

Pd-Catalyzed Photoinduced Interceptive Decarboxylative Allylation

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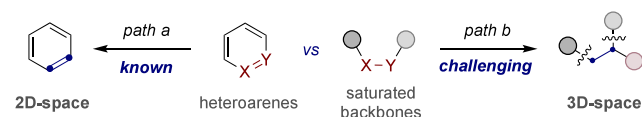
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ABSTRACT: Herein, we describe a photoinduced Pd-catalyzed interceptive decarboxylative allylation of allyl esters. Our protocol provides a new gateway to enable atom pair swaps or a series of contractions and elongations, thus offering unconventional disconnections and a modular yet broadly applicable tool for rapidly and reliably accessing sp^3 architectures in drug discovery.

The ability to rapidly and reliably generate molecular complexity from simple precursors is central in organic synthesis.¹ A particularly attractive endeavor is the design of techniques that engineer molecules by deleting, incorporating, or swapping atoms in their core structures with predictable site-selectivity.² Despite the advances realized with heteroarenes (Scheme 1, path a),^{3,4} atom-pair mutations that forge

Scheme 1. Atom-Pair Mutations for 2D- and 3D-Space

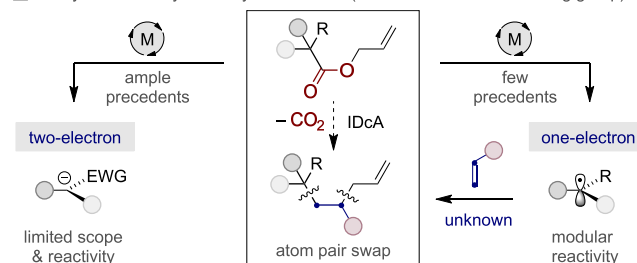
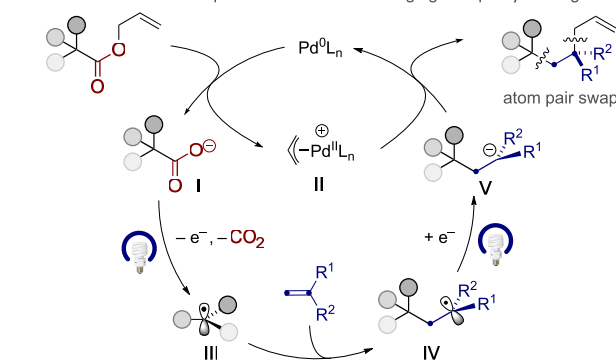


sp^3 -fragments predominantly rely on stoichiometric promoters,⁵ cyclic amines,⁶ or ring-strain release.⁷ Given that an increased number of sp^3 -hybridized carbons improves several molecular attributes that contribute to clinical success,⁸ a catalytic, yet broadly applicable, transformation that forges sp^3 -architectures from simple acyclic saturated motifs might constitute a rewarding strategy in drug discovery (path b).⁹

Driven by the seminal work of Tsuji and Saegusa,¹⁰ Pd-catalyzed decarboxylative allylations (DcA) have reached remarkable levels of sophistication.¹¹ While interceptive decarboxylative allylations (IDcA) might offer a new vehicle for enabling atom-pair mutations in simple acyclic allyl esters,^{12,13} these processes currently rely on two-electron manifolds requiring esters with electron-poor groups (Scheme 2, top left).¹⁴ Notwithstanding the improved modularity of open-shell species for bond formation when compared to two-electron manifolds,¹⁵ a one-electron catalytic IDcA strategy currently constitutes an uncharted cartography (top right).¹⁶ If successful, such a protocol would not only expand the repertoire of atom-pair swap strategies beyond heteroarenes (Scheme 1, path a) but also offer new retrosynthetic disconnections when forging sp^3 -architectures. We hypothesized that a Pd-catalyzed photoinduced decarboxylation of allyl esters with appropriate olefin acceptors might be suited for our purposes, resulting in two consecutive sp^3 – sp^3 bond-forming reactions with a net loss of CO_2 (Scheme 2, bottom). We anticipated that a photoinduced one-electron decarboxylation

Scheme 2. Decarboxylative sp^3 Mutations in Allyl Esters

catalytic decarboxylative allylation events (EWG = electron-withdrawing group)

this work: one-electron photoinduced IDcA for forging multiple sp^3 linkages

of **I** en route to **III** might not only overcome existing limitations in classical IDcA but also offer opportunities for accessing new chemical space when building up sp^3 -architectures.^{17–19} Herein, we report the realization of this goal, culminating in a broadly applicable protocol that results in not only an atom-pair swap but also a series of contractions and elongations depending on the substrate and acceptor utilized.

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Our investigations began by evaluating the photoinduced IDCa of **1a** with **2a** (Table 1). At the outset of our

Table 1. Optimization of the Reaction Conditions^a

entry	deviation from standard conditions	3a (%) ^b
1	none	86 (80) ^c
2	L2 (3.75 mol%) instead of L1	85
3	PPh ₃ (7.5 mol%) instead of L1	83
4	L3 (7.5 mol%) instead of L1	31
5	P(OPh) ₃ (7.5 mol%) instead of L1	0
6	utilizing Pd(OAc) ₂ (2.5 mol%)	21
7	utilizing Pd(dmdba) ₂ (2.5 mol%)	69
8	no K ₂ CO ₃	65
9	MeCN as solvent	77
10	DME as solvent	6
11	4CzIPN (2.5% mol) instead of PC1	72
12	no Pd ₂ (dba) ₃ /L1/PC1/light	0

^aConditions: **1a** (0.10 mmol), **2a** (0.12 mmol), PC1 (1 mol %), Pd₂(dba)₃ (1.25 mol %), L1 (3.75 mol %), and K₂CO₃ (0.10 mmol) in DMF (0.1 M) at 20 °C under 451 nm blue LED irradiation for 16 h. ^bGC yield using dodecane as internal standard. ^cIsolated yield, 0.2 mmol scale, 4 h.

L1: L2: L3:

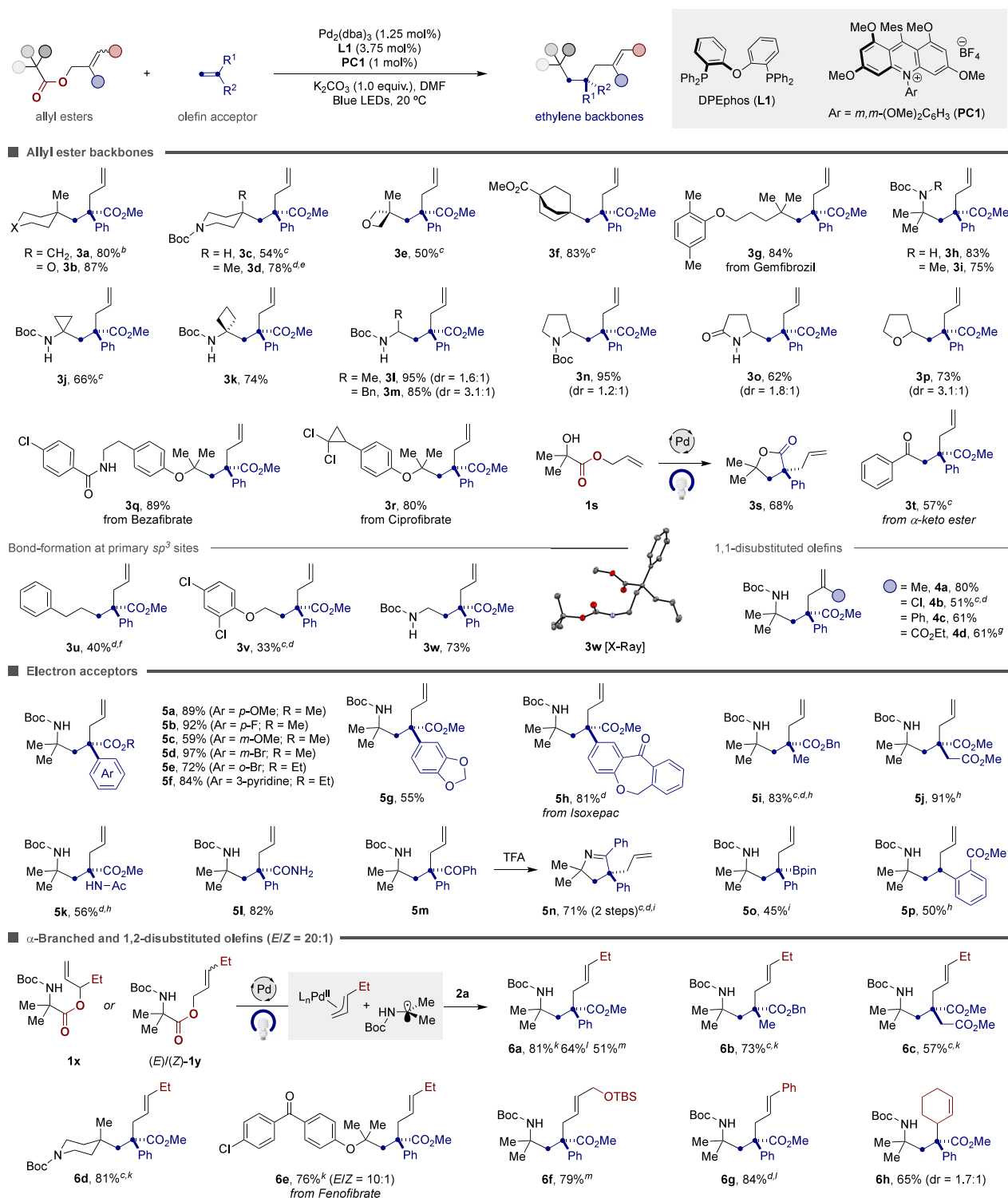
Ar = *m,m*-(OMe)₂C₆H₃ (PC1) 4CzIPN

investigations, it was not clear whether **3a** could be easily within reach given the propensity of in situ generated alkyl open species toward undesired homocoupling of allyl radical intermediates,^{20,21} one-electron DcA (**3a'**),¹⁶ Giese-type additions (**3a''**),²² or unproductive hydrogen-atom transfer (HAT). After some experimentation, a combination of Pd₂(dba)₃ (1.25 mol %), L1 (3.75 mol %), PC1 (1 mol %),²³ and K₂CO₃ (1.0 equiv) in DMF (0.1 M) at 20 °C under blue light-emitting diode (LED) irradiation afforded **3a** in 80% isolated yield. Although similar yields were obtained with L2 or PPh₃ (entries 2 and 3), poor results were found with a Pd/L3 regime. In all of these cases, however, non-negligible amounts of **3a'** and **3a''** were obtained in the crude mixtures. Moreover, not even traces of **3a** were obtained with P(OPh)₃ as the ligand (entry 5). In addition, Pd precatalysts, bases, and solvents other than Pd₂(dba)₃, K₂CO₃, and DMF resulted in markedly lower yields of **3a** (entries 6–10). Likewise, the utilization of 4CzIPN instead of PC1 did not improve the results (entry 11). As anticipated, control experiments revealed that the Pd source, L1, and light irradiation were required for the reaction to occur (entry 12). The lack of reactivity in the absence of photocatalyst reinforces its critical role for accessing III and V via single-electron transfer (SET) events (Scheme 2).¹⁷

Next, we turned our attention to assessing the generality of our photoinduced IDCa of allyl esters. As shown in Table 2, our protocol could accommodate a variety of functional

groups, including alcohols (**1s**), aryl halides (**3q**, **5d**, **5e**) or boronic esters (**5o**), among others. In addition, the reaction could be conducted with allyl esters containing heterocyclic cores such as tetrahydropyrans (**3b**), piperidines (**3c**, **3d**), oxetanes (**3e**), or caged structures (**3f**). Importantly, our method was amenable to scale-up, delivering **3d** in 78% yield at 5 mmol scale.²⁴ Equally interesting is the ability to promote rapid diversification of various α -amino acids, resulting in a formal homologation that results in the corresponding γ -amino acid congeners **3h**–**3o** in one step with yields up to 95%. Moreover, α -keto esters or α -oxy esters could also be utilized as counterparts; while the former led to **3t** in 57% yield, the use of the latter enabled the incorporation of two-carbon fragments in advanced compounds such as bezafibrate (**3q**) or ciprofibrate (**3r**). In addition, the preparation of **3s** illustrates that the reaction not only tolerates alcohol motifs but might also be leveraged as a new entry point to prepare lactones in one pot. The successful preparation of **3u**–**3w** stands as a testament that sp^3 – sp^3 bond formation can be conducted at primary alkyl sites, albeit in lower yields. As shown for **4a**–**4d**, allyl esters bearing 1,1-disubstituted olefins posed no problems. Next, we evaluated the influence of the electron acceptor on the reaction. As shown in Table 2, a variety of 2-aryl acrylates could be used as acceptors, delivering the targeted products **5a**–**5g** in good yields, even with advanced synthetic intermediates (**5h**). Although one might argue that the coexistence of halogen atoms and low-valent Pd species might interfere with the targeted photoinduced IDCa strategy, this was not the case, and **3q**, **4b**, **5d**, and **5e** were all prepared in good yields, thus providing additional functional handles for further transformations via conventional metal-catalyzed cross-couplings. As illustrated by the successful preparation of **5i** and **5j**, our protocol could be extended to 2-alkyl acrylates with a similar ease. Equally effective was the reaction with electron acceptors bearing ketones (**5m**), amides (**5l**), or boronic esters (**5o**). A simple exposure to TFA in the former afforded 1-pyrroline **5n** in 71% yield, whereas the latter provides an additional handle for subsequent manipulation via conventional C–B cleavage. Even the utilization of simple monosubstituted styrenes posed no problems, delivering **5p** in 50% yield. The synthesis of **5k** is particularly important, as it formally enables the incorporation of an α -amino acid function by means of a decarboxylative olefin insertion into simple allyl esters. Interestingly, high yields and linear selectivities ($E/Z = 20:1$) could be obtained regardless of whether E/Z -disubstituted olefins (**1y**) or α -branched congeners (**1x**) were utilized in the allyl ester backbone, a phenomenon previously observed in two-electron manifolds (Table 2, bottom).²⁵ Further studies revealed the successful incorporation of substrates bearing carbamates (**6a**–**6d**), halogens (**6e**), or silyl ethers (**6f**). Even the presence of styrenes or cyclohexenes did not interfere with productive IDCa reaction, giving rise to the targeted compounds **6g** and **6h** in good yields.²⁶

Encouraged by these results, we anticipated that our strategy could be expanded beyond an atom-pair swap in conventional IDCa reactions. As shown in Scheme 3, this turned out to be the case. Specifically, the utilization of pyruvic acid derivative (**7a**) resulted in a one-atom contraction via CO and CO₂ extrusion, leading to **8a** in 57% yield.²⁷ In addition, a two-atom contraction could be within reach from **7b**, giving rise to **8b** via 2-fold extrusion of CO₂.²⁸ Moreover, a two-atom elongation could be accomplished by utilizing 1,3-diene **2b** as acceptor,

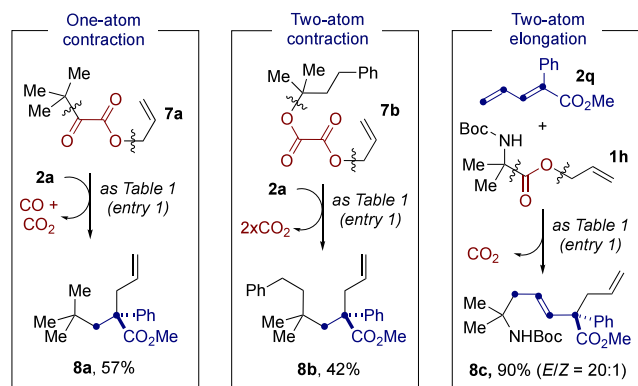
Table 2. Formal Atom Pair Swap via Photoinduced One-Electron IDCa of Allyl Esters with Olefin Acceptors^a

^aAllyl ester (0.20 mmol), olefin acceptor (1.20 equiv), Pd₂(dba)₃ (1.25 mol %), L1 (3.75 mol %), PC1 (1 mol %), and K₂CO₃ (1 equiv) in DMF (0.1 M) at 20 °C under 451 nm blue LED irradiation (1 W) for 12–18 h. Isolated yields are an average of at least two independent runs. ^b4 h reaction time. ^cPC1 (2.5 mol %). ^dPd₂(dba)₃ (2.5 mol %) and L1 (7.5 mol %). ^e5 mmol scale with two 427 nm Kessil lamp irradiation (45 W) for 18 h. ^fPC1 (5.0 mol %) with 427 nm 45W blue-LED irradiation for 72 h. ^g2a (3.0 equiv). ^hUtilizing 4CzIPN (2.5 mol %). ⁱBoc deprotection with TFA at rt for 1 h. ^j2o (2.5 equiv), and no K₂CO₃ was utilized. ^kUtilizing α -branched allyl ester as precursor. ^lUtilizing (*E*)-linear allyl esters as precursors. ^mUtilizing (*Z*)-linear allyl esters as precursor.

resulting in the incorporation of a four-carbon fragment.²⁹ The modularity and versatility of our strategy are further illustrated in Scheme 4. Specifically, exposure of boron-containing **5o** to

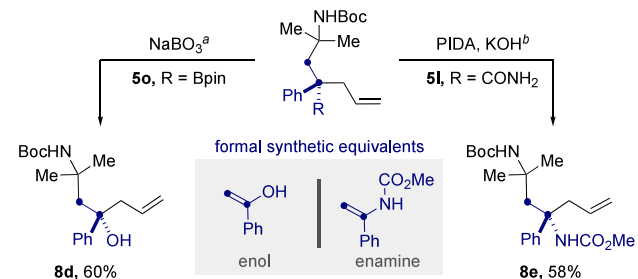
NaBO₃·4H₂O resulted in **8d** in 60% yield. Similarly, a Hofmann rearrangement of **5l** bearing an amide function cleanly delivered **8e**.³⁰ These results are particularly note-

Scheme 3. Beyond Conventional IDCA Reactions

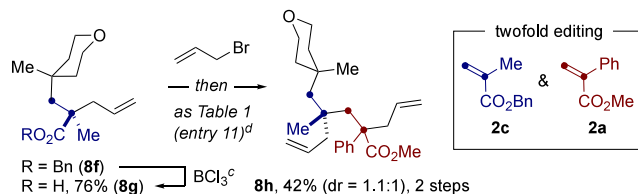


Scheme 4. Postmodification Events

overcoming polarity-mismatched limitations in electron-acceptors



iterative photoinduced IDCA scenarios (four x sp^3 – sp^3 bond-formations)



^aNaBO₃·4H₂O (3 equiv), THF:H₂O (1:1, 0.075 M), rt, 6 h.

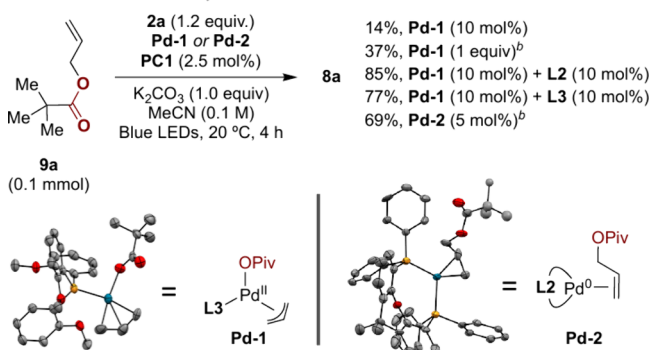
^bPhI(OAc)₂ (1.2 equiv), KOH (2 equiv), MeOH (0.1 M), 60 °C, 30 min. ^cBCl₃ (3.3 equiv), CH₂Cl₂ (0.1 M), 0 °C, 4 h. ^d(i) Allyl bromide (2.5 equiv), K₂CO₃ (2.5 equiv), DMF (0.3 M), rt, 18 h; (ii) allyl ester (0.2 mmol), 2a (1.2 equiv), Pd₂(dba)₃ (2.50 mol %), L1 (7.50 mol %), 4CzIPN (5 mol %), K₂CO₃ (1 equiv) in DMF (0.1 M) at 20 °C under 451 nm blue LED irradiation (1 W) for 18 h.

worthy given that the means to access **8d** and **8e** can formally be visualized as a polarity-mismatched radical addition,³¹ which readily incorporates the enol form of acetophenone or an enamine as counterparts in an IDCA-type scenario. The flexibility of our protocol is further illustrated in the preparation of **8h** via two consecutive photoinduced IDCA events that forge four different sp^3 – sp^3 linkages.

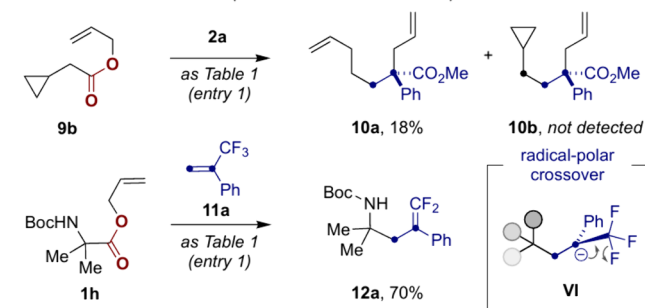
Next, we turned our attention to studying the underpinnings of our photoinduced IDCA reaction (Scheme 5). To this end, we evaluated the reactivity of **9a** with Pd-1 and Pd-2 which were easily synthesized by simple salt metathesis of allylPdCl dimer with AgOPiv followed by addition of L2 or L3.³² Interestingly, low yields of **8a** were obtained regardless of whether Pd-1 was utilized in a stoichiometric or catalytic manner, likely due to the inherent low stability of the monoligated Pd center. It is worth noting, however, that the reaction could be significantly improved in the presence of 10 mol % of L2 (85% yield) or L3 (77% yield). These results reinforce the notion that coordination of two phosphine

Scheme 5. Preliminary Mechanistic Studies

stoichiometric & catalytic studies with well-defined Pd-1 and Pd-2^a



radical clock and radical-polar crossover mechanistic probes



^aAll reactions conducted at 0.10 mmol scale in MeCN (0.1 M) at 20 °C under 451 nm blue LED irradiation (1 W) for 4 h. Full conversion of **9a** or Pd-1 was observed in all cases. ^b0.025 mmol scale, PC1 (10 mol %).

fragments to the Pd center is particularly important for the reaction to occur, an observation that likely suggests the intermediacy of cationic π -allyl complexes (**II**, Scheme 2) via dissociation of the pivalate fragment at the coordination sphere of the Pd center.³³ This observation was indirectly corroborated by obtaining substantial amounts of **8a** by exposure of **9a** to Pd-2 (5 mol %). The formation of **III** (Scheme 2) was inferred from radical-clock experiments, exclusively leading to **10a** from **9b**.³⁴ Moreover, the radical-polar crossover via **V** (Scheme 2) was assessed by exposure of **1h** to (3,3,3-trifluoroprop-1-en-2-yl)benzene **11a**, resulting in clean formation of **12a** by rapid β -fluoride elimination from **VI**.³⁵

In summary, we have developed a de novo Pd-catalyzed photoinduced one-electron IDCA for simple acyclic allyl esters. The method is characterized by its mild conditions and broad scope, offering a new entry point to enable either a formal atom-pair swap or a series of atom contractions and elongations, depending on the substrate and electron-acceptor utilized. This strategy not only expands our repertoire in IDCA reactions but also facilitates rapid and reliable access to architectures of relevance in medicinal chemistry via unconventional bond disconnections.³⁶ Further extensions to other related processes are underway in our laboratory.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.5c03044>.

Experimental procedures; spectral and crystallographic data (PDF)

Accession Codes

Deposition Numbers 2419954–2419955 and 2423643 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe [Access Structures service](#).

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F.-L.H. and F.S.M. contributed equally.

Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

Cbz, carbazole; Mes, mesityl; dba, dibenzylideneacetone; dmdba, bis(3,5,3,5-dimethoxydibenzylideneacetone); TFA, trifluoroacetic acid; PIDA, (diacetoxyiodo)benzene

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