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Pd(II)-Catalyzed Enantioselective C–H Activation/C–O Bond Formation: Synthesis of Chiral Benzofuranones

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Abstract

Pd(II)-catalyzed enantioselective C–H activation of phenylacetic acids followed by an intramolecular C–O bond formation afforded chiral benzofuranones. This reaction provides the first example of enantioselecctive C–H functionalizations through Pd(II)/Pd(IV) redox catalysis.

The ability to synthesize molecules in a rapid and efficient manner still represents a major challenge in the field of organic synthesis. Of significant interest are methods that provide access to fundamental building blocks in a chemoselective and enantioselective manner from readily available starting materials in a step-economical fashion. In this context, C–H bond functionalization offers a unique opportunity to access molecules of synthetic interest from readily available starting materials.[1,2] Specifically, the functionalization of phenylacetic acids and derivatives thereof have led to the development of C–C and C–X bond forming reactions. We envisioned that α,α-disubstituted benzofuran-2-ones, a valuable synthon and pharmacophore found in numerous natural products and drug scaffolds could be readily attainable from the C–H bond functionalization of phenylacetic acid derivatives (Scheme 1).[3]

We hypothesized that for such an approach to be successful, the phenylacetic acid would need to undergo cyclometallation to arrive at the 6-membered palladacycle, with subsequent reductive elimination facilitated by oxidation of the Pd(II) metallacycle to a Pd(IV) cyclometalated intermediate by a bystanding oxidant (Scheme 1).[4] Indeed, we have previously shown that addition of bystanding oxidants are suitable for facilitating reductive elimination in the synthesis of γ-lactams[4b] and 2,3-dihydrobenzofurans.[4e] Herein, we report the direct synthesis of α,α-disubstituted benzofuran-2-ones[5] via a Pd(II)/Pd(IV)-catalyzed C–H activation/C–O bond formation.[6,7] Moreover, the use of MPAA ligands allows for the enantioselective synthesis[8,9] of benzofuran-2-ones through a desymmetrization[10] to provide the respective products in excellent enantioselectivities, thus providing a developed method providing a complimentary strategy to current methods.[11]

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Supporting Information.
Experimental procedure and characterization of all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

The Authors declare no competing financial interest.

Our study commenced by examining the C–H activation/C–O cyclization of 1-phenylcyclopentanecarboxylic acid (**1a**) in the presence of $Pd(OAc)_2$ (10 mol %) and KOAc (2.0 equiv.). Although a wide range of oxidants failed to give the desired lactone product, such as Cu(II) and Ag(I) salts (See SI), we found that **2a** could be obtained in 42% yield with $PhI(OAc)_2$, a generally effective oxidant for the Pd(II)/Pd(IV) catalytic cycle.[12] It should be noted that acetoxylation of the C–H bond, a common product obtained with this oxidant is not observed under the optimized reaction conditions. To improve the yield of the reaction we surveyed common additives and ligands (Table 1). Disappointingly, additives such as benzoquinone and acetic acid failed to improve the yield as **2a** was obtained in 22% and 32% respectively (entry 1 and 2). Additionally, the use of other common carboxylic acids (entry 4 and 5) failed to improve the yield compared to the non-ligated conditions (entry 1).

Guided by previous findings that C-H functionalizations can be promoted by MPAA ligands,[13] we subsequently focused on amino acid derivatives, and under the optimized reaction conditions with 30 mol % of Ac-Ala-OH **2a** was obtained in 70% yield (entry 6). The use of 30% ligand is necessary for effective binding due to the presence of large excess of acetates. Replacement of Ac-Ala-OH with Boc-Ala-OH the product is obtained in 54% yield (entry 7). Additionally, we observed that the N-protecting group on the amino acid played a pivotal role as with Ac-Gly-OH provides **2a** in 69% yield while Boc-Gly-OH provides **2a** in 58% yield. Surprisingly, an increase of the steric bulk on the amino acid side chain in an effort to improve the yield failed compared to that of Ac-Gly-OH (entries 10 through 13). It is noteworthy, that at this point very negligible effects in yield were observed with the N-protecting group. However, optimal results were obtained with 30 mol % Boc-Val-OH and 7.5 mol % of $Pd(OAc)_2$ to give **2a** in 92% yield (entry 14).

With the optimized reaction conditions in hand, we next investigated the substrate scope of the phenylacetic acid directed C–H lactonization to provide a platform for subsequent enantioselective studies. A variety of α,α-disubstituted phenylacetic acids were cyclized to give the corresponding γ-lactones in modest to excellent yield with either Boc-Val-OH or Ac-Gly-OH as suitable ligand (Chart 1). Both electron-donating groups, such as *para*-Me (**2b)** and *para*-OMe (**2c)** give the benzofuran-2-none products in 94% and 80% yield respectively. Additionally, electron withdrawing substituent's placed on the aromatic ring **2d** and **2e** give the cyclized products with diminished yields of 67% and 58%. To survey the influence of the Thorpe-Ingold effect on the cyclization **2f** and **2g** were isolated in 56% and 90% yield. Gratifyingly, lactonization of α,α-dimethyl phenylacetic acid **2h** provides the desired product in 87% yield.

Subsequent substitution of the arene with electron rich substituent's **2i**, **j**, **k,** and **2o** of α,α-dimethyl phenylacetic acid are isolated in good yields (83–94%). Additionally, the placement of electron deficient substituents on the aromatic ring **2l**, **m**, **n** and **2p** provide the respective products in slightly diminished yields (56%–70%). Gratifyingly, when the thiophene derived phenylacetic acid is employed the cyclized product **2q** is obtained in 50% yield. Moreover, substitution of the α,α-dialkyl group for di-butyl **2r** and non-symmetric alkyl groups **2s**, **t**, **u**, and **2v** all provide the benzofuranone products in good yields (84%–92%). Meanwhile, phenyl acetic acid with either *ortho*-substituted group at the phenyl ring or hydrogen at the α-position is not compatible with our catalytic system.

With the newly developed C–H lactonization protocol of phenylacetic acid, we proceeded to develop a set of conditions for the enantioselective synthesis of benzofuran-2-ones systematically with mono-*N*-protected amino acid ligands that would proceed through a desymmetrization. Although, enantioselective C–H bond functionalizations still represent a considerable challenge, enantioselective desymmetrization processes have been reported

through the Pd(II)/Pd(0)[8] and Pd(0)/Pd(II)[9] redox manifolds to provide valuable synthons in high enantioselectivities. Starting with **3a** as the model substrate we began our optimization studies and readily identified that Boc-protected amino acids provide optimal yields in the desymmetrization reaction. A systematic study of the side chain of the amino acid ligand was conducted to improve upon the enantioselectivities (Table 2).

Starting with Boc-L Alanine (Boc-Ala-OH) **4a** is obtained in 71% yield and 85% ee (entry 1). An increase in steric bulk of the amino acid side chain to Boc-Val-OH provided an enantioselectivity of 95% with a yield of 58% (entry 2). However, the use of Boc-Leu-OH affords **4a** in 64% yield and 96% ee (entry 3); the use of Boc-Ile-OH gives the desired product in 70% yield and 96% ee (entry 4). Further investigation into the amino acid side chain (entry 5 and 6) provided **4a** in lower yields (66–68%) with good enantioselectivities (92–96%) compared to that of Boc-Ile-OH as the ligand. Additionally, lower catalyst loading to 5 mol % of $Pd(OAc)_2$ gave **4a** in 92% ee (entry 7). Noteworthy, is the effect of ligand loading on enantioselectivity, with a palladium loading of 5 mol% and 20 mol% of Boc-Ile-OH **4a** is obtained in 87% ee (entry 8). However, an increase of ligand loading to 40 mol % affords **4a** in 95% ee and an improved yield of 78% (entry 9). This effect of increased ligand loading and higher enantioselectivities is attributed to generating a sufficient quantity of the amino acid Pd(II) catalyst; particularly as the formation of acetic acid can facilitate ligand exchange and giving rise to $Pd(OAc)_2$. The non-ligated reaction can subsequently occur to provide racemic product and lower enantioselectivities.

Having identified a suitable amino acid ligand affording high enantioselectivities, we proceeded to establish the scope of the asymmetric C–H lactonization. A diverse class of diphenylacetic acid substrates was subjected to the reaction to provide the benzofuranones (Chart 2). Alkyl-substituted diphenylacetic acids **4b**, **c**, **d** were cyclized with high enantioselectivities (94–96%) and good yields (56–86%). The reaction was also found to tolerate substrates containing heteroatoms as **4e**, **f**, **g** were isolated in moderate yields (37–51%) with enantioselectivities of 89–95%. Lastly, replacement of the α-methyl for an ethyl undergoes cyclization to afford **4h** in 85% yield and 91% ee.

This rare example of enantioselective C–H activation/C–O bond formation also provides valuable mechanistic insight into the asymmetric C–H activation. The absolute configuration of **4b** (Chart 2) was confirmed to be *R* by X-ray crystallographic analysis, which further support previously proposed stereochemical model (Figure 1),[8b] even though these reactions proceed through different redox catalysis.

In summary, we have developed a Pd(II)-catalyzed enantioselective C–H activation/C–O cyclization of arylacetic acids to afford chiral benzofuranones. This reaction provides the first example of enantioselective C–H functionalizations through Pd(II)/Pd(IV) redox catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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14. At this stage, a stepwise route involving C-H bond acetoxylation/lactonization cannot be excluded (For detailed investigation using ^{18}O-labeled experiment, see SI). For related studies see: Huang C, Ghavtadze N, Chattopadhyay B, Gevorgyan V. J Am Chem Soc. 2011; 133:17630. [PubMed: 21999512] Huang C, Ghavtadze N, Godoi B, Gevorgyan V. Chem Eur J. 2012; 18:9789. [PubMed: 22847834]

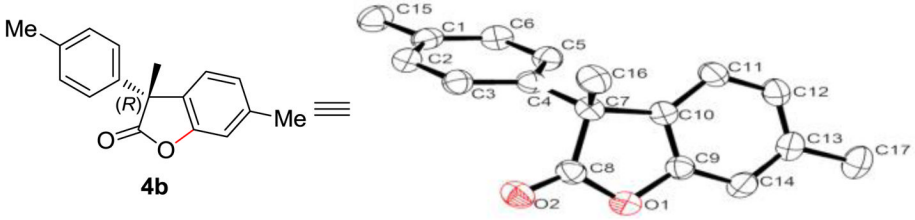
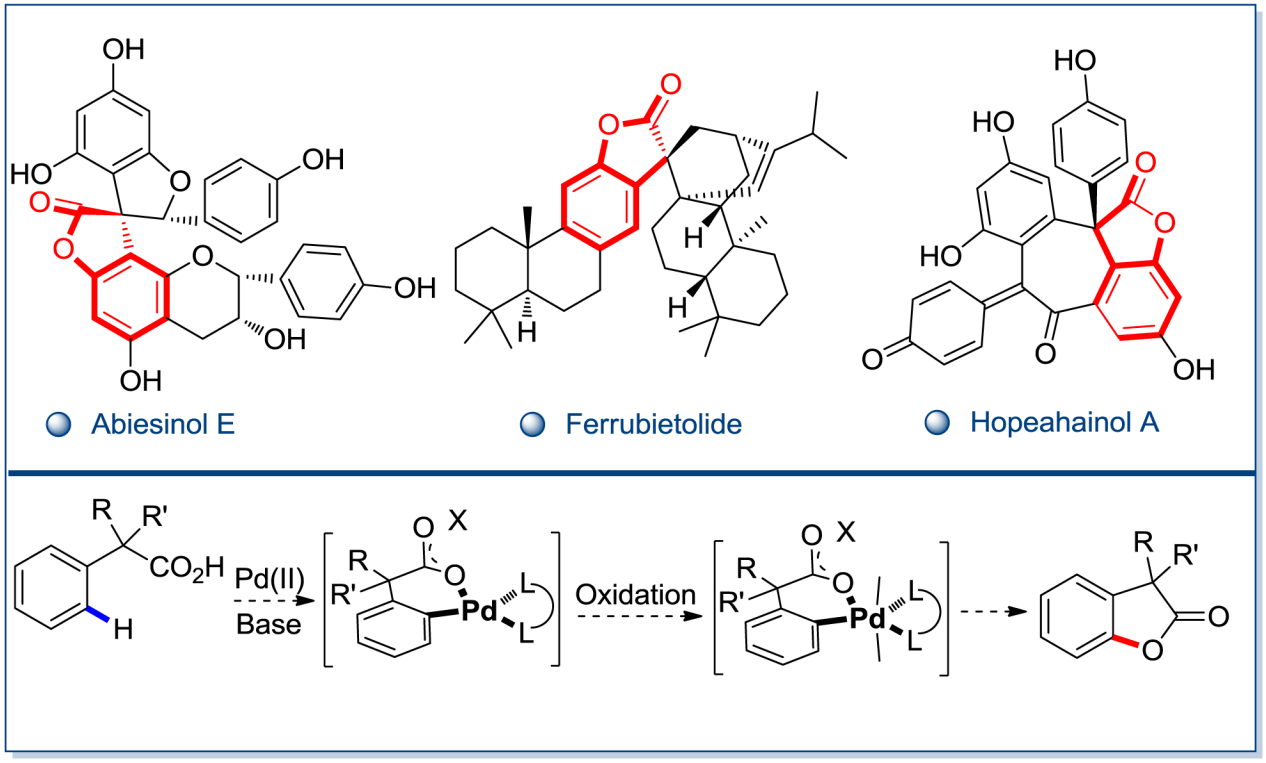


Figure 1.
Absolute Configuration of Benzofuranone 4b



Scheme 1.
Sampling of Natural Products Containing the Benzofuran-2-one Core and Approach to This Scaffold

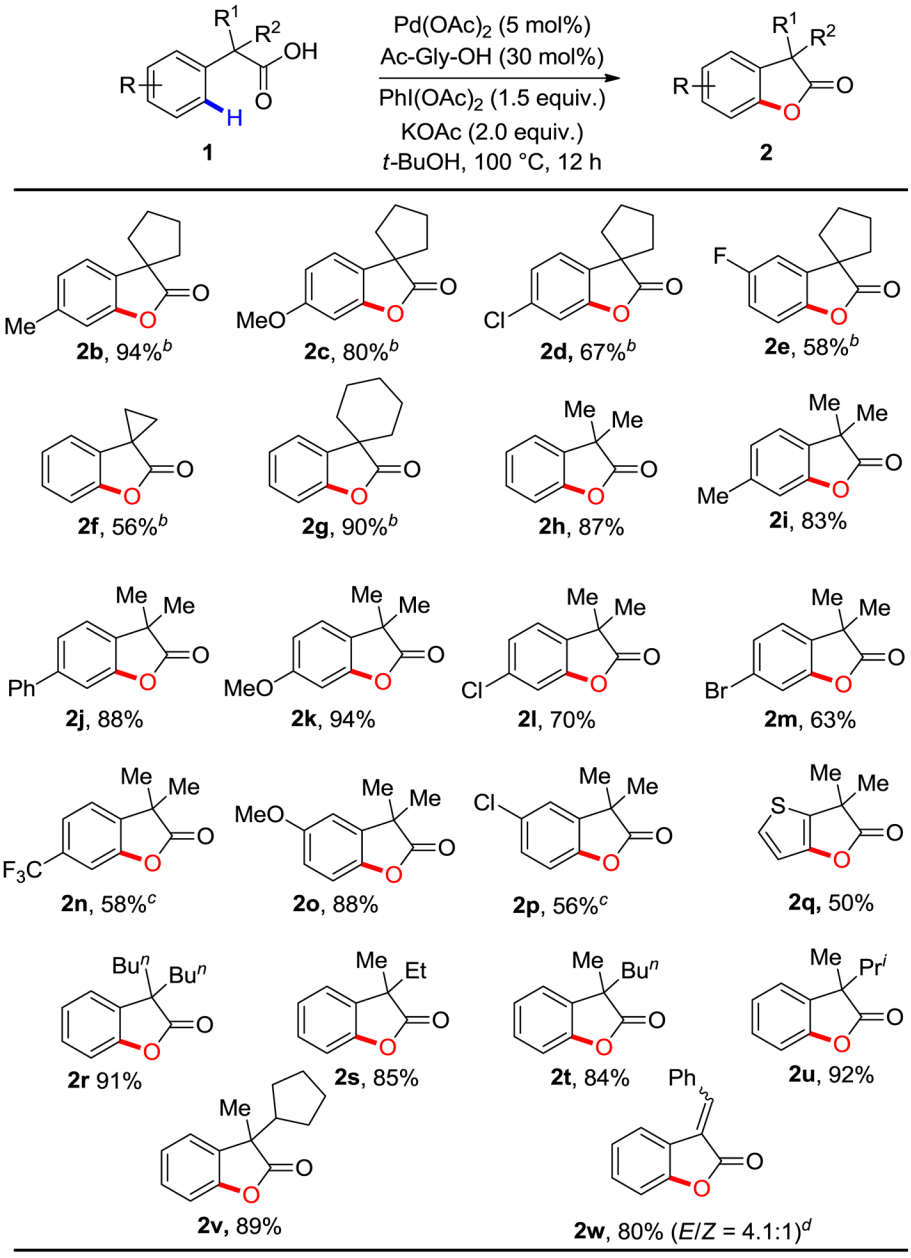


Chart 1. Scope of Phenylacetic Acid Substrates[a]

[a] Isolated yield. [b] $Pd(OAc)_2$ (7.5 mol %) and Boc-Val-OH (30 mol %) were used at 80 °C. [c] $Pd(OAc)_2$ (10 mol %) was used. [d] The *E*/*Z* ratio was determined by ^{1}H-NMR. [e] Most of S.M. was recovered and small amount of them decomposed when the conversions were low.

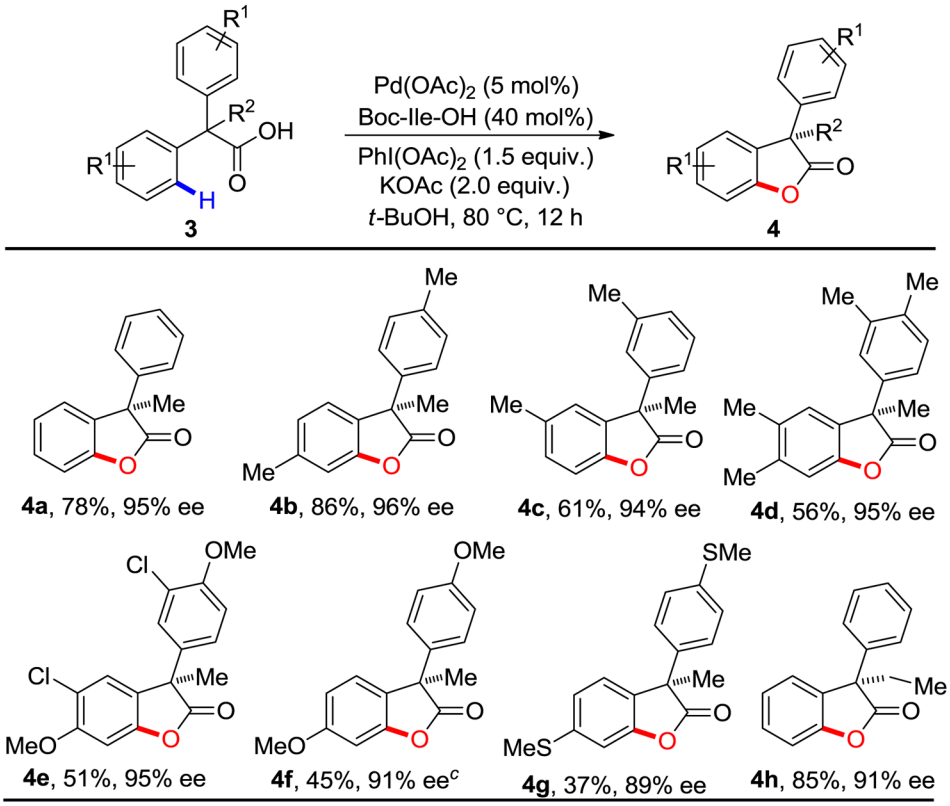
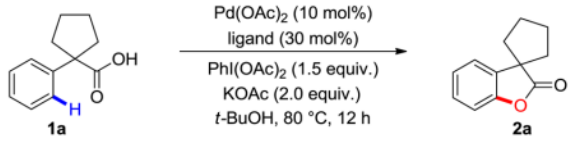


Chart 2. Substrate Scope of the Asymmetric Pd(II)-Catalyzed C-H Lactonization of Diphenylacetic Acids[a,b]

[a] Isolated yield. [b] ee was determined by HPLC analysis on chiral stationary phase. [c] 70 °C, 24 h.

Table 1

The Influence of Additives and Ligands on Reactivity



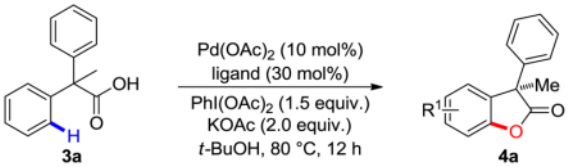
entry	ligand	yield (%)[a]
1	none	42
2	BQ	22
3	HOAc	32
4	t-$BuCO_2H$	37
5	$AdCO_2H$	36
6	Ac-Ala-OH	70
7	Boc-Ala-OH	54
8	Ac-Gly-OH	69
9	Boc-Gly-OH	58
10	Ac-lle-OH	63
11	Boc-lle-OH	66
12	Ac-Leu-OH	66
13	Boc-Leu-OH	63
14[b]	***Boc-Val-OH***	**92**

[a] Isolated yield.

[b] $Pd(OAc)_2$ (7.5 mol %).

Table 2

Influence of Amino Acid Ligands on Enantioselectivity



entry	ligand	yield (%)[a]	ee (%)[b]
1	Boc-Ala-OH	71	85
2	Boc-Val-OH	58	95
3	Boc-Leu-OH	64	92
4	Boc-Ile-OH	70	96
5	Boc-Phe-OH	66	96
6	Boc-^{t}Leu-OH	68	92
7[c]	Boc-Ile-OH	70	92
8[c,d]	Boc-Ile-OH	74	87
9[c,e]	***Boc-Ile-OH***	***78***	***95***
10	Ac-Ile-OH	42	60

[a] Isolated yield.

[b] Determined by HPLC analysis on chiral stationary phase.

[c] $Pd(OAc)_2$ (5 mol %) was used.

[d] Ligand (20 mol %) was used.

[e] Ligand (40 mol %) was used.