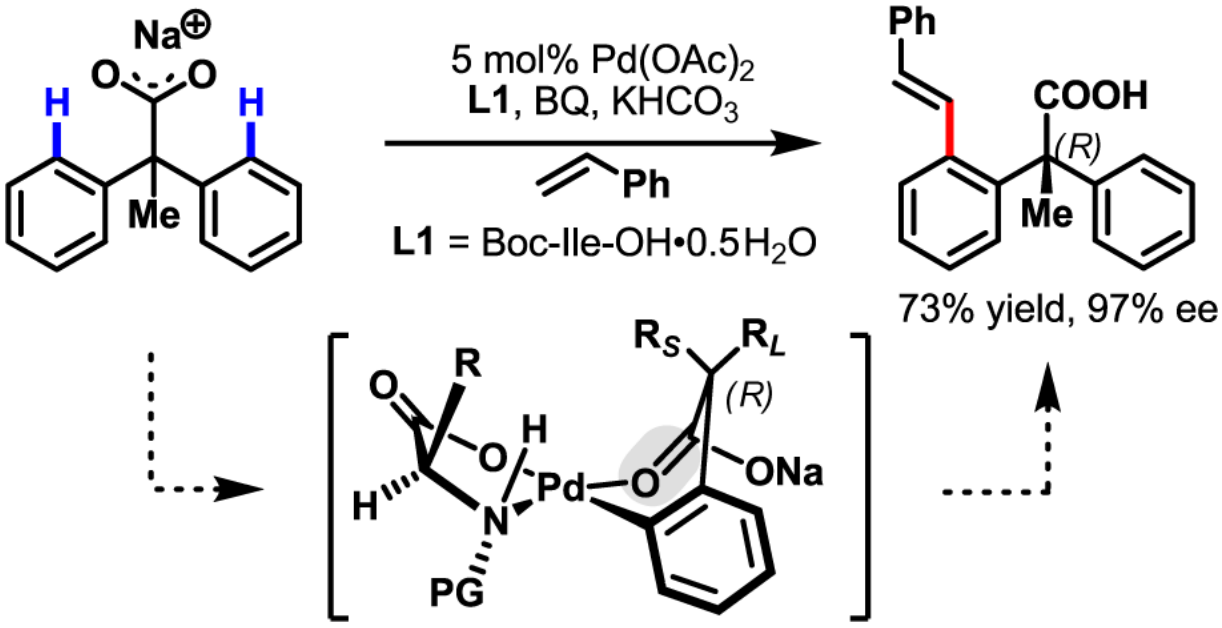
Published in final edited form as:
J Am Chem Soc. 2010 January 20; 132(2): 460–461. doi:10.1021/ja909571z.

Pd(II)-Catalyzed Enantioselective C-H Olefination of Diphenylacetic Acids

Bing-Feng Shi, **Yang-Hui Zhang**, **Jonathan K. Lam**, **Dong-Hui Wang**, and **Jin-Quan Yu***
Department of Chemistry, The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA

Abstract



Pd(II)-catalyzed enantioselective C-H olefination of diphenylacetic acid substrates has been achieved through the use of mono-protected chiral amino acid ligands. The absolute configuration of the resulting olefinated products is consistent with that of a proposed C-H insertion intermediate.

Despite substantial progress in developing various Pd-catalyzed C–heteroatom and C-C bond forming reactions *via* C-H activation,1 achieving enantioselectivity in these reactions through a stereoselective Pd insertion step remains a significant challenge.2–9 In our ongoing studies to design and evaluate new ligands to effect asymmetric C-H cleavage, two major problems have become apparent. First, the simultaneous binding of both the substrate and the chiral ligand to the Pd(II) center is often difficult to achieve. Second, even if such complexes are assembled, the ligand often strongly inhibits C-H activation, either because it induces an unwanted conformational change or adversely affects the electronic properties of the Pd(II) center.

yu200@scripps.edu.

Supporting Information Available: X-ray diffraction analysis for **2e**, experimental procedure and characterization of all new compounds (PDF). This material is available free of charge *via* the Internet at http://pubs.acs.org.

We have recently found that mono-protected amino acid ligands and 2-benzylpyridine substrates coordinate with Pd(II) in a one-to-one ratio with high fidelity.[3] Importantly, the resulting chiral Pd(II) complexes were found to induce asymmetric C-H cleavage with high enantioselectivity (up to 95% ee). Of critical importance for the viability of this process is the precise match between the binding ability of the pyridine substrate and the chiral ligand. This observation, however, calls into question whether this chiral ligand scaffold is broadly applicable to synthetically useful substrates, including those that contain weakly coordinating functional groups. Herein, we report an enantioselective C-H olefination reaction of α,α-diphenylacetic acids using mono-protected amino acids as chiral ligands. This new development represents an encouraging step towards the realization of synthetically useful Pd-catalyzed enantioselective C-H activation reactions.

We previously reported that both inorganic and organic cations dramatically accelerate carboxyl-directed C-H activation reactions.10 Our current hypothesis, based on the structure of a C-H insertion intermediate,[10b] is that the σ-chelation of the carbonyl oxygen of the carboxylate salt with Pd(II) is responsible for the facile C-H cleavage promoted by the complex-induced proximity effect. Following this hypothesis, we anticipated that a chiral carbon–Pd intermediate **B** could be formed in analogy to intermediate **A**, which is formed following enantioselective C-H activation using a pyridyl directing group. Subsequently, we envisioned this intermediate undergoing olefination to give the corresponding chiral product (Figure 1). The proposed boat conformations of **A** and **B** are based on a crystal structure of a similar 1,4-cyclohexadiene-like cyclopalladated compound.[3]

To test this hypothesis, we began by establishing reaction conditions for a Pd(II)-catalyzed olefination reaction of α,α-diphenylacetic acid **1a** using Boc-*L*-isoleucine (Boc-Ile-OH) **L1** as a chiral ligand. Following a procedure developed for the racemic olefination of phenylacetic acid substrates,[11] the olefination reaction of **1a** in the presence of **L1** gave the desired product in 46% yield, accompanied by substantial amounts of the decarboxylation byproduct. Nonetheless, the high enantioselectivity (95% ee) observed was encouraging (Table 1, entry 1). Through extensive screening, we found that by using the preformed sodium salt of **1a** as the starting material and $KHCO_3$ as the base, the yield could be improved to 73%, with 97% ee (entry 3). Surprisingly, the unique combination of the sodium salt of **1a** and $KHCO_3$ was crucial for the success of the reaction. Other alternatives decreased both the enantioselectivity and yield (entries 4–14). We then screened an array of mono-protected α-amino acids (Table 2). Boc-Ile-OH was the optimal chiral ligand, with Boc-Tyr(*t*-Bu)-OH giving similar enantioselectivity (96% ee) but significantly lower yield (45%).

We next proceeded to establish the scope of the styrene coupling partner. *para*- and *meta*-Alkyl substituted styrenes gave high enantioselectivity (92–97% ee, Table 3, entries 2, 3 and 7) while *ortho*-methyl substituted styrene gave only 81% ee (entry 4). *para*-Chlorostyrene afforded both high enantioselectivity (96% ee) and reactivity (74% yield); however, *para*-fluorostyrene gave both decreased yield and enantioselectivity (entry 6).

Different carboxylic acid substrates were also subjected to this reaction protocol. Alkyl-substituted sodium carboxylates **1h**–**1k** were converted to the corresponding products with good to high enantioselectivity (entries 8–11). Boc-Tyr(*t*-Bu)-OH was found to be better chiral ligand for sodium carboxylates **1h**, **1j** and **1k**. The reaction was also found to tolerate substrates containing electron-donating groups (*p*-OPiv, **1l**, entry 12) and moderately electron-withdrawing groups (*p*-Cl, **1m**, entry 13), although olefination of **1m** gave **2m** in only 35% yield. 3,4-Disubstituted substrates were also olefinated effectively giving moderate to high levels of enantioselectivity (entries 14–16). Reactions of sodium 2,2-diphenylbutanoate **1q** and sodium 2,2-diphenylpentanoate **1r** with styrene gave lower enantioselectivity (entries 17–18). Unfortunately, the reaction of α-hydrogen-containing **1s** only gave 58% ee, and it was found

that **2s** was partially racemized under the reaction conditions (entry 19). Notably, the absolute configuration of the olefination product **2e** was determined to be *R* by X-ray crystallographic analysis (Figure 2), which was consistent with the proposed intermediate **B** (Figure 1).

Acrylates were also found to be efficient coupling partners under these conditions, affording 99% ee. However, a mixture of the desired olefination product and the corresponding conjugated addition product was obtained (Scheme 1). The use of sodium carboxylate salt also improved the yield.

Finally, these olefinated products could be readily converted to aldehydes or lactones by simple chemical transformations with complete retention of stereochemistry (Scheme 2).

In summary, we have demonstrated that *mono*-protected α-amino acids are effective chiral ligands for Pd(II)-catalyzed enantioselective C-H activation reactions of carboxylic acid substrates. Expansion of this asymmetric technology to enantioselective sp^3 C-H functionalization is underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge The Scripps Research Institute, the National Institutes of Health (NIGMS, 1 R01 GM084019-01A1), Amgen and Lilly for financial support.

References

(1). For recent reviews see: (a) Dick AR, Sanford MS. Tetrahedron 2006;62:2439.. (b) Daugulis O, Zaitsev VG, Shabashov D, Pham Q-N, Lazareva A. Synlett 2006:3382.. (c) Yu J-Q, Giri R, Chen X. Org. Biomol. Chem 2006;4:4041. [PubMed: 17312954] . (d) Campeau L-C, Stuart DR, Fagnou K. Aldrichimica Acta 2007;40:35.. (e) Rubin M, Rubina M, Gevorgyan V. Chem. Rev 2007;107:3117. [PubMed: 17622181]

(2). For a review on stereoselective C-H functionalization, see: Giri R, Shi B-F, Engle KM, Maugel N, Yu J-Q. Chem. Soc. Rev 2009;38:3242. [PubMed: 19847354]

(3). Shi B-F, Maugel N, Zhang Y-H, Yu J-Q. Angew. Chem., Int. Ed 2008;47:4761.

(4). For a Ru-catalyzed atropselective alkylation, see: Kakiuchi F, Le Gendre P, Yamada A, Ohtaki H, Murai S. Tetrahedron: Asymmetry 2000;11:2647.

(5). For a Pd(0)-catalyzed enantioselective arylation see: Albicker MR, Cramer N. Angew. Chem., Int. Ed 2009;48:9139.

(6). For enantioselective hydroarylation and hydroacylations see: (a) Bosnich B, Wang X. Organometallics 1994;13:4131. (b) Mikami K, Hatano M, Terada M. Chem. Lett 1999:55.. (c) Thalji RK, Ellman JA, Bergman RG. J. Am. Chem. Soc 2004;126:7192. [PubMed: 15186153] . (d) Coulter MM, Dornan PK, Dong VM. J. Am. Chem. Soc 2009;131:6932. [PubMed: 19415904] . (e) Shibata, Yu; Tanaka, K. J. Am. Chem. Soc 2009;131:12552. [PubMed: 19685873]

(7). For enantioselective carbenoid and nitrenoid insertions, see: (a) Davies HML, Manning JR. Nature 2008;451:417. [PubMed: 18216847] . (b) Doyle MP. J. Org. Chem 2006;71:9253. [PubMed: 17137350] . (c) Du Bois J, Zalatan DN. J. Am. Chem. Soc 2008;130:9220. [PubMed: 18582043] . (d) Milczek E, Boudet N, Blakey S. Angew. Chem., Int. Ed 2008;47:6825.

(8). For enantioselective Heck and cross-coupling reactions see: (a) Sato Y, Sodeoka M, Shibasaki M. J. Org. Chem 1989;54:4738.. (b) Carpenter NE, Kucera DJ, Overman LE. J. Org. Chem 1989;54:5846.. (c) Arp FO, Fu GC. J. Am. Chem. Soc 2005;127:10482. [PubMed: 16045323]

(9). For enantioselective oxidation of alcohols see: (a) Ferreira EM, Stoltz BM. J. Am. Chem. Soc 2001;123:7725. [PubMed: 11481006] . (b) Jensen DR, Pugsley JS, Sigman MS. J. Am. Chem. Soc 2001;123:7475. [PubMed: 11472200]

(10). (a) Mei T-S, Giri R, Maugel N, Yu J-Q. Angew. Chem., Int. Ed 2008;47:5215. (b) Giri R, Yu J-Q. J. Am. Chem. Soc 2008;130:14082. [PubMed: 18834125]

(11). Wang D-H, Engle KM, Shi B-F, Yu J-Q. Science. DOI: 10.1126/science.1182512.

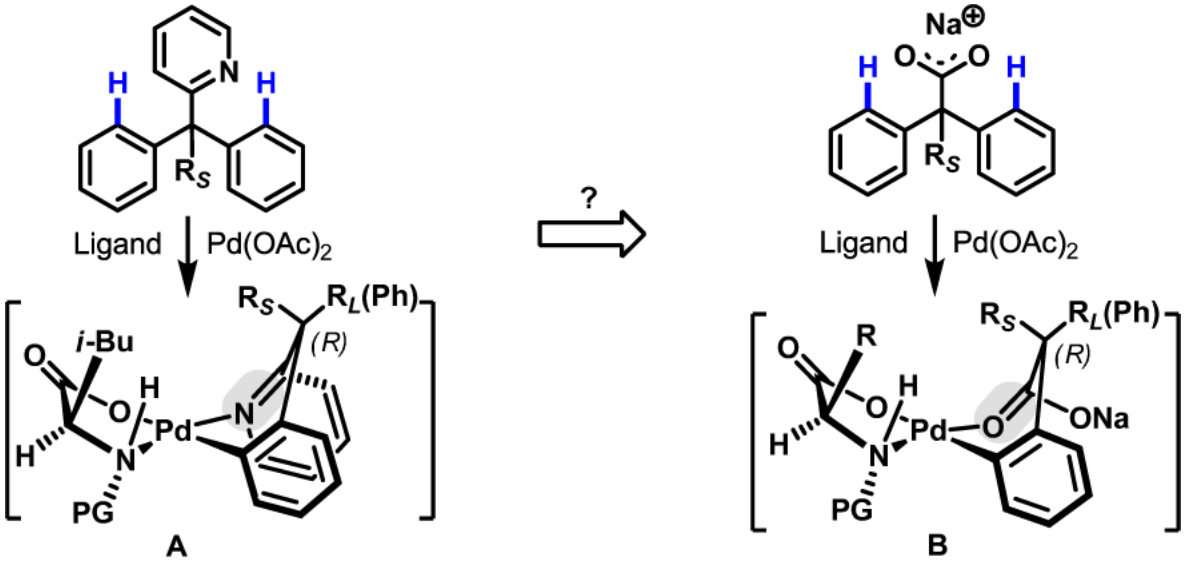


Figure 1.

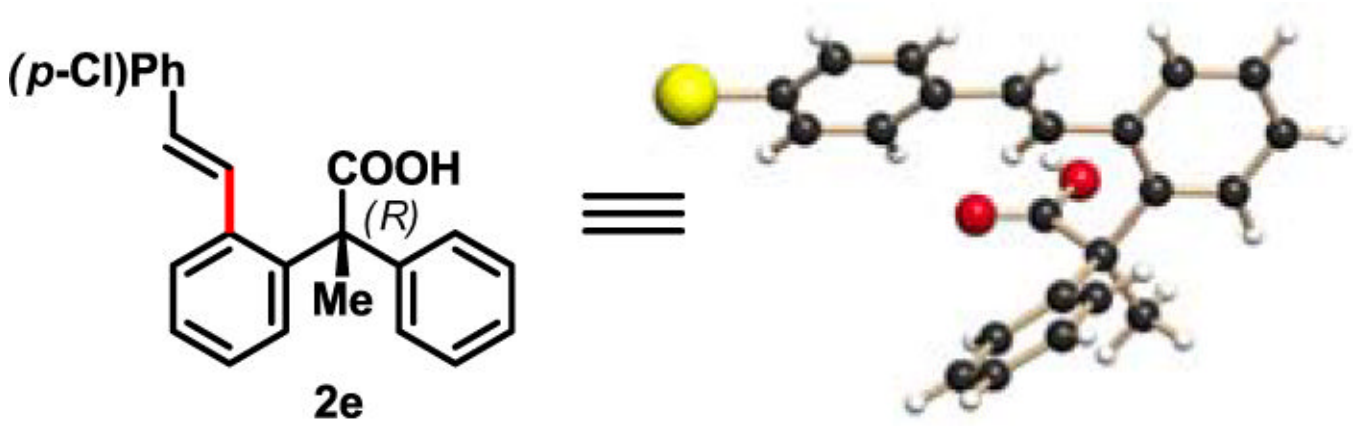
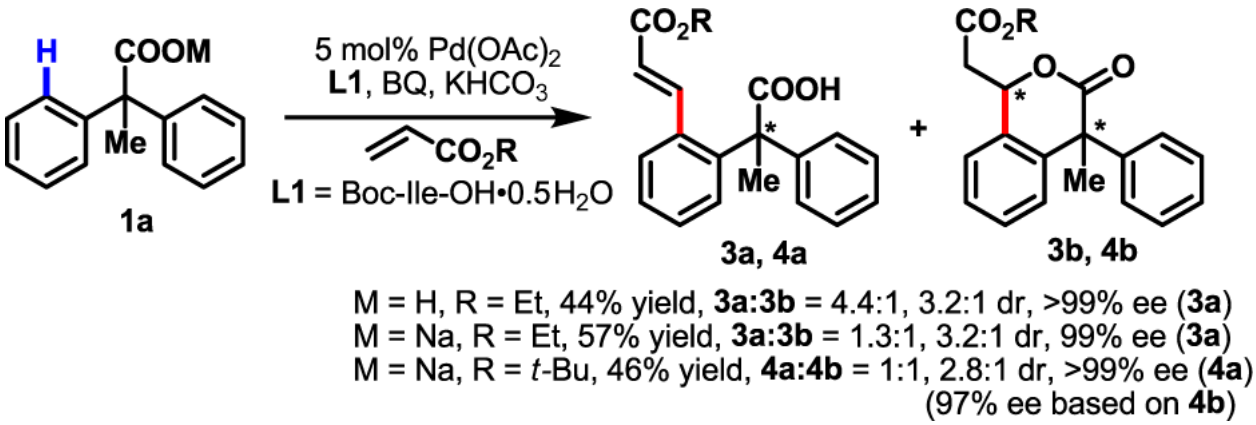


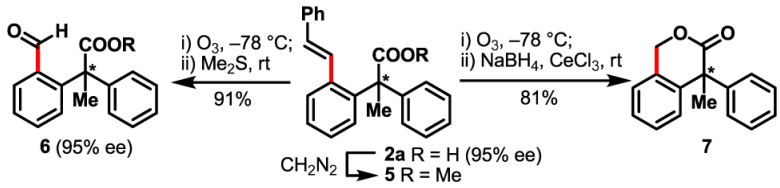
Figure 2.
Absolute Configuration of Olefination Product **2e**



Scheme 1.

Enantioselective C-H Activation/Olefination Using Acrylates as the Coupling Partners[a,b]

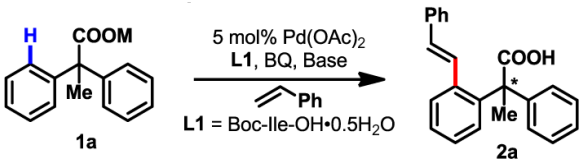
[a] The reaction conditions are identical to those described in Table 1; [b] The ratio of products and dr were determined by ^{1}H NMR.



Scheme 2.
Derivatization of the Olefination Products

Table 1

Effect of Inorganic Cations and Bases[a]



Entry	M	Base	% Yield[b]	%ee[c]
1	H	$KHCO_3$[d]	46	95
2	Na	-	51	36
3	Na	$KHCO_3$	73[e]	97
4	NH_4	$KHCO_3$	-	-
5	K	$KHCO_3$	49	84
6	Cs	KCH2O_3	-	-
7	Na	K_2CO_3	25	87
8	Na	$NaHCO_3$	56	89
9	Na	Na_2CO_3	61	91
10	Na	Cs_2CO_3	-	-
11	Na	K_2HPO_4	37	83
12	Na	Li_2CO_3	44	85
13	Na	NaOTs[f]	57	79
14	K	$NaHCO_3$	53	91

[a] 0.5 mmol **1a**, 5 mol% $Pd(OAc)_2$, 10 mol% **L1**, 5 mol% BQ, 0.5 equiv. Base, 1 atm O_2 in 3 mL *tert*-amyl alcohol at 90 °C for 48 h;

[b] The yield was determined by ^{1}H NMR using CH_2Br_2 as a calibrated internal standard.

[c] ee was determined by chiral HPLC;

[d] 2 equiv. $KHCO_3$;

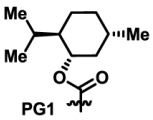
[e] Isolated yield;

[f] 1 equiv. NaOTs.

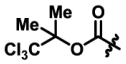
Table 2

Evaluation of Amino Acids[a]

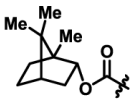
Entry	Ligand	% Yield	% ee
1	Boc-Ala-OH	46	54
2	Boc-Abu-OH	51	67
3	Boc-Nva-OH	63	61
4	Boc-Nle-OH	59	81
5	Boc-Val-OH	39	93
6	Boc-Ser(Bzl)-OH	61	91
7	Boc-Phe-OH	25	93
8	Boc-Thr(*t*-Bu)-OH	50	86
9	Boc-Tyr(*t*-Bu)-OH	45	96
10	Boc-Tle-OH	43	94
11	Boc-Ile-OH•0.5H_2O	73	97
12	Boc-Leu-OH	60	86
13	Formyl-Leu-OH	44	79
14	**PG1**-Leu-OH	57	84
15	**PG2**-Leu-OH	44	69
16	**PG3**-Leu-OH	37	65



PG1



PG2

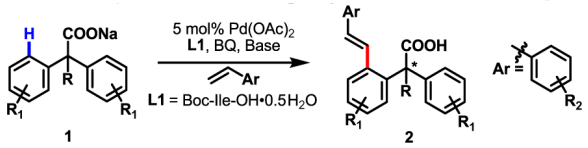


PG3

[a]The reaction conditions are identical to those described in Table 1.

Table 3

Enantioselective C-H Activation/Olefination Using Substituted Styrenes as the Coupling Partners[a]



Entry	2	R	R_1	R_2	% Yield[b]	% ee[c](Config)
1	**2a**	Me	H	H	73	97
2	**2b**	Me	H	*p*-Me	71	97
3	**2c**	Me	H	*m*-Me	63	92
4	**2d**	Me	H	*o*-Me	51	80
5	**2e**	Me	H	*p*-CI	74	96 (R)[d]
6	**2f**	Me	H	*p*-F	51	89
7	**2g**	Me	H	*p*-*t*-Bu	51	95
8	**2h**	Me	*p*-Me	H	63	90[e]
9	**2i**	Me	*m*-Me	H	58	92
10	**2j**	Me	3,4-Dimethyl	H	63	82[e]
11	**2k**	Me	*p*-*t*-Bu	H	45	88[e]
12	**2l**	Me	*p*-OPiv	H	51	95
13	**2m**	Me	*p*-CI	H	35	87
14	**2n**	Me	3-chloro-4-methoxy	H	47	90
15	**2o**	Me	3-methyl-4-methoxy	H	40	75
16	**2p**	Me	4-methoxy-3-trifluoromethyl	H	39	89
17	**2q**	Et	H	H	61	72
18	**2r**	Pr	H	H	52	76[e]
19	**2s**	H	H	H	69	58[f]

[a] The reaction conditions are identical to those described in Table 1;

[b] Isolated yield;

[c] ee was determined by chiral HPLC;

[d] The absolute configuration was determined by analysis of the X-ray crystal structure;

[e] Boc-Tyr(*t*-Bu)-OH was used as ligand;

[f] Racemization occurred during the reaction.