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Palladium-Catalyzed Intermolecular Aminoacetoxylation of Alkenes and the Influence of $PhI(OAc)_2$ on Aminopalladation Stereoselectivity

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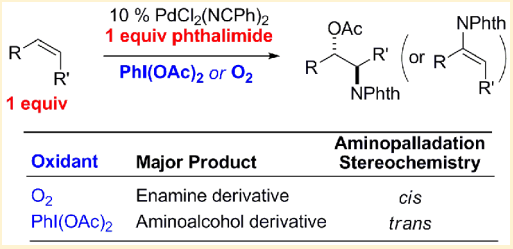
Supporting Information

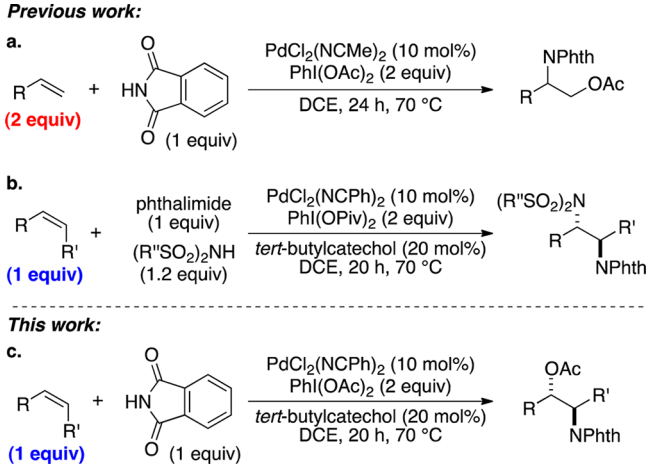
ABSTRACT: A modified protocol has been identified for Pd-catalyzed intermolecular aminoacetoxylation of terminal and internal alkenes that enables the alkene to be used as the limiting reagent. The results prompt a reassessment of the stereochemical course of these reactions. X-ray crystallographic characterization 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.



Oxidant	Major Product	Aminopalladation Stereochemistry
O_2	Enamine derivative	*cis*
$PhI(OAc)_2$	Aminoalcohol derivative	*trans*

In recent years, a number of palladium-catalyzed methods have been reported for aminoacetoxylation[1] and diamination[2] of alkenes with hypervalent iodine [$PhI(O_2CR)_2$] as the stoichiometric oxidant. These difunctionalization reactions are initiated by nucleopalladation of the alkene,[3] followed by $PhI(O_2CR)_2$-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 2 equiv 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



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 on the basis of 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.

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

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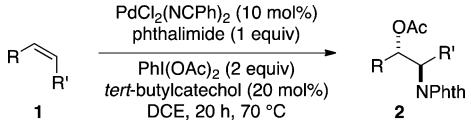
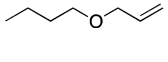
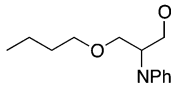
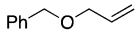
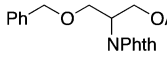
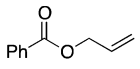
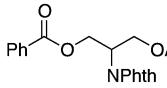
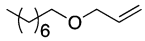
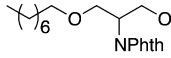
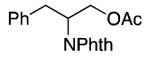
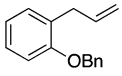
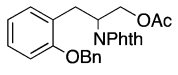
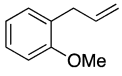
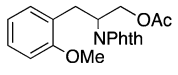
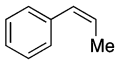
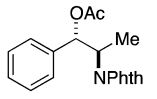
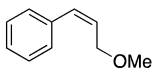
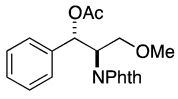
Table 1. Aminoacetoxylation of Alkenes



entry	alkene		product		yield (%)[a]
1		**1a**		**2a**	72
2		**1b**		**2b**	66
3		**1c**		**2c**	71
4		**1d**		**2d**	40
5		**1e**		**2e**	56
6		**1f**		**2f**	50
7		**1g**		**2g**	51
8		**1h**		**2h**	81
9		**1i**		**2i**	61

[a]Isolated yield after chromatography.

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 assignment based on NMR data was 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 matches that of the diamination reaction in Scheme 1b, which was similarly supported by X-ray crystallography.[2c]

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 $PhI(OAc)_2$ 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 S_N2-type transition state with inversion of

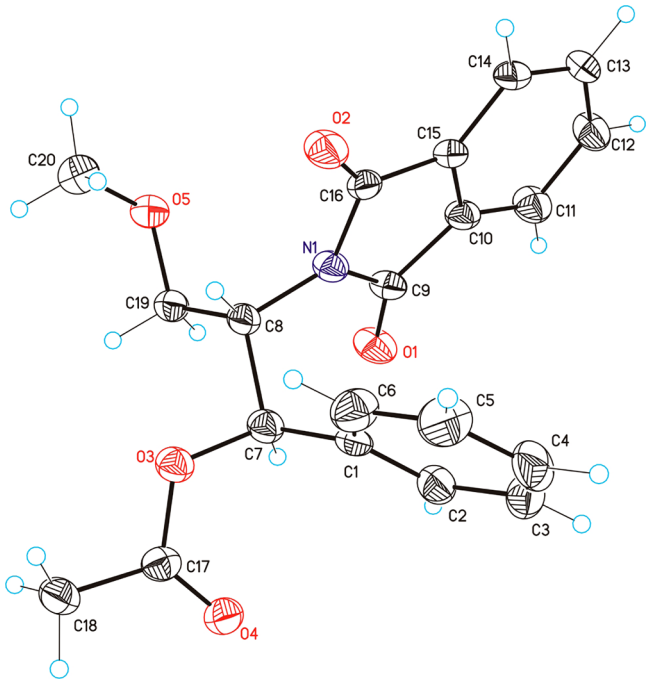
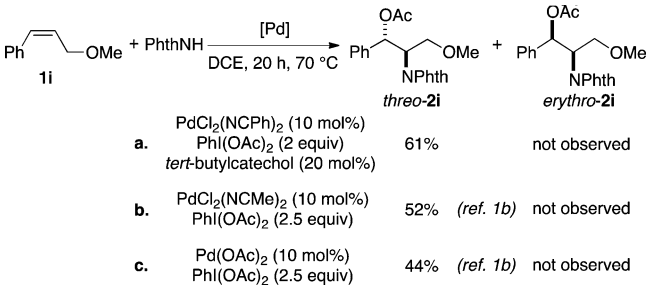


Figure 1. X-ray crystal structure of *threo*-**2i**.

Scheme 2. Exclusive Formation *threo*-2i Across Related Catalyst Systems



a.	$PdCl_2(NCPh)_2$ (10 mol%) $PhI(OAc)_2$ (2 equiv) *tert*-butylcatechol (20 mol%)	61%		not observed
b.	$PdCl_2(NCMe)_2$ (10 mol%) $PhI(OAc)_2$ (2.5 equiv)	52%	*(ref. 1b)*	not observed
c.	$Pd(OAc)_2$ (10 mol%) $PhI(OAc)_2$ (2.5 equiv)	44%	*(ref. 1b)*	not observed

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.

Liu and Stahl previously tested the reactivity of substrate **1i** under aerobic oxidation conditions [i.e., in the absence of $PhI(OAc)_2$], and found that a $Pd(OAc)_2/O_2$ 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]

The identity of the oxidant [O_2 vs $PhI(OAc)_2$] 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 reaction 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**-d_1 as a probe for the stereoselectivity of the aminopalladation step. Wacker-type oxidative amination could

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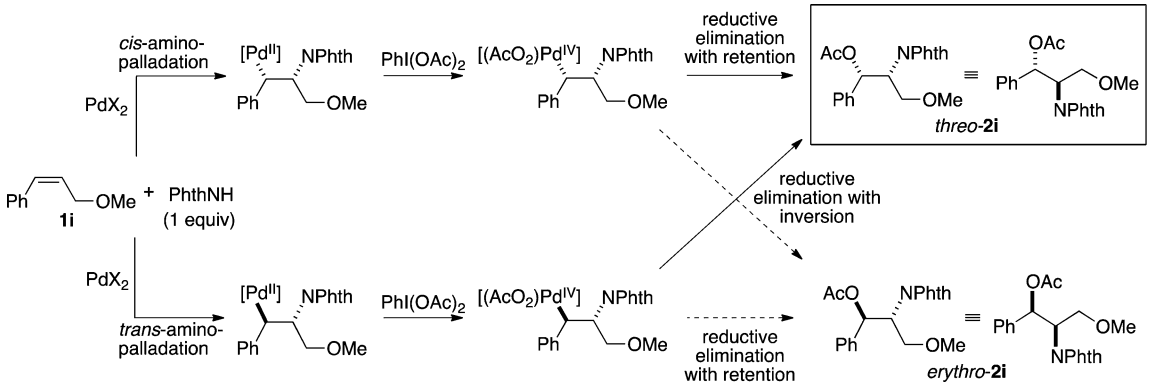
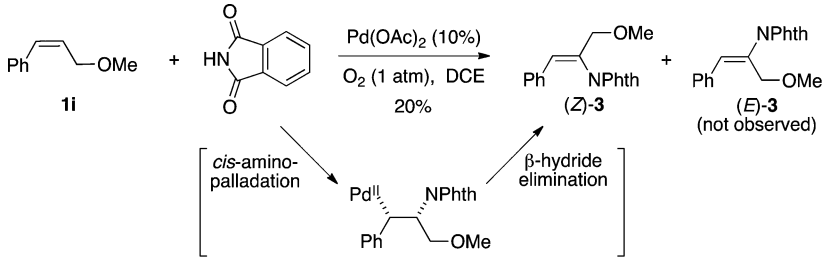
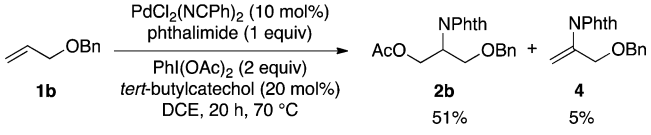
Scheme 3. Stereochemical Pathways for the Aminoacetoxylation of Substrate 1i



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



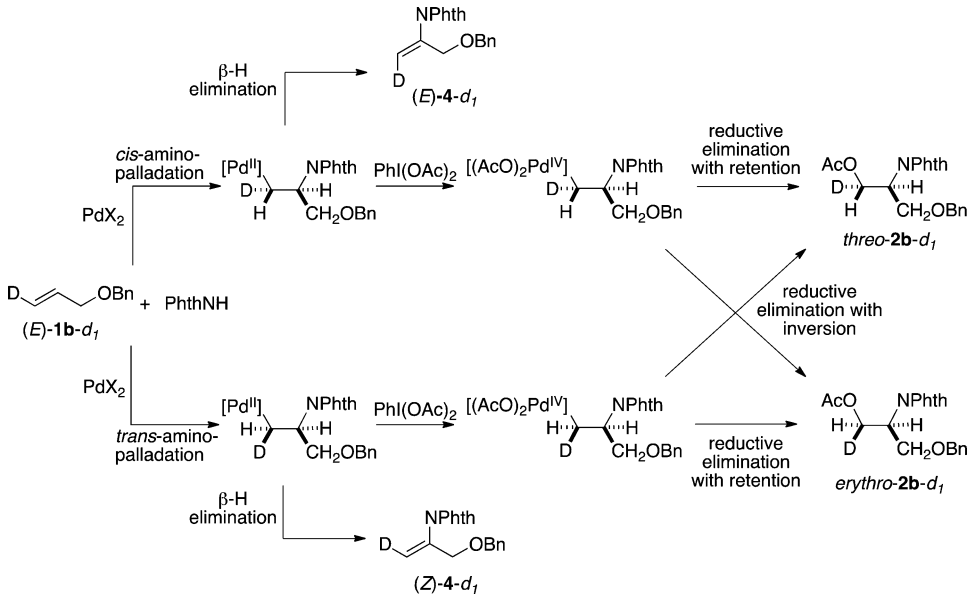
Scheme 5. Aminoacetoxylation of 1b Yields Wacker-Type Amination Byproduct 4



afford products (*E*)-**4**-d_1 or (*Z*)-**4**-d_1, and aminoacetoxylation could afford *threo*-**2b**-d_1 or *erythro*-**2b**-d_1,[11] and the product identity can be used to gain insight into the stereochemical course of the reactions (Scheme 6).

Use of substrate (*E*)-**1b**-d_1 under aminoacetoxylation conditions yielded Wacker-type oxidative amination product (*Z*)-**4**-d_1 and a diastereomeric mixture of aminoacetoxylation products *threo*-**2b**-d_1 and *erythro*-**2b**-d_1 (Scheme 7a,b). Formation of enimide (*Z*)-**4**-d_1 is the product expected from *trans*-aminopalladation of the alkene. Since none of the *cis*-aminopalladation product (*E*)-**4**-d_1 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**-d_1 was subjected to aerobic conditions analogous to the aminoacetoxylation conditions (Scheme 7b vs 7c), the oxidative amination product (*E*)-**4**-d_1 was

Scheme 6. Stereochemical Pathways for the Reaction of Deuterated Substrate (*E*)-1b-d_1



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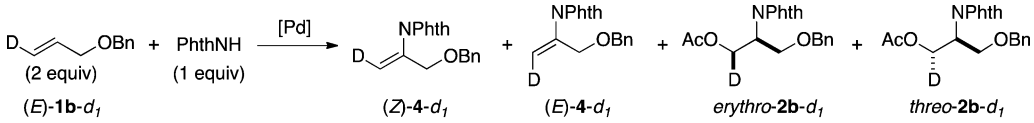
Scheme 7. Reaction of Deuterated Substrate 4-d_1 Under Aminoacetoxylation and Aerobic Amidation Conditions



a.	$PdCl_2(NCMe)_2$ (10 mol%) $PhI(OAc)_2$ (2 equiv) DCE, 24 h, 70 °C	12%	0%	28%	39%
b.	$Pd(OAc)_2$ (10 mol%) $PhI(OAc)_2$ (2 equiv) DCE, 24 h, 70 °C	21%	0%	19%	23%
c.	$Pd(OAc)_2$ (10 mol%) O_2 (balloon) DCE, 18 h, 70 °C	0%	5%	0%	0%

observed as the sole product [5% yield; 70% recovered (*E*)-**1b**-d_1]. 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]

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 amino-acetoxylation of terminal and internal alkenes. Furthermore, we have obtained evidence that $PhI(OAc)_2$ influences the stereochemical course of $Pd(OAc)_2$-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 × 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 stir bar is charged with 59 mg of phthalimide (0.4 mmol, 1.0 equiv) and 15 mg of bis(benzonitrile)-palladiumdichloride (0.04 mmol, 0.1 equiv). Then, 0.6 mL of absolute dichloroethane are added via syringe, and the solution is stirred at 70 °C for 1 h. At this point, 260 mg of iodosobenzene diacetate (0.80 mmol, 2.0 equiv) 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 20 h. After cooling to room temperature, the solution is washed with a 2% solution of KOH (5 mL) and extracted with CH_2Cl_2 (4 × 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-dioxoisoindolin-2-yl)propyl acetate (2a). Obtained as colorless oil; 92 mg, 72% yield. ^{1}H 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 ν (cm^{-1}): 2958, 2932, 2871, 1743, 1709. HRMS calcd for $C_{17}H_{21}NO_5Na$: 342.1317, found 342.1304.

3-(Benzyloxy)-2-(1,3-dioxoisoindolin-2-yl)propyl acetate (2b). Obtained as colorless oil; 93 mg, 66% yield. ^{1}H 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 ν (cm^{-1}): 3063, 3031, 2950, 2871, 1741, 1707. HRMS calcd for $C_{20}H_{19}NNaO_5$: 376.1161, found 376.1150.

3-Acetoxy-2-(1,3-dioxoisoindolin-2-yl)propyl benzoate (2c). Obtained as yellow oil; 104 mg, 71% yield. ^{1}H 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 ν (cm^{-1}): 3023, 2961, 2929, 1175, 1711, 1601. HRMS calcd for $C_{20}H_{17}NNaO_6$: 390.0954, found 390.0936.

2-(1,3-Dioxoisoindolin-2-yl)-3-(octyloxy)propyl acetate (2d). Obtained as yellow oil; 60 mg, 40% yield. ^{1}H 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 ν (cm^{-1}): 2926, 2855, 1776, 1710. HRMS calcd for $C_{21}H_{29}NNaO_5$: 398.1943, found 398.1940.

2-(1,3-Dioxoisoindolin-2-yl)-3-phenylpropyl acetate (2e). Obtained as colorless oil; 73 mg, 56% yield. ^{1}H 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, $CDCl_3$): 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 ν (cm^{-1}): 3062, 3028, 2927, 1771, 1707. HRMS calcd for $C_{19}H_{17}NNaO_4$: 346.1055, found 346.1067.

3-(2-(Benzyloxy)phenyl)-2-(1,3-dioxoisoindolin-2-yl)propyl acetate (2f). Obtained as yellow oil; 90 mg, 50% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 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),

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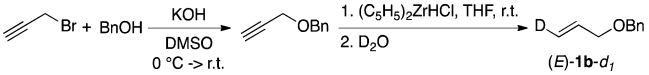
5.06−5.12 (m, 2H), 6.75 (t, J = 7.2 Hz, 1H), 6.86 (d, J = 8.1 Hz, 1H), 7.06 (dd, J = 7.4, 1.7 Hz, 1H), 7.12 (td, J = 7.9, 1.7 Hz, 1H), 7.33 (d, J = 7.3 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.49 (d, J = 7.3 Hz, 2H), 7.66 (dd, J = 5.5, 3.0 Hz, 2H), 7.74 (dd, J = 5.4, 3.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): 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 ν (cm^{-1}): 3064, 3030, 2929, 2871, 1738, 1708. HRMS calcd for $C_{26}H_{23}NNaO_5$: 452.1474, found 452.1474.

2-(1,3-Dioxoisoindolin-2-yl)-3-(2-methoxyphenyl)propyl acetate (2g). Obtained as yellow oil; 76 mg, 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): 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 ν (cm^{-1}): 3020, 2959, 2937, 1774, 1709. HRMS calcd for $C_{20}H_{19}NNaO_5$: 376.1161, found 376.1168.

2-(1,3-Dioxoisoindolin-2-yl)-1-phenylpropylacetate (2h). Obtained as a white solid; 105 mg, 81% yield. mp 112−113 °C (CH_2Cl_2/hexane). ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (126 MHz, $CDCl_3$): 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 ν (cm^{-1}): 3035, 2984, 2927, 2854, 1770, 1704. HRMS calcd for $C_{19}H_{17}NO_4Na$: 346.1055, found 346.1072.

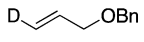
Synthesis of Deuterated Substrate Probe (*E*)-1b-d_1.



(*E*)-**1b**-d_1

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 rt before being diluted with Et_2O and H_2O. The organic layer was separated, washed with H_2O, dried (Na_2SO_4), 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 $(C_5H_5)_2ZrHCl$ (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 D_2O (7.4 mL), and stirring was continued overnight. The mixture was then diluted with Et_2O, dried over $MgSO_4$, filtered and concentrated. The mixture was then purified by chromatography giving 1.26 g (86%) of the product.



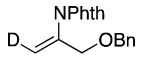
(*E*)-**1b**-d_1

Compound (*E*)-**1b**-d_1 is a known compound.[18] ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 ^{1}H NMR spectroscopic analysis (see below and the Supporting Information).

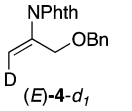
(a). With PhI(OAc)$_2$ as Oxidant. In a dried glass tube, $Pd(CH_3CN)_2Cl_2$ (5.2 mg, 0.02 mmol, 10 mol %) or $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %), $PhI(OAc)_2$ (128.8 mg, 0.04 mmol, 2 equiv), phthalimide (29.4 mg, 0.2 mmol, 1.0 equiv) were dissolved in DCE (0.25 mL), and then (*E*)-**1b**-d_1 (59.6 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**-d_1, *erythro*-**2b**-d_1 and *threo*-**2b**-d_1.

(b). With O_2 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) and charged with oxygen, and then (*E*)-**1b**-d_1 (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**-d_1.



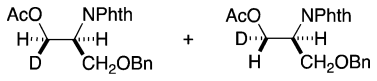
(*Z*)-**4**-d_1

(*Z*)-**4**-d_1. ^{1}H NMR (400 MHz, $CDCl_3$): 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).



(*E*)-**4**-d_1

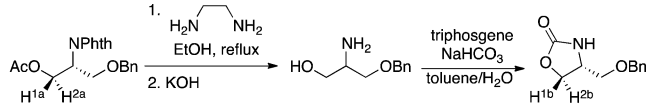
(*E*)-**4**-d_1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (m, 2H), 7.75 (m, 2H), 7.27 (m, 5H), 5.43 (s, 1H), 4.54 (s, 2H), 4.35 (s, 2H).



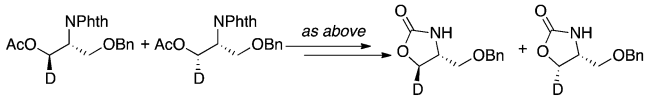
erythro-**2b**-d_1 *threo*-**2b**-d_1

erythro-**2b**-d_1 and *threo*-**2b**-d_1. ^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{20}H_{22}DN_2O_5$: 372.1664, found 372.1668. IR ν (cm^{-1}): 3088, 3063, 3031, 2868, 1740, 1708.

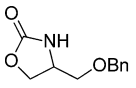
The structure of isomers *erythro*-**2b**-d_1 and *threo*-**2b**-d_1 were characterized by conversion to a heterocyclic product with diagnostic J-coupling and chemical shift differences. Protio derivative **2b** was converted to **5b**[20] to identify the chemical shifts of the two protons H^{1a} and H^{2a}. The chemical shifts of H^{1a} and H^{2a} were assigned on the basis of the J-values in the ^{1}H 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).



2b **5b**

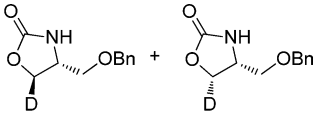


threo-**2b**-d_1 *erythro*-**2b**-d_1 *threo*-**5b**-d_1 *erythro*-**5b**-d_1



5b

5b. ^{1}H NMR (400 MHz, C_6D_6): 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).



threo-**5b**-d_1 *erythro*-**5b**-d_1

threo-**5b**-d_1 and *erythro*-**5b**-d_1. ^{1}H NMR (400 MHz, C_6D_6): 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).

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR spectra for stereochemical analyses; ^{1}H and ^{13}C NMR spectra of new compounds; X-ray crystallographic data (CIF). 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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■ REFERENCES

(1) (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690−7691. (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179−7181. (c) For a related aminoetherification reaction, see: Desai, L. V.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 5737−5740.

(2) (a) Iglesias, Á.; Pérez, E. G.; Muñiz, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 8109−8111. (b) Muñiz, K.; Kirsch, J.; Chávez, P. *Adv. Synth. Catal.* **2011**, *353*, 689−694. (c) Martínez, C.; Muñiz, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 7031−7034.

(3) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2309. (b) Beccali, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318−5365. (c) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142−1152. (d) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910−1923. (e) Jensen, K. H.; Sigman, M. S. *Org. Biomol. Chem.* **2008**, *6*, 4083−4088. (f) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981−3019.

(4) For leading references, see: (a) Canty, A. J.; Denney, M. C.; Skelton, B. W.; White, A. H. *Organometallics* **2004**, *23*, 1122−1131. (b) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790−12791. (c) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302−309. (d) Deprez, N. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 11234−11241. (e) Powers, D. C.; Lee, E.; Ariafard, A.; Sanford, M. S.; Yates, B. F.; Canty, A. J.; Ritter, T. *J. Am. Chem. Soc.* **2012**, *134*, 12002−12009. (f) Powers, D. C.; Ritter, T. *Acc. Chem. Res.* **2012**, *45*, 840−850. (g) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412−9423. (h) Hickman, A. J.; Sanford, M. S. *Nature* **2012**, *484*, 177−185.

(5) Single crystal X-ray analysis of **2h** also established the relative stereochemistry to be *threo*, which suggests a unified pathway for internal alkenes (see the Supporting Information for details).

(6) Fles, D.; Majhofer, B.; Kovac, M. *Tetrahedron* **1968**, *24*, 3053−3057.

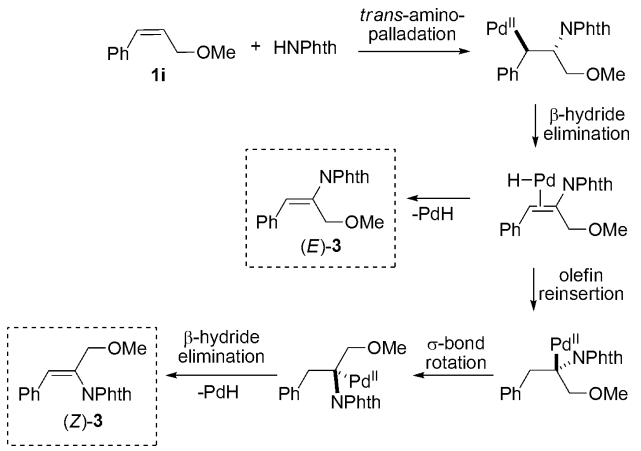
(7) (a) Sibbald, P. A.; Rosewall, C. F.; Swartz, R. D.; Michael, F. E. *J. Am. Chem. Soc.* **2009**, *131*, 15945−15951. (b) Iglesias, Á.; Álvarez, R.; de Lera, Á. R.; Muñiz, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 2225−2228. Reductive elimination from Pd^{IV}−alkyl complexes with inversion of stereochemistry is also supported by analogy to fundamental studies of Pt^{IV}−alkyl complexes: (c) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576−2587. (d) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2182−2192 and references therein.

(8) Byers, P. K.; Canty, A. J.; Crespo, M.; Puddephatt, R. J.; Scott, J. D. *Organometallics* **1988**, *7*, 1363−1367.

(9) For examples of discrete Pd^{II} complexes in which oxidative cleavage of a Pd^{II}−C bond may proceed with either inversion or retention of stereochemistry, see: (a) Coulson, D. R. *J. Am. Chem. Soc.* **1969**, *91*, 200−202. (b) Wong, P. K.; Stille, J. K. *J. Organomet. Chem.* **1974**, *70*, 121−132. (c) Bäckvall, J.-E. *Tetrahedron Lett.* **1977**, *18*, 467−468. (d) Bäckvall, J.-E. *Tetrahedron Lett.* **1978**, *19*, 163−166. (e) Zhu, G.; Ma, S.; Lu, X.; Huang, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 271−273.

(10) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542−9543. (b) For a relevant precedent involving C_{sp3}−O reductive elimination from Pt^{IV}, see: Khusnutdinova, J. R.; Newman, L. L.; Zavalij, P. Y.; Lam, Y. F.; Vedernikov, A. N. *J. Am. Chem. Soc.* **2008**, *130*, 2174−2175.

(11) Substrate (*E*)-**1b**-d_1 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.

(15) For further analysis of anionic ligand effects in amidopalladation reactions, see: (a) Ye, X.; Liu, G.; Popp, B. V.; Stahl, S. S. *J. Org. Chem.* **2011**, *76*, 1031−1044. (b) Ye, X.; White, P. B.; Stahl, S. S. *J. Org. Chem.* **2013**, *78*, 2083−2090.

(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.

dx.doi.org/10.1021/jo400671q | *J. Org. Chem.* 2013, 78, 6309−6315

H.; Chang, S. *J. Am. Chem. Soc.* **2011**, *133*, 16382−16385. (c) Moriyama, K.; Ishida, K.; Togo, H. *Org. Lett.* **2012**, *14*, 946−949.
(18) Yagi, K.; Oikawa, H.; Ichihara, A. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 1038−1040.
(19) Product **4** is a known compound: Rogers, M. M.; Kotov, V.; Chatwichien, J.; Stahl, S. S. *Org. Lett.* **2007**, *9*, 4331−4334.
(20) Product **5b** is a known compound. The ^{1}H NMR was consistent with the data in the literature: Bégis, G.; Cladingboel, D. E.; Jerome, L.; Motherwell, W. B.; Sheppard, T. D. *Eur. J. Org. Chem.* **2009**, 1532−1548.

dx.doi.org/10.1021/jo400671q | *J. Org. Chem.* 2013, 78, 6309−6315