



Published in final edited form as:

J Am Chem Soc. 2013 January 30; 135(4): 1236–1239. doi:10.1021/ja311259x.

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

Xiu-Fen Cheng^{†,§}, Yan Li^{†,§}, Yi-Ming Su[†], Feng Yin[†], Jian-Yong Wang[†], Jie Sheng[†], Harit U. Vora[‡], Xi-Sheng Wang^{*,†}, and Jin-Quan Yu[‡]

[†]Department of Chemistry, University of Science and Technology of China, 96 Jinzhai Road, Hefei, Anhui 230026, China

[‡]Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

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 enantioselective 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 bystander oxidant (Scheme 1).⁴ Indeed, we have previously shown that addition of bystander 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-ones⁵ 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 desymmetrization¹⁰ to provide the respective products in excellent enantioselectivities, thus providing a developed method providing a complimentary strategy to current methods.¹¹

Corresponding Author: xswang77@ustc.edu.cn.

§Author Contributions:

X.-F. C. and Y. L. contributed equally.

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-one 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

We gratefully acknowledge the Chinese Academy of Sciences, the Ministry of Education (SRFDP 20123402110040), the National Science Foundation of China (No. 21102138), the National Institutes of Health (NIGMS, 1 R01 GM084019-04), University of Science and Technology of China (USTC) for financial support. We thank Prof. Liu-Zhu Gong and Prof. Shi-Kai Tian from USTC for their help of HPLC analysis.

References

- For selected reviews, see: Daugulis O, Do HQ, Shabashov D. *Acc Chem Res.* 2009; 42:1074. [PubMed: 19552413] Chen X, Engle KM, Wang DH, Yu JQ. *Angew Chem Int Ed.* 2009; 48:5094. Xu LM, Li BJ, Yang Z, Shi ZJ. *Chem Soc Rev.* 2010; 39:712. [PubMed: 20111789] Lyons TW, Sanford MS. *Chem Rev.* 2010; 110:1147. [PubMed: 20078038] Yeung CS, Dong VM. *Chem Rev.* 2011; 111:1215. [PubMed: 21391561] Wencel-Delord J, Dröge T, Liu F, Glorius F. *Chem Soc Rev.* 2011; 40:4740–4761. [PubMed: 21666903]
- For selected reviews of C–H functionalization in total synthesis, see: Taber DF, Stiriba SE. *Chem Eur J.* 1998; 4:990. Godula K, Sames D. *Science.* 2006; 312:67. [PubMed: 16601184] Davies HML, Manning JR. *Nature.* 2008; 451:417. [PubMed: 18216847] Ishihara Y, Baran PS. *Synlett.* 2010:1733. Gutekunst WR, Baran PS. *Chem Soc Rev.* 2011; 40:1976. [PubMed: 21298176] McMurray L, O'Hara F, Gaunt MJ. *Chem Soc Rev.* 2011; 40:1885. [PubMed: 21390391] Brückl T, Baxter RD, Ishihara Y, Baran PS. *Acc Chem Res.* 2012; 45:826. [PubMed: 22017496] Yamaguchi J, Yamaguchi AD, Itami K. *Angew Chem Int Ed.* 2012; 51:8960.
- (a) Wada SI, Hitomi T, Tanaka R, Tokuda H. *Chem Biodivers.* 2010; 7:2303. [PubMed: 20860032] (b) Wada S-I, Hitomi T, Tanaka R. *Helv Chim Acta.* 2009; 92:1610. (c) Shen Z, Falshaw CP, Haslam E, Begley MJ. *J Chem Soc, Chem Comm.* 1985:1135. (d) Onan KD, Kelley CJ, Patarapanich C, Leary JD, Aladesanmi AJ. *J Chem Soc, Chem Comm.* 1985:121. (e) Ge HM, Zhu CH, Shi DH, Zhang LD, Xie DQ, Yang J, Ng SW, Tan RX. *Chem-Eur J.* 2008; 14:376. [PubMed: 17943703] (f) Nicolaou KC, Kang Q, Wu TR, Lim CS, Chen DYK. *J Am Chem Soc.* 2010; 132:7540. [PubMed: 20462209] (g) Nicolaou KC, Wu TR, Kang Q, Chen DYK. *Angew Chem Int Ed.* 2009; 48:3440.
- For a review on bystanding oxidant, see: Engle KM, Mei TS, Wang X, Yu JQ. *Angew Chem Int Ed.* 2011; 50:1478. For selected examples: see: Jordan-Hore JA, Johansson CCC, Gulias M, Beck EM, Gaunt MJ. *J Am Chem Soc.* 2008; 130:16184. [PubMed: 18998652] Mei TS, Wang X, Yu JQ. *J Am Chem Soc.* 2009; 131:10806. [PubMed: 19606861] Wang X, Lu Y, Dai HX, Yu JQ. *J Am Chem Soc.* 2010; 132:12203. [PubMed: 20715820] Wei Y, Yoshikai N. *Org Lett.* 2011; 13:5504. [PubMed: 21950683] Zhang SY, He G, Zhao Y, Wright K, Nack WA, Chen G. *J Am Chem Soc.* 2012; 134:7313. [PubMed: 22486219]
- For selective examples of synthesis of benzofuran-2-ones: Huntress EH, Hearon WM. *J Am Chem Soc.* 1941; 63:2762. Shankaran K, Soan CP, Snieckus V. *Tetrahedron Lett.* 1985; 26:6001. Motallebi S, Müller P. *Helv Chim Acta.* 1993; 76:2803. Anacardio R, Arcadi A, Anniballe DG, Marinelli F. *Synthesis.* 1995:831. Satoh T, Tsuda T, Kushino Y, Miura M, Nomura MJ. *Org Chem.* 1996; 61:6476. Moody CJ, Doyle KJ, Elliott MC, Mowlem TJ. *J Chem Soc, Perkin Trans 1.* 1997:2413. Ye F, Alper H. *Adv Synth Catal.* 2006; 348:1855. Huang C, Chattopadhyay B, Gevorgyan V. *J Am Chem Soc.* 2011; 133:12406. [PubMed: 21766826] Molander GA, Cavalcanti LN. *J Org Chem.* 2011; 76:623. [PubMed: 21192650] Zhu C, Wang R, Falck JR. *Org Lett.* 2012; 14:3494. [PubMed: 22731862]
- For Pd-catalyzed carboxyl-directed allylic and benzylic C(sp³)–H activation/C–O bond formation to synthesis lactones, see: Covell DJ, White MC. *Angew Chem Int Ed.* 2008; 47:6448. Takenaka K, Akita M, Tanigaki Y, Takizawa S, Sasai H. *Org Lett.* 2011; 13:3506. [PubMed: 21657245] Novák P, Correa A, Gallardo-Donaire J, Martin R. *Angew Chem Int Ed.* 2011; 50:12236.
- For Pd-catalyzed hydroxyl-directed C–H activation/C–O bond formation, see: Xiao B, Gong TJ, Liu ZJ, Liu JH, Luo DF, Xu J, Liu L. *J Am Chem Soc.* 2011; 133:9250. See also ref. 4e–f. [PubMed: 21609019]
- (a) Shi BF, Mangel N, Zhang YH, Yu JQ. *Angew Chem Int Ed.* 2008; 47:4882. (b) Shi BF, Zhang YH, Lam JK, Wang DH, Yu JQ. *J Am Chem Soc.* 2010; 132:1460. [PubMed: 20073459] (c) Wasa W, Engle KM, Lin DW, Yoo EJ, Yu JQ. *J Am Chem Soc.* 2011; 133:19598. [PubMed: 22059375]
- For Pd(0)-catalyzed C–H functionalization reactions using chiral phosphine or carbene ligands, see: Albicher MR, Cramer N. *Angew Chem Int Ed.* 2009; 48:9139. Renaudat A, Jean-Gérard L, Jazzar R, Kefalidis CE, Clot E, Baudoin O. *Angew Chem Int Ed.* 2010; 49:7261. Nakanishi M, Katayev D, Besnard C, Kündig EP. *Angew Chem Int Ed.* 2011; 50:7438. Anas S, Cordi A, Kagan HB. *Chem Commun.* 2011; 47:11483. Shintani R, Otomo H, Ota K, Hayashi T. *J Am Chem Soc.* 2012; 134:7305. [PubMed: 22506681]

10. For selected reviews about asymmetric desymmetrization, see: Willis MC. *J Chem Soc, Perkin Trans 1*. 1999;1765. García-Urdiales E, Alfonso I, Gotor V. *Chem Rev*. 2005; 105:313. [PubMed: 15720156] Studer A, Schleth F. *Synlett*. 2005:3033. Rovis T, Mikami K, Lautens M. *New Frontiers in Asymmetric Catalysis*. John Wiley & Sons, Inc New York 2007:275–309. Atodiresei I, Schiffrers I, Bolm C. *Chem Rev*. 2007; 107:5683. [PubMed: 18072807] For a recent example on asymmetric Ullman C–N coupling, see: Zhou F, Guo J, Liu J, Ding K, Yu S, Cai Q. *J Am Chem Soc*. 2012; 134:14326. [PubMed: 22913611]
11. For selective examples of enantioselective synthesis of benzofuranones: Grigg R, Putnikovic B, Urch CJ. *Tetrahedron Lett*. 1996; 37:695. Hills ID, Fu GC. *Angew Chem Int Ed*. 2003; 42:3921. Shaw SA, Aleman P, Vedejs E. *J Am Chem Soc*. 2003; 125:13368. [PubMed: 14583027] Trost BM, Cramer N, Silverman SM. *J Am Chem Soc*. 2007; 129:12396. [PubMed: 17880222] Li X, Hu S, Xi Z, Zhang L, Luo S, Cheng JP. *J Org Chem*. 2010; 75:8697. [PubMed: 21105671] Zhu CL, Zhang FG, Meng W, Nie J, Cahard D, Ma JA. *Angew Chem Int Ed*. 2011; 50:5869. Cao Y, Jiang X, Liu L, Shen F, Zhang F, Wang R. *Angew Chem Int Ed*. 2011; 50:9124. Cassani C, Tian X, Escudero-Adán EC, Melchiorre P. *Chem Commun*. 2011; 47:233.
12. Yoneyama T, Crabtree RH. *J Mol Catal A: Chem*. 1996; 108:35. Dick AR, Hull KL, Sanford MS. *J Am Chem Soc*. 2004; 126:2300. [PubMed: 14982422] See also ref 4e & 4g; For reviews on Pd(II)/Pd(IV)-catalyzed C–H functionalization, see: Muñoz K. *Angew Chem Int Ed*. 2009; 48:9412. Hickman AJ, Sanford MS. *Nature*. 2012; 484:177. See also ref. 1d–e. [PubMed: 22498623]
13. For pioneering study on amino acid ligand-accelerated C–H functionalization: Wang DH, Engle KM, Shi BF, Yu JQ. *Science*. 2010; 327:315. [PubMed: 19965380]
14. At this stage, a stepwise route involving C–H bond acetoxylation/lactonization cannot be excluded (For detailed investigation using ¹⁸O-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]

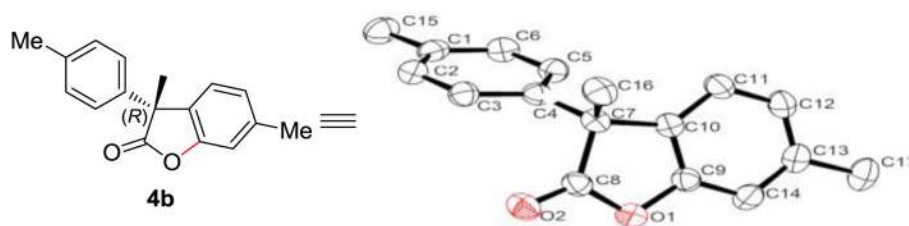
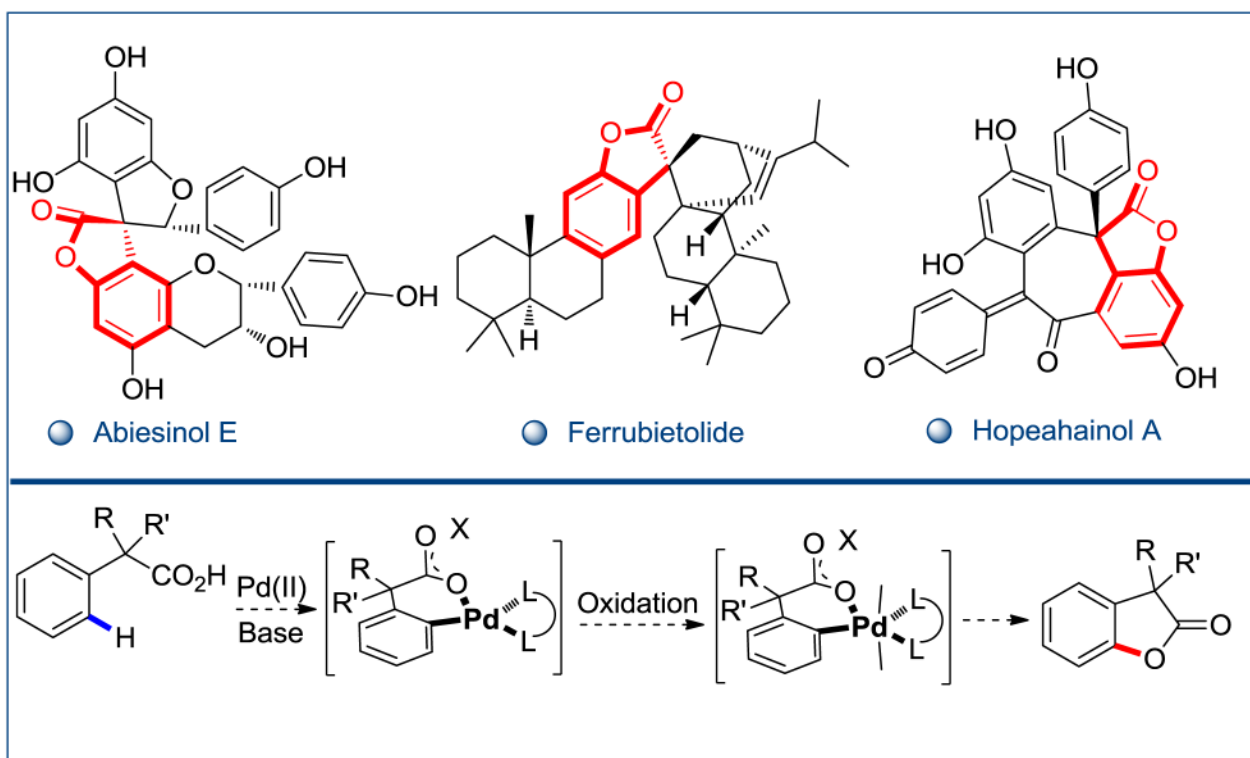


Figure 1.
Absolute Configuration of Benzofuranone 4b



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

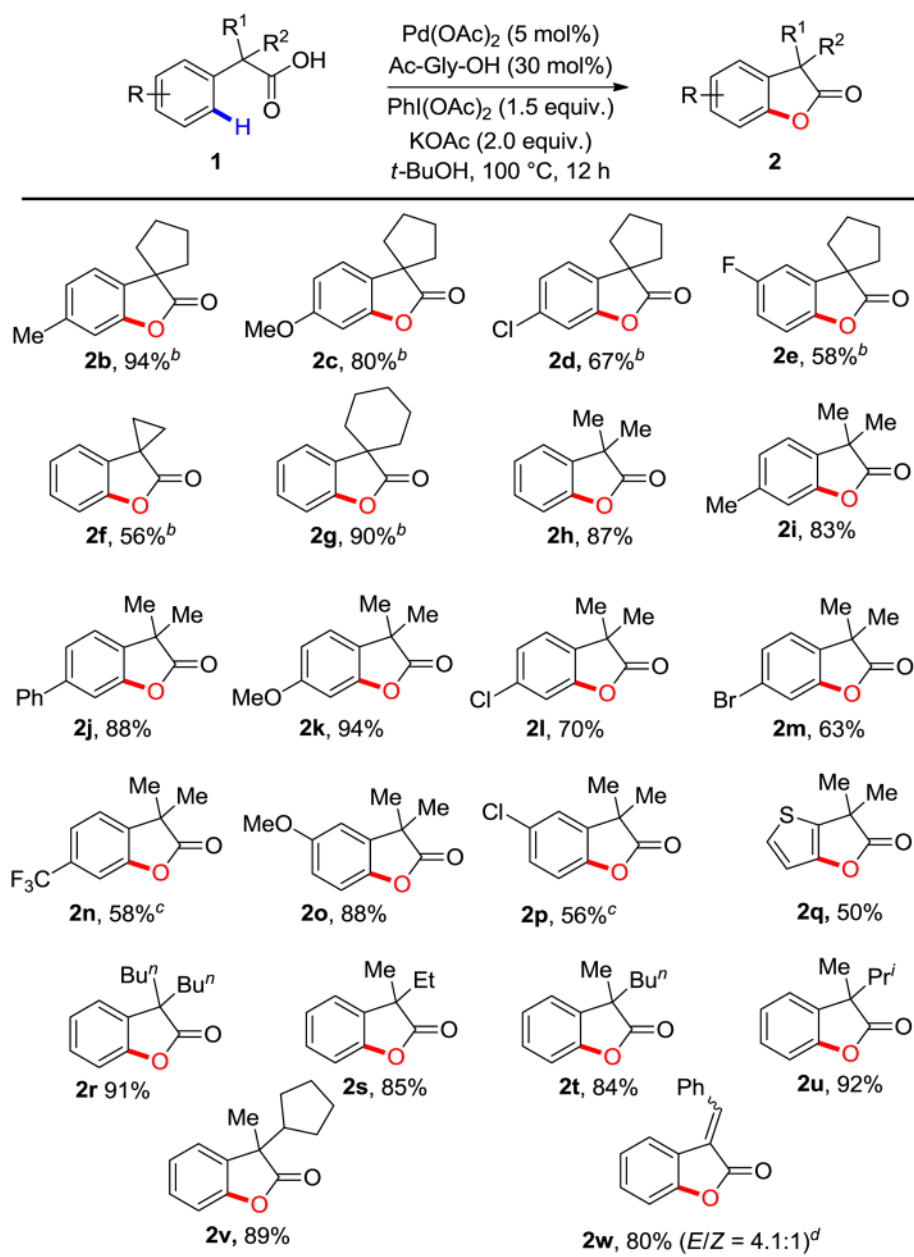


Chart 1. Scope of Phenylacetic Acid Substrates^a

^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 ¹H-NMR. ^e Most of S.M. was recovered and small amount of them decomposed when the conversions were low.

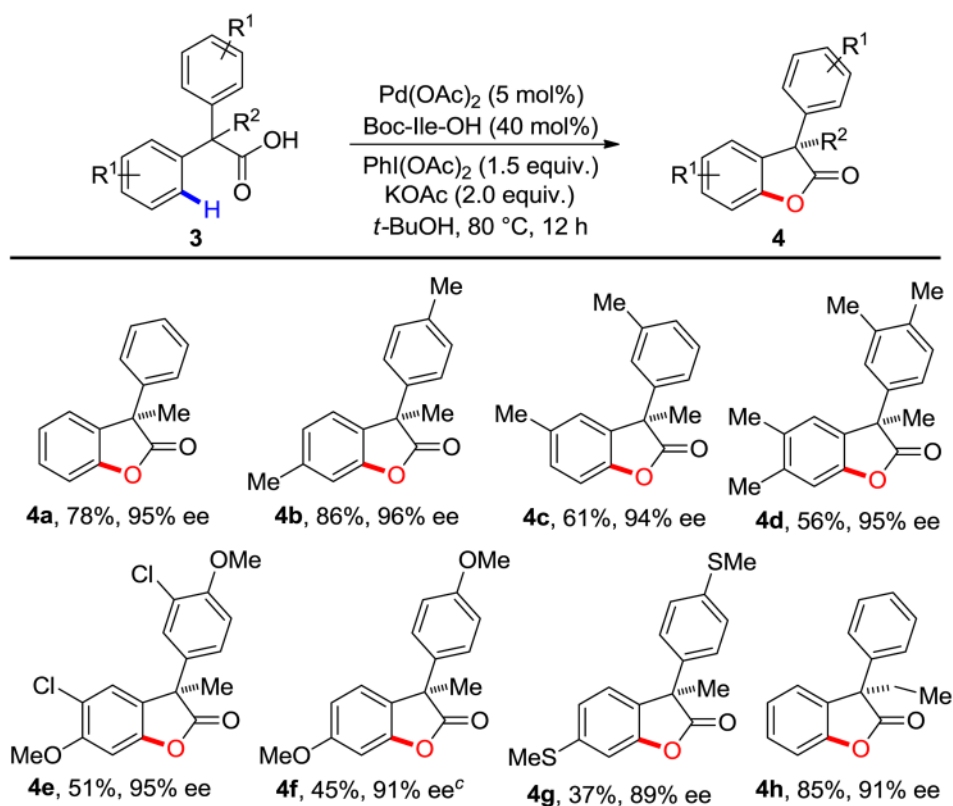
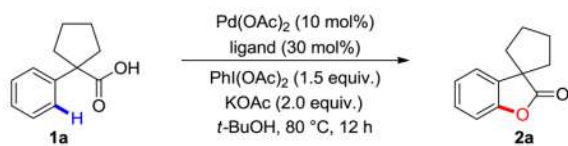


Chart 2. Substrate Scope of the Asymmetric Pd(II)-Catalyzed C-H Lactonization of Diphenylacetic Acids^{a,b}

^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

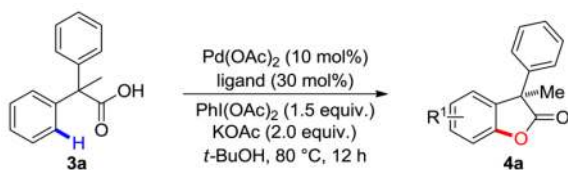


entry	ligand	yield (%) ^a
1	none	42
2	BQ	22
3	HOAc	32
4	<i>t</i> -BuCO ₂ H	37
5	AdCO ₂ H	36
6	Ac-Ala-OH	70
7	Boc-Ala-OH	54
8	Ac-Gly-OH	69
9	Boc-Gly-OH	58
10	Ac-Ile-OH	63
11	Boc-Ile-OH	66
12	Ac-Leu-OH	66
13	Boc-Leu-OH	63
14 ^b	<i>Boc-Val-OH</i>	92

^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-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.