Pd-Catalyzed Conversion of Alkynyl-λ^3-iodanes to Alkenyl-λ^3-iodanes via Stereoselective 1,2-Iodine(III) Shift/1,1-Hydrocarboxylation

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S Supporting Information

ABSTRACT: Alkynyl-λ^3-iodanes have been established as alkynyl cation equivalents for the alkynylation of carbon- and heteroatom-based nucleophiles. Herein, we report an unprecedented reaction mode of this compound class, which features a Pd(II)-assisted 1,2-I(III) shift of an alkynylbenziodoxole. A Pd(II) catalyst mediates this shift and the subsequent interception of the transient vinylidene species with carboxylic acid (1,1-hydrocarboxylation). The product of this stereoselective rearrangement−addition reaction, β-oxyalkenylbenziodoxole, represents a novel and useful building block for further synthetic transformations.

Trivalent iodine compounds (λ^3-iodanes) have been widely used in organic synthesis as selective oxidants and electrophilic ligand-transfer reagents.[1] Among λ^3-iodane ligand-transfer reagents, alkynyl-λ^3-iodanes have been successfully used for the alkynylation of carbon- and heteroatom-based nucleophiles,[1,2] which complements the scope of conventional alkynylation reactions involving nucleophilic acetylides. The alkynylation of a nucleophile with an alkynyl-λ^3-iodane is typically rationalized by a sequence of nucleophile addition to the β-position, reductive elimination of the I(III) moiety, and 1,2-shift of the R or Nu group (steps $a−c$) to give the alkyne **A**, while this sequence may be interrupted by protonation (step d) to give a simple adduct **B** or by vinylidene C−H insertion (step e) to give a cyclic product **C** or **C′** (Scheme 1a).[2a] Furthermore, different mechanisms may be operative in alkynylation reactions that involve transition metal catalysts[3] or radical intermediates[4] or that proceed in the absence of either.[5] Nonetheless, most alkynyl-λ^3-iodane reaction products, excluding cycloaddition products as well as other rare exceptions,[6] fall into the **A**, **B**, **C** (**C′**) categories or derivatives thereof.

Herein, we report the discovery and development of a Pd(II)-catalyzed reaction of alkynylbenziodoxole **1** with carboxylic acid **2**, which features an unprecedented mode of nucleophile addition to alkynyl-λ^3-iodane, involving a hitherto elusive 1,2-I(III) shift (Scheme 1b).[7,8] A Pd(II)−1,5-cyclooctadiene (cod) catalyst promotes the 1,2-shift of the benziodoxole moiety together with the addition of **2** to the α-position of **1** (1,1-hydrocarboxylation), which affords β-oxyalkenylbenziodoxole **3** in a *trans* fashion. The reaction can be rationalized in terms of a consecutive 1,2-I(III) shift of **1** complexed by Pd(carboxylate)₂ (**Int1**) and a migratory insertion of the vinylidene−Pd(carboxylate)₂ species (**Int2**), followed by protonation of the resulting β-iodo(III)alkenyl−

Scheme 1. Reaction Pathways for Alkynyl-λ^3-iodanes[a]

(a) Common reaction patterns
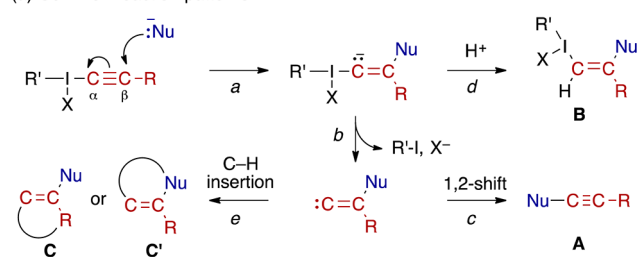
(b) This work: 1,2-I(III) shift/1,1-hydrocarboxylation
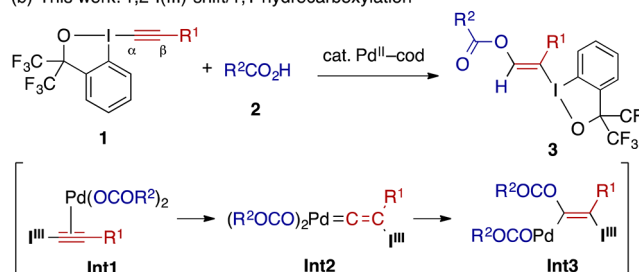
[a] I^{III} denotes the benziodoxole moiety hereafter.

Pd(carboxylate) species (**Int3**). While being inert to the Pd(II) catalyst, the alkenyl−I(III) moiety of **3** allows its use as a novel synthetic building block in further synthetic transformations.

We recently developed a Pd(OAc)₂-catalyzed three-component coupling reaction of alkynylbenziodoxoles, carboxylic acids, and imines to form multisubstituted furans.[6b] The present 1,2-I(III) shift/1,1-hydrocarboxylation reaction was discovered in our attempt to gain mechanistic insight into this reaction by control reactions in the absence of an imine (Table 1). A mixture of alkynylbenziodoxole **1a** and benzoic acid (**2a**, 10 equiv) in the presence of Pd(OAc)₂ alone led to the decomposition of **1a** into intractable products with a quick color change from clear yellow to black. In contrast, the addition of cod (50 mol %) to the reaction system prevented the color change and resulted in the unexpected adduct **3a** in 12% yield (entry 1), accompanied by a homocoupling of **1a** (i.e., 1,4-diphenylbuta-1,3-diyne, ca. 40%). Subsequently, we observed substantial improvement in the yield of **3a** using [Pd(allyl)Cl]₂ as the precatalyst (entry 2). Building on this observation, we could eventually ascertain that [Pd(2-

Table 1. Effect of Pd Sources and Ligands on 1,2-I(III) Shift/1,1-Hydrocarboxylation[a]
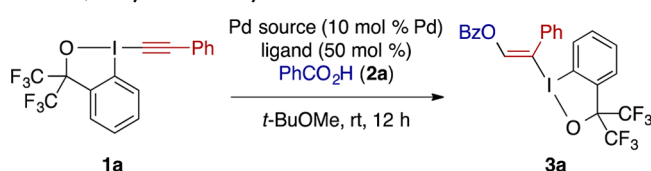
| entry	Pd source	ligand	yield (%)[b]
1	Pd(OAc)$_2$	cod	12
2	[Pd(allyl)Cl]$_2$	cod	50
3	[Pd(2-methylallyl)Cl]$_2$	cod	73
4	[Pd(allyl) (OAc)]$_2$	cod	81
5	[Pd(2-methylallyl)(OAc)]$_2$	cod	97 (95)
6	[Pd(2-methylallyl)(OAc)]$_2$	–	54
7	[Pd(2-methylallyl)(OAc)]$_2$	coe	68

[a]Conditions: **1a** (0.1 mmol), **2a** (1.0 mmol), Pd source (10 mol % Pd), ligand (50 mol %), *t*-BuOMe (0.067 M), rt, 12 h. [b]Determined by ^{19}F NMR spectroscopy using 1,4-bis(trifluoromethyl)benzene as an internal standard. Isolated yield shown in parentheses.

methylallyl)(OAc)]$_2$ allows a clean conversion of **1a** to **3a** in near-quantitative yield (entries 3−5). Besides the Pd precatalyst, the cod ligand also plays an important role, as the yield of **3a** dropped substantially in its absence or upon replacing it with cyclooctene (coe) (entries 6 and 7). Note that simple conjugate addition of **2a** to **1a** (i.e., the type **B** product in Scheme 1a) was not observed in any of the screening experiments.[9]

Table 2 summarizes the scope of the 1,2-I(III) shift/1,1-hydrocarboxylation of alkynylbenziodoxoles. For alkynyl-benziodoxoles derived from a variety of (hetero)arylacetylenes, especially those bearing electron-withdrawing groups, the reaction proceeded smoothly and afforded the desired trisubstituted alkenylbenziodoxoles **3a−3k** in moderate to excellent yields (47−95%) with exclusive *trans*-stereoselectivity. However, the reaction was sensitive toward the presence of electron-donating groups on the aryl moiety. For example, the use of 4-methoxyphenyl(ethynyl)benziodoxole did not furnish the desired product, but led to the decomposition into unknown compounds. The reaction is scalable, as evident from the reaction of 5 mmol (2.35 g) of **1a** and 50 mmol (6.10 g) of **2a**, which afforded 2.80 g (4.75 mmol, 95% yield) of **3a**. Alkynylbenziodoxoles derived from alkylacetylenes, enynes, and diynes were also amenable to the reaction with **2a**, producing alkenylbenziodoxoles **3l−3o** in good yield. Notably, the 2-fold addition of **2a** to bis-alkynylbenziodoxole was achieved to furnish bis-alkenylbenziodoxole **3p** in 85% yield.

The 1,2-I(III) shift/1,1-hydrocarboxylation of **1a** proved feasible for a variety of carboxylic acids other than **2a**. Electron-rich and/or sterically hindered aromatic acids afforded the desired adducts **3q**, **3s**, and **3t** in high yields (87−98%), while electron-deficient 4-chlorobenzoic acid generated the product **3r** only in a modest yield regardless of full conversion of **1a**.[10] Furthermore, the adducts of thiophene- and furan-2-carboxylic acids (**3u** and **3v**) were obtained in good yields, and alkylcarboxylic acids, including a *N*-Boc-protected amino acid, also participated in the reaction (see the products **3w−3y**).

The reaction of ^{13}C-labeled alkynylbenziodoxole **1a**-^{13}C with **2a** under the optimized conditions afforded **3a**-^{13}C, whose ^{1}H and ^{13}C NMR spectra confirmed bonding of the ^{13}C atom to the benzoate group and showed a vinylic hydrogen signal with a

Table 2. Scope of 1,2-I(III) Shift/1,1-Hydrocarboxylation[a]
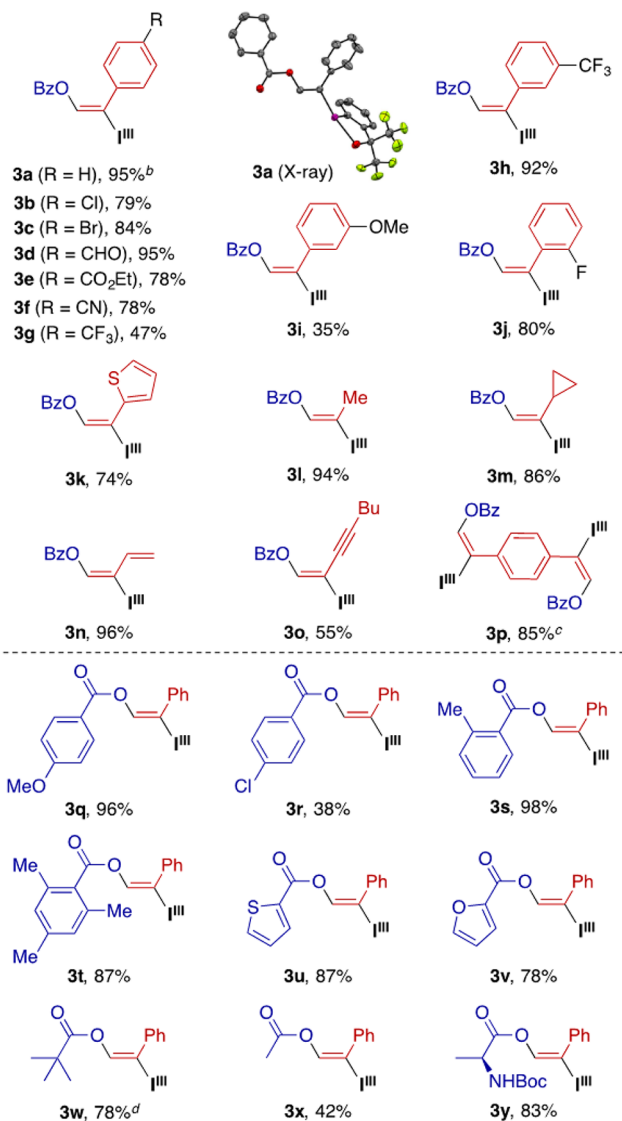
[a]The reaction was performed under the conditions in Table 1, entry 5. [b]5 mmol scale with respect to **1**. [c]0.1 mmol of bis(alkynyl)-benziodoxole and 2 mmol of **2a** were used. [d]2 mmol scale with respect to **1a**.

J_{C-H} coupling constant of 196 Hz (eq 1). This result unambiguously supports the 1,2-migration of the I(III) center.
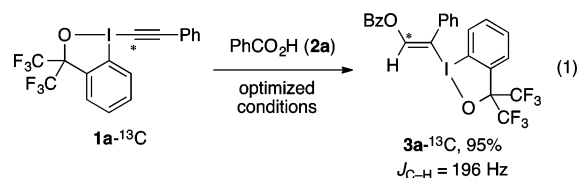
We propose that the present reaction involves the 1,2-I(III) shift of the Pd(II) carboxylate-ligated alkynylbenziodoxole (**Int1**) and the migratory insertion of the resulting vinylidene−

Pd species (**Int2**) as outlined in Scheme 1b. The feasibility of these processes is supported by the results of preliminary density functional theory (DFT) calculations using propynyl-benziodoxole **1l** as a model substrate and Pd(OAc)$_2$ as a model catalyst (Figure 1a). Both the 1,2-I(III) shift and the migratory
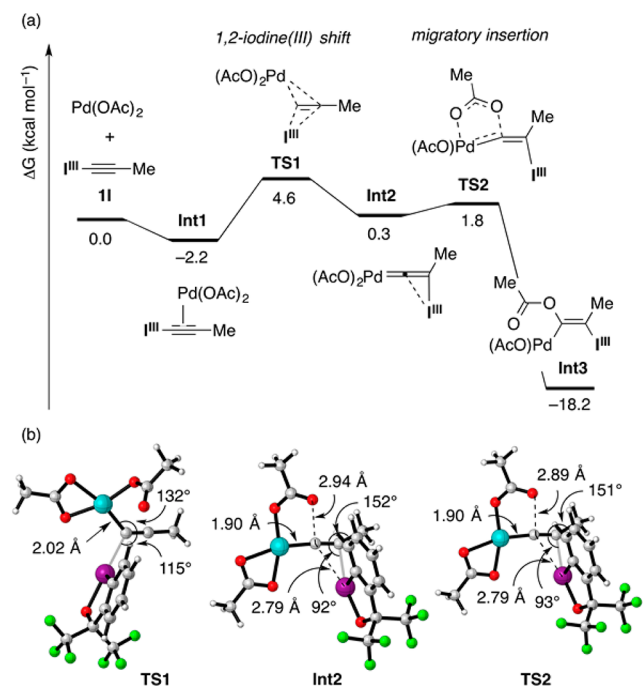

Figure 1. (a) Energy profile of the 1,2-I(III) shift and the migratory insertion. (b) DFT-optimized molecular structures. Color code: gray = C; white = H; green = F; purple = I; red = O; turquoise = Pd (see the Supporting Information for computational details).

insertion proved kinetically feasible ($\Delta G^{\ddagger} < 7$ kcal mol^{-1}), affording β-iodo(III)alkenylpalladium species **Int3** in an exergonic manner ($\Delta G = -18.2$ kcal mol^{-1}). Figure 1b shows the structures of the Y-shaped transition state for the 1,2-I(III) shift (**TS1**), vinylidene−Pd species **Int2**, and the five-membered cyclic transition state for the vinylidene insertion (**TS2**). **Int2** features a relatively distorted geometry around the β-carbon atom ($<C^{\alpha}-C^{\beta}-I = 92°$, $<C^{\alpha}-C^{\beta}-Me = 152°$) and undergoes little structural change upon transformation to **TS2**, which is consistent with the small activation barrier (1.5 kcal mol^{-1}) calculated. It should be noted that the incoming carboxy oxygen and the benziodoxole moiety in **TS2** are located *trans* with respect to each other, which is consistent with the *trans* selectivity of the 1,1-hydrocarboxylation. According to the analysis of the lowest unoccupied molecular orbital (LUMO) of **Int2** (see Figure S4), this stereoselectivity may be ascribed to a favorable orbital interaction between the electrophilic vinylidene α-carbon atom and the nucleophilic carboxy oxygen atom that can be achieved in the side opposite the benziodoxole moiety. While we do not understand how cod and 2-methylallyl ligands affect the reaction pathway, according to the observation of the reaction color (vide supra), one of possible roles of these ligands would be to prevent the decomposition of the Pd(II) catalyst into Pd black.

The stereochemically well-defined alkenylbenziodoxoles obtained from the present 1,1-hydrocarboxylations offer diverse opportunities for further synthetic transformations. To illustrate this point, stereochemically pure trisubstituted alkene **6** was

synthesized in two steps: a Pd-catalyzed Stille coupling of alkenylbenziodoxole **3w** with tributyl(4-methoxyphenyl)-stannane via a C−I(III) bond cleavage[11] afforded alkenyl pivalate **5**, which was subsequently subjected to an Fe-catalyzed stereoretentive cross-coupling with butylmagnesium bromide (Scheme 2a).[12] A Sonogashira coupling of alkenylbenziodoxole

Scheme 2. Selected Product Transformations
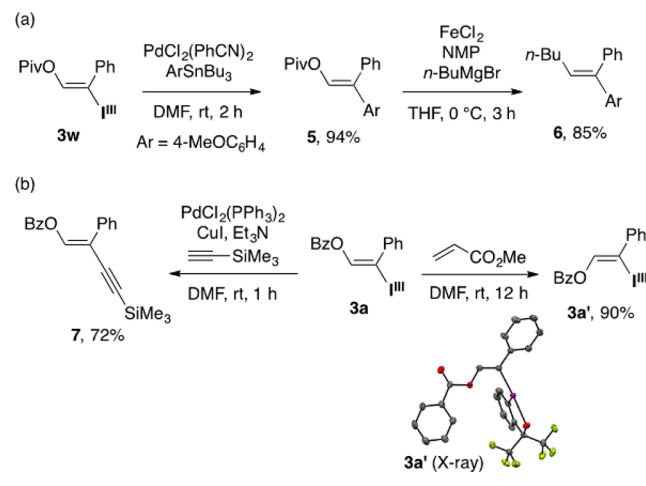
3a took place smoothly to afford enyne **7** (Scheme 2b, left), while an attempted Heck reaction of **3a** with methyl acrylate resulted in the decomposition of **3a**. Interestingly, the latter unsuccessful attempt led to the unexpected finding that a simple exposure of **3a** to methyl acrylate results in a clean E/Z isomerization to afford the Z-isomer **3a′** (Scheme 2b, right).

In summary, we have developed a Pd(II)-catalyzed transformation of alkynylbenziodoxoles and carboxylic acids into stereochemically well-defined alkenylbenziodoxoles, which involves a 1,2-I(III) shift followed by a 1,1-hydrocarboxylation. The reaction represents a new mode of nucleophile addition to alkynyl-λ^3-iodanes and also a new example of metal-mediated alkyne-to-vinylidene conversion via a 1,2-group shift.[13,14] The synthetic utility of the unique β-oxyalkenylbenziodoxole products shall be expanded further in light of the rapid recent developments in (catalytic) transformations of hypervalent iodine reagents.[1] We also anticipate the development of a new 1,2-I(III) shift/1,1-difunctionalization of alkynylbenziodoxoles employing a nucleophile and an electrophile other than carboxylate and proton, respectively.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b06247.

> Detailed experimental procedures and spectral data (PDF)
> Crystallographic data (CIF, CIF)

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Notes
The authors declare no competing financial interest.

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