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α-Oxocarboxylic Acids as Three-Carbon Insertion Units for Palladium-Catalyzed Decarboxylative Cascade Synthesis of Diverse Fused Heteropolycycles

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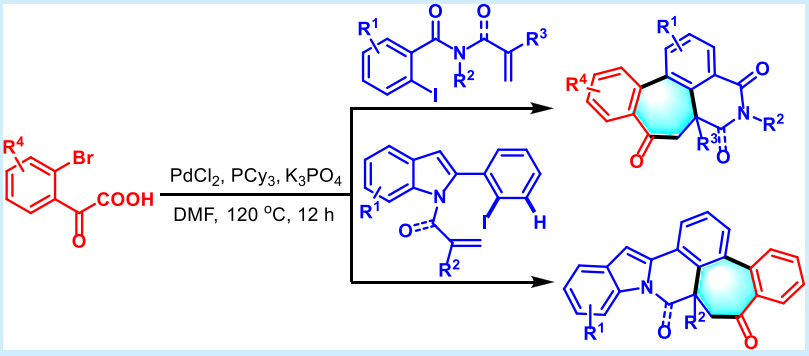
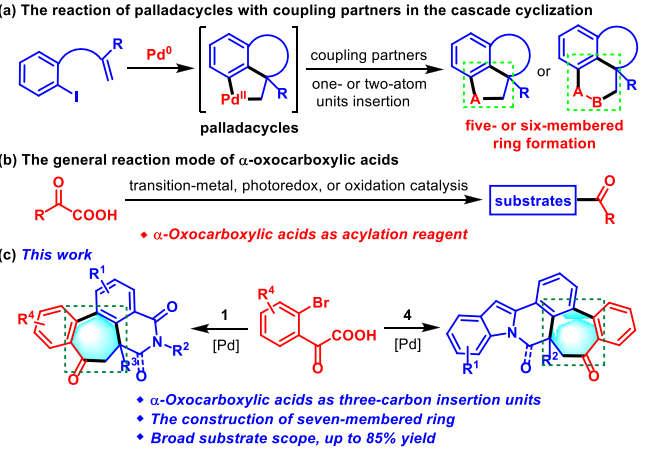


ABSTRACT: A novel palladium-catalyzed decarboxylative cascade cyclization for the assembly of diverse fused heteropolycycles by employing α-oxocarboxylic acids as three-carbon insertion units is reported. This protocol enables the synthesis of isoquinolinedione- and indolo[2,1-*a*]isoquinolinone-fused benzocycloheptanones in moderate to good yields by the use of different aryl iodides, including alkene-tethered 2-iodobenzamides and 2-(2-iodophenyl)-1*H*-indoles. Notably, the approach achieves simultaneous construction of both six- and seven-membered rings via sequential intramolecular carbopalladation, C−H activation, and decarboxylation.

Cascade reactions that enable the construction of multiple bonds in a single operation have emerged as a powerful tool for the synthesis of diverse carbo- and heterocycles due to its high efficiency and step-economy.[1,2] Among them, of particular interest to synthetic chemists is palladium-catalyzed cascade cyclization of alkene-tethered aryl halides involving palladacycles owing to not only the existing C−H activation process but also the versatility of palladacycles generated by an intramolecular carbopalladation/C−H activation sequence.[2] In earlier studies, the pioneering work reported by Grigg and co-workers[3] achieved the construction of heteropolycycles via direct reductive elimination of palladacycles, and this strategy was further developed by several other groups.[4,5] Afterward, another novel transformation of palladacycles involving sequential [1,4]-Pd shift, C−H activation, and reductive elimination process was disclosed by Zhu et al.[6] However, these reported conversions were limited to the inherent C−H bond as the terminated functional group, thus resulting in poor product diversity. Recently, significant breakthroughs in this field have been made in the capture of palladacycles by coupling partners (Scheme 1a).[7−9] Despite great progress, the scope of these coupling partners (such as diaziridinones, α-diazocarbonyl compounds, dibromomethane, aryl iodides, arynes, *o*-bromobenzoic acids, [60]fullerene, and activated alkynes) was

Scheme 1. Palladium-Catalyzed Cascade Cyclization and the Reaction Mode of α-Oxocarboxylic Acids



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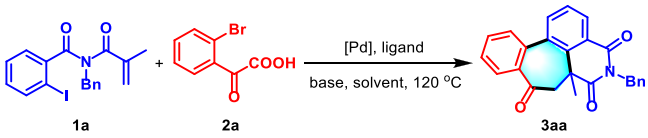
generally limited to construct five- and six-membered rings by inserting one- or two-atom units. Methods for forging a seven-membered ring are still elusive so far. Therefore, developing new coupling reagents to target this goal is in great demand.

α-Oxocarboxylic acids have become among the most versatile synthons for constructing C−C and C−heteroatom bonds in organic synthesis.[10] A myriad of elegant methods via decarboxylative coupling have been reported by Ge, Wang, Duan, and Goossen et al.[11,12] However, the overwhelming majority of methods focus on the use of α-oxocarboxylic acids as an acylation reagent under transition-metal, photoredox, or oxidation catalysis (Scheme 1b). Accordingly, the exploitation of a new transformation model of α-oxocarboxylic acids is urgently required. Inspired by our interest in the cascade reactions involving the functionalization of palladacycles,[9,12] we envision that α-oxocarboxylic acids can couple with palladacycles to construct polycyclic compounds. Herein, we report a palladium-catalyzed decarboxylative cascade cyclization of alkene-tethered aryl iodides with 2-(2-bromoaryl)-2-oxoacetic acids for the synthesis of diverse fused heteropolycycles (Scheme 1c). Notably, a seven-membered ring can be formed by 2-(2-bromoaryl)-2-oxoacetic acids as three-carbon insertion units.

Our investigation commenced with the cascade reaction of *N*-benzyl-2-iodo-*N*-methacryloylbenzamide **1a** with 2-(2-bromophenyl)-2-oxoacetic acid **2a** (Table 1). Fortunately, the anticipated tetracyclic isoquinolinedione-fused benzocycloheptanone **3aa** was obtained in 40% yield under common catalytic conditions composed of $Pd(OAc)_2$, PPh_3, and K_3PO_4 in DMA at 120 °C (entry 1). Various parameters were subsequently examined to acquire the optimal reaction conditions. $PdCl_2$ was proven to be the most efficient catalyst by investigating several palladium salts, such as $PdCl_2(PPh_3)_2$, $PdCl_2$, and $Pd(PPh_3)_4$ (entries 2−4). The removal of ligand PPh_3 was found to have a negative effect on this decarboxylative tandem reaction (entry 5). Other ligands were then screened, and PCy_3 gave a better outcome. Unfortunately, attempts using other bases, such as K_2CO_3, Cs_2CO_3, and KOAc, indicated that all of them were inferior to K_3PO_4 (entries 10−12). We next turned our attention to solvents. Replacing DMA with DMF could promote the conversion efficiency (entry 13), whereas other solvents resulted in significantly diminished or even trace yields (entries 14−16). Eventually, both decreasing and increasing reaction temperature displayed worse efficiency than this result at 120 °C (entries 17 and 18). Satisfactorily, the reaction scaled up to 1 mmol of **1a** could yield 67% of product **3aa** (entry 13).

With the optimal reaction conditions determined, we set out to investigate the generality of this transformation (Scheme 2). The scope of imides **1** was initially examined. This protocol was applicable to a broad range of imides **1**, thus affording isoquinolinedione-fused benzocycloheptanones **3aa**−**pa** in

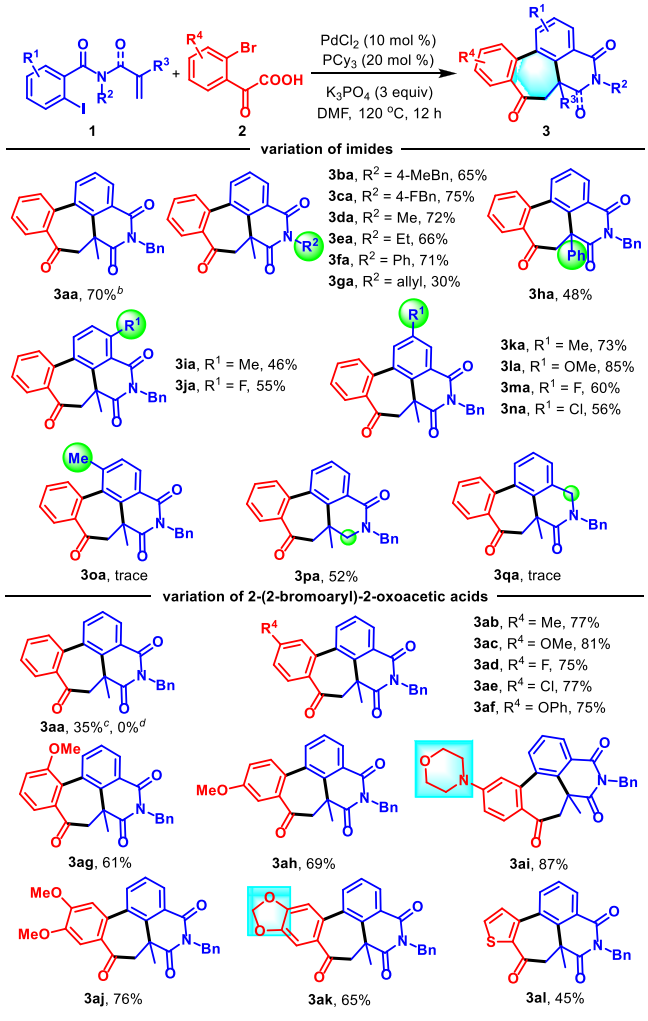
Table 1. Optimization of the Reaction Conditions[a]



entry	[Pd]	ligand	base	solvent	yield (%)[b]
1	$Pd(OAc)_2$	PPh_3	K_3PO_4	DMA	40
2	$PdCl_2(PPh_3)_2$	PPh_3	K_3PO_4	DMA	trace
3	$PdCl_2$	PPh_3	K_3PO_4	DMA	66
4	$Pd(PPh_3)_4$	PPh_3	K_3PO_4	DMA	trace
5	$PdCl_2$		K_3PO_4	DMA	59
6	$PdCl_2$	dppf	K_3PO_4	DMA	26
7	$PdCl_2$	P*t*-Bu_3	K_3PO_4	DMA	46
8	$PdCl_2$	X-phos	K_3PO_4	DMA	63
9	$PdCl_2$	PCy_3	K_3PO_4	DMA	68
10	$PdCl_2$	PCy_3	K_2CO_3	DMA	trace
11	$PdCl_2$	PCy_3	Cs_2CO_3	DMA	trace
12	$PdCl_2$	PCy_3	KOAc	DMA	45
13	$PdCl_2$	PCy_3	K_3PO_4	DMF	75 (67)[e]
14	$PdCl_2$	PCy_3	K_3PO_4	DMSO	45
15	$PdCl_2$	PCy_3	K_3PO_4	MeCN	32
16	$PdCl_2$	PCy_3	K_3PO_4	toluene	trace
17[c]	$PdCl_2$	PCy_3	K_3PO_4	DMF	67
18[d]	$PdCl_2$	PCy_3	K_3PO_4	DMF	39

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.5 equiv), [Pd] (10 mol %), ligand (20 mol %), base (3 equiv), and solvent (2 mL) at 120 °C under N_2 for 12 h. [b]Isolated yield. [c]At 100 °C. [d]At 140 °C. [e]**1a** (1 mmol) was used.

Scheme 2. Synthesis of Isoquinolinedione-Fused Benzocycloheptanones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (1.5 equiv), $PdCl_2$ (10 mol %), PCy_3 (20 mol %), K_3PO_4 (3 equiv), and DMF (2 mL) at 120 °C under N_2 for 12 h. [b]*N*-Benzyl-2-bromo-*N*-methacryloylbenzamide was used. [c]2-(2-Iodophenyl)-2-oxoacetic acid was used. [d]2-(2-Chlorophenyl)-2-oxoacetic acid was used.

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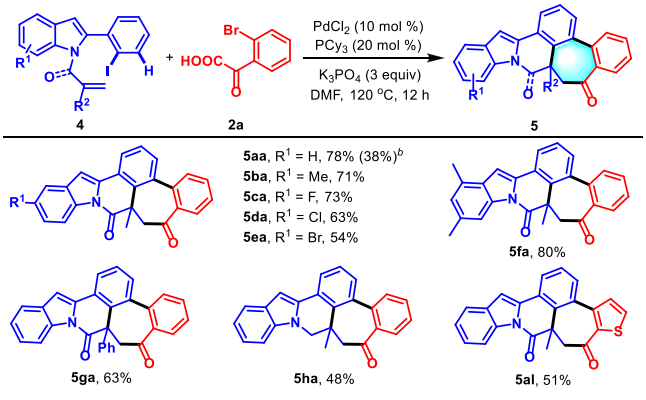
moderate to good yields. Various substituents on the nitrogen atom, such as 4-MeBn, 4-FBn, Me, Et, Ph, and allyl groups, were well-tolerated, and the desired products **3ba**–**ga** were afforded in 30–75% yields. Importantly, imide **1h** with a phenyl group on the alkene was able to undergo this cascade cyclization to furnish product **3ha** in 48% yield. Regarding the 2-iodobenzamide moiety, a range of functional groups (Me, OMe, F, and Cl) in an *ortho* or *meta* position relative to the amide group all could survive, furnishing products **3ia**–**na** in 46–85% yields. However, imide **1o** derived from 2-iodo-4-methylbenzamide was not a viable substrate. The results indicated that the steric effect had a vital influence on the construction of a seven-membered ring. Substrates **1p** and **1q** containing only one amide group were also tested, and **1q** showed poor reactivity. Remarkably, substrate derived from 2-bromobenzamide was perfectly accommodated to provide product **3aa** in 70% yield.

The scope of 2-(2-bromoaryl)-2-oxoacetic acids was then explored (Scheme 2). A range of 2-oxocarboxylic acids **2b**–**k** were subjected to the optimal reaction conditions to furnish isoquinolinedione-fused benzocycloheptanones **3ab**–**ak** in 61–87% yields. Various substituents on the benzene ring, including both electron-donating (Me, OMe, and OPh) and electron-withdrawing groups (F and Cl), were well-tolerated (**3ab**–**ah**). Their electronic property and position had no obvious effect on the reaction efficiency. Note that morpholinyl-, dimethyloxy-, or dioxolyl-substituted 2-(2-bromoaryl)-2-oxoacetic acids could be smoothly converted into products **3ai**–**ak**. Gratifyingly, 2-(3-bromothiophen-2-yl)-2-oxoacetic acid also exhibited good reactivity, providing product **3al** in 45% yield. Furthermore, 2-(2-iodophenyl)-2-oxoacetic acid was also a suitable substrate. However, only 35% of **3aa** was isolated due to the formation of the decarboxylation/decarbonylation side product.[9d] Unfortunately, this protocol was not compatible with 2-(2-chlorophenyl)-2-oxoacetic acid.

To highlight the applicability of this cyclization cascade, we next attempted the feasibility of the reaction of alkene-tethered 2-(2-iodophenyl)-1*H*-indoles **4a** with 2-oxocarboxylic acids **2a** (Scheme 3). To our delight, indolo[2,1-*a*]isoquinolinone-fused benzocycloheptanone **5aa** was formed in 78% yield under the above reaction conditions. Notably, the replacement of an iodine atom with a bromine atom on the 2-(2-iodophenyl)-1*H*-indole could also furnish product **5aa**, albeit with a lower yield. Subsequently, a series of 2-(2-iodophenyl)-1*H*-indoles **4b**–**i** were examined. Substrates **4b**–**f** bearing diverse substituents (Me, F, Cl, and Br) on the indole undergo this cascade reaction with **2a** to deliver the target products **5ba**–**fa** in 54–80% yields. 2-Phenylacryl- or 2-methylallyl-substituted indoles were also competent substrates, affording products **5ga** and **5ha** in moderate yields. Notably, the reaction of 2-(3-bromothiophen-2-yl)-2-oxoacetic acid with **4a** proceeded efficiently, delivering 51% of the target product **5al**. Unfortunately, 2-(2-iodophenyl)-1*H*-benzo[*d*]imidazole **1i** was unreactive.

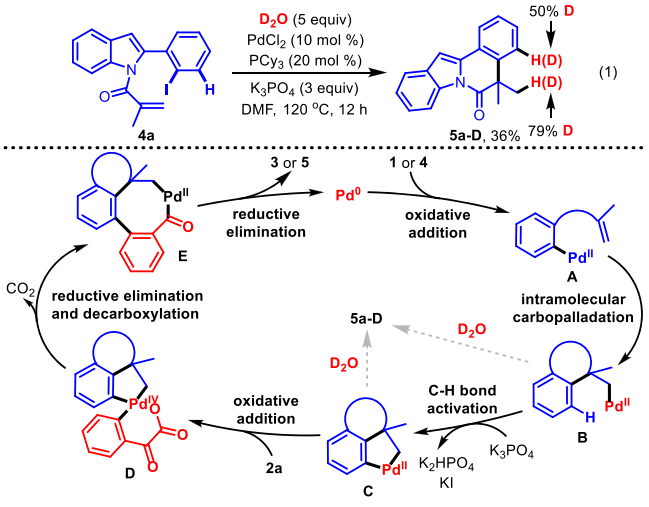
Scheme 3. Synthesis of Indolo[2,1-*a*]isoquinolinone-Fused Benzocycloheptanones[a]



[a]Reaction conditions: **4** (0.2 mmol), **2a** (1.5 equiv), $PdCl_2$ (10 mol %), PCy_3 (20 mol %), K_3PO_4 (3 equiv), and DMF (2 mL) at 120 °C under N_2 for 12 h. [b]Alkene-tethered 2-(2-bromophenyl)-1*H*-indole was used.

To gain insights into the reaction mechanism, the isotope experiment was carried out by adding 5 equiv of D_2O under the optimal reaction conditions. The result indicated that palladacycle **C** was formed in the reaction process. On the basis of our experimental results and previous work,[13] a plausible catalytic cycle for this transformation was illustrated as Scheme 4. First,

Scheme 4. Control Experiment and Possible Reaction Mechanism



oxidation addition of the C–I bond to Pd(0) followed by intramolecular carbopalladation forms intermediate **B**, which undergoes C–H activation to generate fused palladacycle **C**. Then, palladacycle **C** undergoes an oxidative addition with the C–Br bond of 2-oxocarboxylic acid **2a** to afford Pd(IV) species **D** with the assistance of an *ortho*-chelating carboxyl group, which has been demonstrated by the related reports.[13] Immediately after, sequential reductive elimination and decarboxylation of intermediate **D** produces eight-membered palladacycle **E**. Eventually, this catalytic cycle is accomplished by reductive elimination of palladacycle **E**, thus resulting in the formation of products **3** or **5** as well as active Pd(0) species.

In conclusion, we have disclosed an efficient method for synthesizing diverse fused heteropolycycles via a palladium-catalyzed decarboxylative cascade cyclization of aryl iodides, including alkene-tethered 2-iodobenzamides and 2-(2-iodophenyl)-1*H*-indoles. In this novel conversion, 2-oxocarboxylic acids are employed as coupling reagents to achieve three-carbon unit insertion via an intramolecular Heck/C–H activation/decarboxylation sequence, thus forging isoquinolinedione- and indolo[2,1-*a*]isoquinolinone-fused benzocycloheptanones in moderate to good yields. Remarkably, a seven-membered ring is constructed in this reaction. Further applications of 2-oxocarboxylic acids are underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00493.

Experimental procedures, full characterization of products, and NMR spectra (PDF)

Accession Codes

CCDC 2059100 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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