 61.6, 66.7, 73.0, 123.4, 127.6, 127.7, 128.4, 131.8, 134.1, 137.6, 168.2, 170.6. IR $\nu(\text{cm}^{-1})$: 3063, 3031, 2950, 2871, 1741, 1707. HRMS: calcd for $\text{C}_{20}\text{H}_{19}\text{NNaO}_5$: 376.1161, found: 376.1150.

3-Acetoxy-2-(1,3-dioxoisindolin-2-yl)propyl benzoate (2c). Obtained as yellow oil; 104 mg, 71% of yield. ^1H NMR (400 MHz, CDCl_3): δ = 2.05 (s, 3H), 4.66 (dd, J = 6.9, 4.5 Hz, 2H), 4.75 (dd, J = 11.4, 5.7 Hz, 1H), 4.81 (dd, J = 11.4, 7.7 Hz, 1H), 4.90–4.96 (m, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.55 (t, J = 7.5 Hz, 1H), 7.76 (dd, J = 5.4, 3.0 Hz, 2H), 7.88 (dd, J = 5.5, 3.0 Hz, 2H), 7.97 (d, J = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ = 20.8, 49.7, 61.3, 61.9, 123.6, 128.5, 129.9, 131.7, 133.3, 134.4, 166.1, 168.1, 170.6. IR $\nu(\text{cm}^{-1})$: 3023, 2961, 2929, 1175, 1711, 1601. HRMS: calcd for $\text{C}_{20}\text{H}_{17}\text{NNaO}_6$: 390.0954, found: 390.0936.

2-(1,3-Dioxoisindolin-2-yl)-3-(octyloxy)propyl acetate (2d). Obtained as yellow oil; 60 mg, 40% of yield. ^1H NMR (400 MHz, CDCl_3): δ = 0.87 (t, J = 7.1 Hz, 3H), 1.18–1.28 (m, 10H), 1.48–1.51 (m, 2H), 2.01 (s, 3H), 3.40 (dt, J = 9.3, 6.6 Hz, 1H), 3.49 (dt, J = 9.1, 6.4 Hz, 1H), 3.83 (dd, J = 10.0, 6.0 Hz, 1H), 3.93 (dd, J = 10.0, 8.3 Hz, 1H), 4.47–4.57 (m, 2H), 4.71–4.77 (m, 1H), 7.75 (dd, J = 5.5, 3.1 Hz, 2H), 7.87 (dd, J = 5.4, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, CDCl_3): δ = 14.2, 20.9, 22.8, 26.2, 29.3, 29.5, 29.6, 31.9, 50.3, 61.8, 67.4, 71.4, 123.5, 131.9, 134.2, 168.4, 170.8. IR $\nu(\text{cm}^{-1})$: 2926, 2855, 1776, 1710. HRMS: calcd for $\text{C}_{21}\text{H}_{29}\text{NNaO}_5$: 398.1943, found: 398.1940.

2-(1,3-Dioxoisindolin-2-yl)-3-phenylpropyl acetate (2e). Obtained as colorless oil; 73 mg, 56% of yield. ^1H NMR (400 MHz, CDCl_3): δ = 1.99 (s, 3H), 3.20 (dd, J = 13.9, 6.4 Hz, 1H), 3.36 (dd, J = 14.0, 10.0 Hz, 1H), 4.50 (dd, J = 11.3, 4.7 Hz, 1H), 4.62 (dd, J = 11.3, 9.3 Hz, 1H), 4.88–4.75 (m, 1H), 7.37–7.08 (m, 5H), 7.70 (dd, J = 5.5, 3.0 Hz, 2H), 7.79 (dd, J = 5.4, 3.1 Hz, 2H). ^{13}C NMR (126 MHz,

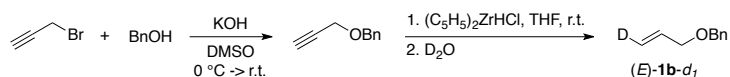
CDCl₃): δ = 20.7, 34.9, 51.8, 63.4, 123.2, 126.8, 128.6, 128.9, 131.6, 133.9, 136.8, 168.2, 170.6. **IR** $\nu(\text{cm}^{-1})$: 3062, 3028, 2927, 1771, 1707. **HRMS**: calcd for C₁₉H₁₇NNaO₄: 346.1055, found: 346.1067.

3-(2-(Benzyloxy)phenyl)-2-(1,3-dioxoisindolin-2-yl)propyl acetate (2f). Obtained as yellow oil; 90 mg, 50% of yield. **¹H NMR (400 MHz, CDCl₃)**: δ = 1.93 (s, 3H), 3.30 (dd, J = 7.8, 5.1 Hz, 2H), 4.47 (dd, J = 11.2, 4.9 Hz, 1H), 4.63 (dd, J = 11.3, 9.1 Hz, 1H), 4.93-4.99 (m, 1H), 5.06-5.12 (m, 2H), 6.75 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 7.06 (dd, J = 7.4, 1.7 Hz, 1H), 7.12 (td, J = 7.9, 1.7 Hz, 1H), 7.33 (d, J = 7.3 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.49 (d, J = 7.3 Hz, 2H), 7.66 (dd, J = 5.5, 3.0 Hz, 2H), 7.74 (dd, J = 5.4, 3.0 Hz, 2H). **¹³C NMR (126 MHz, CDCl₃)**: δ = 20.8, 30.6, 50.5, 63.9, 70.2, 111.8, 120.8, 123.2, 125.8, 127.4, 127.9, 128.4, 128.6, 130.9, 131.8, 133.9, 137.2, 156.9, 168.3, 170.6. **IR** $\nu(\text{cm}^{-1})$: 3064, 3030, 2929, 2871, 1738, 1708. **HRMS**: calcd for C₂₆H₂₃NNaO₅: 452.1474, found: 452.1474.

2-(1,3-Dioxoisindolin-2-yl)-3-(2-methoxyphenyl)propyl acetate (2g). Obtained as yellow oil; 76 mg, 51% of yield. **¹H NMR (400 MHz, CDCl₃)**: δ = 1.98 (s, 3H), 3.19-3.28 (m, 2H), 3.79 (s, 3H), 4.48 (dd, J = 11.4, 4.7 Hz, 1H), 4.68 (dd, J = 11.4, 9.6 Hz, 1H), 4.90 (tdd, J = 9.3, 6.3, 4.7 Hz, 1H), 6.76 (td, J = 7.4, 1.1 Hz, 1H), 6.80 (dd, J = 8.3, 1.0 Hz, 1H), 7.06 (dd, J = 7.5, 1.8 Hz, 1H), 7.15 (td, J = 7.9, 1.8 Hz, 1H), 7.69 (dd, J = 5.5, 3.0 Hz, 2H), 7.79 (dd, J = 5.4, 3.1 Hz, 2H). **¹³C NMR (126 MHz, CDCl₃)**: δ = 20.9, 30.5, 50.6, 55.3, 63.7, 110.4, 120.5, 123.2, 125.4, 128.4, 130.9, 131.9, 133.9, 157.8, 168.4, 170.7. **IR** $\nu(\text{cm}^{-1})$: 3020, 2959, 2937, 1774, 1709. **HRMS**: calcd for C₂₀H₁₉NNaO₅: 376.1161, found: 376.1168.

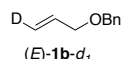
2-(1,3-Dioxoisindolin-2-yl)-1-phenylpropylacetate (2h). Obtained as a white solid; 105 mg, 81% of yield. **m.p.**: 112-113 °C (CH₂Cl₂/hexane). **¹H NMR (400 MHz, CDCl₃)**: δ = 1.60 (d, J = 6.9 Hz, 3H), 2.10 (s, 3H), 4.75 (dq, J = 9.1, 6.9 Hz, 1H), 6.30 (d, J = 9.2 Hz, 1H), 7.14-7.21 (m, 3H), 7.33 (dd, J = 8.1, 1.6 Hz, 2H), 7.62 (dd, J = 5.4 and 3.0 Hz, 2H), 7.69 (dd, J = 5.4, 3.0 Hz, 2H). **¹³C NMR (126 MHz, CDCl₃)**: δ = 15.3, 21.3, 50.4, 76.2, 123.2, 127.8, 128.4, 128.6, 131.6, 134.0, 137.5, 167.8, 169.9. **IR** $\nu(\text{cm}^{-1})$: 3035, 2984, 2927, 2854, 1770, 1704. **HRMS**: calcd for C₁₉H₁₇NO₄Na: 346.1055, found: 346.1072.

Synthesis of deuterated substrate probe (*E*)-1b-*d*₇:



A solution of KOH (2.69 g, 48 mmol) in DMSO (25 mL) was cooled in an ice bath and treated sequentially with benzyl alcohol (6.48 g, 60 mmol) and propargyl bromide (4.76 g, 40 mmol). The reaction mixture was stirred for 1 h at r.t. before being diluted with Et₂O and H₂O. The organic layer was separated, washed with H₂O, dried (Na₂SO₄), filtered, and concentrated in vacuo. Flash chromatography afforded benzyl propargyl ether (5.07 g, 87 %).

The benzyl propargyl ether (1.46 g, 10 mmol) was treated with (C₅H₅)₂ZrHCl (Schwartz reagent, 3.23 g, 12.5 mmol) in anhydrous THF (45 mL). After 10 min, the solution turned black, and the reaction was then quenched with D₂O (7.4 mL), and stirring was continued overnight. The mixture was then diluted with Et₂O, dried over MgSO₄, filtered and concentrated. The mixture was then purified by chromatography giving 1.26 g (86 %) of the product.



Compound (*E*)-**1b**-*d*₁ is a known compound.¹⁸ ¹H NMR (400 MHz, CDCl₃): δ 7.30 (m, 5H), 5.96 (dtt, *J* = 17.2, 6, 1.6 Hz), 5.30 (dt, *J* = 17.2, 1.6 Hz, 1H), 4.53 (s, 2H), 4.03 (dd, *J* = 6, 4.4 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ 138.3, 134.6, 128.4, 127.7, 127.6, 72.1, 71.1 (t, *J* = 1.9 Hz).

Procedures for the reaction of deuterated substrate (*E*)-**1b**-*d*₁ (Scheme 7):

Stereochemical assignments of products (*Z*)-**4**-*d*₁ and (*E*)-**4**-*d*₁ were achieved from NOESY-1D analysis of **4**¹⁹ (see the supporting information). The stereochemical assignments of products *erythro*-**2b**-*d*₁ and *threo*-**2b**-*d*₁ were achieved after derivatization and ¹H NMR spectroscopic analysis (see below and the supporting information).

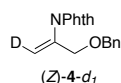
(a) With PhI(OAc)₂ as oxidant

In a dried glass tube, Pd(CH₃CN)₂Cl₂ (5.2 mg, 0.02 mmol, 10 mol %), PhI(OAc)₂ (128.8 mg, 0.04 mmol, 2 equiv.), phthalimide (29.4 mg, 0.2 mmol, 1.0 equiv.) were dissolved in DCE (0.25 mL), and then (*E*)-**1b**-*d*₁ (59.6 mg, 0.4 mmol, 2.0 equiv.) was added. After the reaction mixture was stirred at 70 °C for

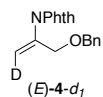
24 h, the residue was purified by column chromatography on silica gel with a gradient eluant of petroleum ether and ethyl acetate to afford (*Z*)-**4-d₁**, *erythro*-**2b-d₁** and *threo*-**2b-d₁**.

(b) With O₂ as the oxidant

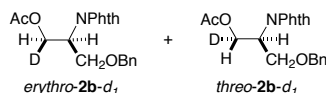
In a dried glass tube, Pd(OAc)₂ (4.5 mg, 0.02 mmol, 10 mol %), phthalimide (29.4 mg, 0.2 mmol, 1.0 equiv.) were dissolved in DCE (0.4 mL), charged with oxygen and then (*E*)-**1b-d₁** (59.6 mg, 0.4 mmol, 2 equiv.) was added. After the reaction mixture was stirred at 70 °C for 18 h, the residue was purified by column chromatography on silica gel with a gradient eluant of petroleum ether and ethyl acetate to afford (*E*)-**4-d₁**.



¹H NMR (400 MHz, CDCl₃): δ 7.88 (m, 2H), 7.75 (m, 2H), 7.27 (m, 5H), 5.65 (s, 1H), 4.53 (s, 2H), 4.36 (s, 2H).



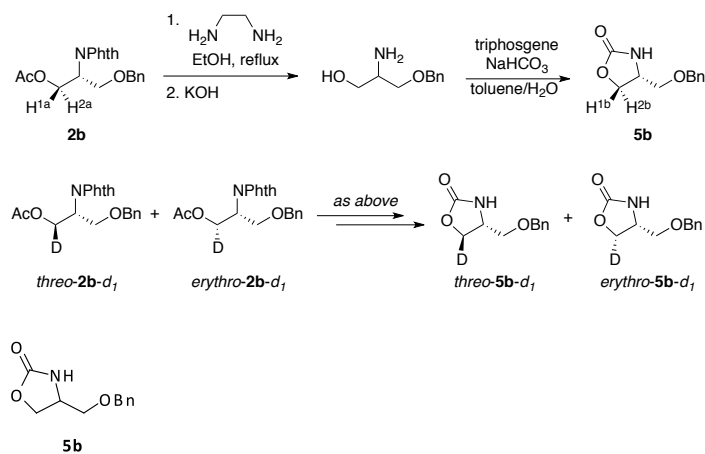
¹H NMR (400 MHz, CDCl₃): δ 7.88 (m, 2H), 7.75 (m, 2H), 7.27 (m, 5H), 5.43 (s, 1H), 4.54 (s, 2H), 4.35 (s, 2H).



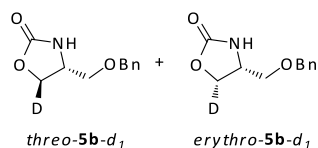
¹H NMR (400 MHz, CDCl₃) δ 1.98 (s, 3H), 3.87 (dd, *J* = 6.4, 3.6 Hz, 1H), 3.96 (dd, *J* = 80, 1.6 Hz, 1H), 4.48-4.57 (m, 3H), 4.74-4.81 (m, 1H), 7.24-7.28 (m, 5H), 7.71-7.74 (m, 2H), 7.83-7.85 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 20.7, 50.0, 61.2 (t, *J* = 22.4 Hz), 66.6, 72.9, 123.3, 127.6, 127.7, 128.3, 131.7, 134.0, 137.5, 168.2, 170.6. HRMS: calcd for C₂₀H₂₂DN₂O₅: 372.1664, found: 372.1668. IR ν(cm⁻¹): 3088, 3063, 3031, 2868, 1740, 1708.

The structure of isomers *erythro*-**2b-d₁** and *threo*-**2b-d₁** were characterized by conversion to a heterocyclic product with diagnostic *J*-coupling and chemical shift differences. Protio-derivative **2b** was converted to **5b**²⁰ to identify the chemical shifts of the two protons H^{1a} and H^{2a}. The chemical shifts of H^{1a}

and H^{2a} were assigned based on the *J*-values in the ¹H NMR spectrum of **5b** in benzene-*d*₆ (see figure S3 in the supporting information). **2b-d**₁ was similarly converted to **5b-d**₁, and the ratio of H^{1b} : H^{2b} corresponded to the ratio of isomers *erythro-2b-d*₁ : *threo-2b-d*₁ (see figure S4 in the supporting information).



¹H NMR (400 MHz, C₆D₆) δ 7.15 (m, 5H), 6.19 (br, s, 1H), 4.07 (s, 2H), 3.58 (dd, *J* = 8.7, 8.7 Hz, 1H), 3.46 (dd, *J* = 8.7, 5.3 Hz, 1H), 3.13 (m, 1H), 2.70 (m, 2H).



¹H NMR (400 MHz, C₆D₆) δ 7.15 (m, 5H), 6.26 (br, s, 1H), 4.07 (s, 2H), 3.56 (d, *J* = 8 Hz, 0.42H), 3.45 (d, *J* = 5.2 Hz, 0.57H), 3.13 (dt, *J* = 6, 6 Hz, 1H), 2.75-2.67 (m, 2H).

Associated Content

Supporting Information: ¹H NMR spectra for stereochemical analyses; ¹H and ¹³C NMR spectra of new compounds; X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org/>.

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Notes

The authors declare no competing financial interest.

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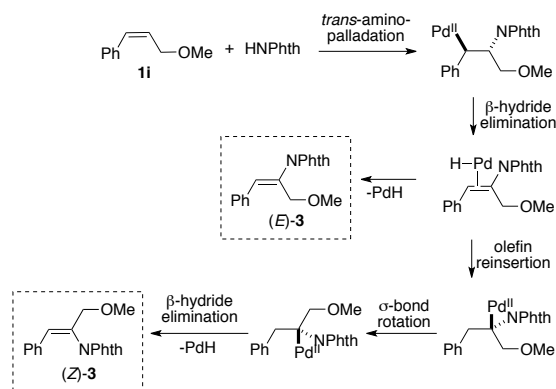
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(11) Substrate (*E*)-**1b-d_I** also avoids the complication associated with potential reversible β-hydride elimination leading to a more thermodynamically favored product rather than the diagnostic alkene isomer. For example, substrate **1i** could exhibit this complication, as depicted below (we thank Prof. Datong Song, University of Toronto, for drawing our attention to this potential complexity):



(12) The poor diastereoselectivity observed for reductive elimination of aminoacetoxylation product *erythro*- vs. *threo*-**2b** contrasts the excellent stereoselectivity observed for reductive elimination of aminoacetoxylation product *threo*-**2i** (cf. Scheme 3) and products derived from other internal alkene substrates. Presumably, the different selectivity is associated with the different reactivity of secondary benzylic vs. primary aliphatic alkyl–Pd intermediates.

(13) A similar analysis of *cis*- vs. *trans*-aminopalladation has been employed in the aminoetherification reaction in ref. 1c.

(14) For discussion of the factors that contribute to nucleopalladation stereoselectivity, see reference 3f and (a) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893–2901. (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335. (c) Keith, J. A.; Henry, P. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9038–9049. (d) Weinstein, A. B.; Stahl, S. S. *Angew. Chem. Int. Ed.* **2012**, *51*, 11505–11509.

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(16) NMR spectroscopic analysis of solutions of Pd(OAc)₂ and PhI(OAc)₂ did not provide evidence for a ground-state interaction between these species, but this result cannot exclude a kinetic effect in which iodine(III) facilitates displacement of acetate by an alkene.

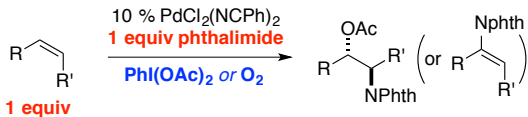
(17) Reactions between phthalimide and PhI(OAc)₂ could afford hypervalent iodine–phthalimide adducts, such as PhI(OAc)(NPhth) and PhI(NPhth)₂; however, it is not clear how the formation of such species would alter the stereochemical course of amidopalladation of the alkene. For references describing species such as PhI(OAc)(NPhth) and PhI(NPhth)₂, see the following: (a) Hadjiarapoglou, L.; Spyroudis, S.; Varvoglis, A. *Synthesis* **1983**, 207–208. (b) Kim, H. J.; Kim, J.; Cho, S. H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382–16385. (c) Moriyama, K.; Ishida, K.; Togo, H. *Org. Lett.* **2012**, *14*, 946–949.

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TOC Graphic:



Oxidant	Major Product	Aminopalladation Stereochemistry
O ₂	Enamine derivative	cis
PhI(OAc) ₂	Aminoalcohol derivative	trans