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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 North Torrey Pines Road, La Jolla, California 92037

Received November 11, 2009; E-mail: yu200@scripps.edu

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 because it either induces an unwanted conformational change or adversely affects the electronic properties of the Pd(II) center.

We recently found that monoprotected 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 monoprotected amino acids as chiral ligands. This new development represents an encouraging step toward 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 that this intermediate would undergo 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. Through 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 observed (95% ee) was encouraging (Table 1, entry 1). Through extensive screening, we found that through the use of 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 monoprotected 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%).

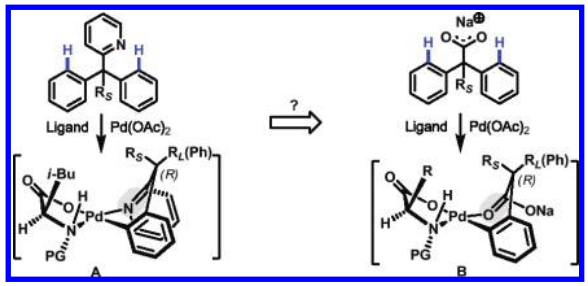
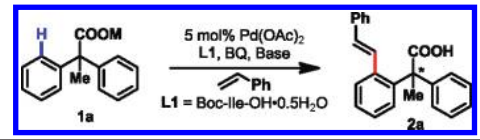


Figure 1

Table 1. Effect of Inorganic Cations and Bases[a]

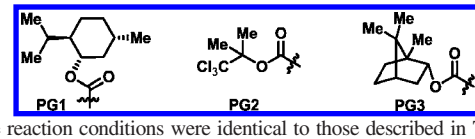


entry	M	base	% yield[b]	% ee[c]	entry	M	base	% yield[b]	% ee[c]
1	H	$KHCO_3$[d]	46	95	8	Na	$NaHCO_3$	56	89
2	Na	−	51	86	9	Na	Na_2CO_3	61	91
3	Na	$KHCO_3$	73[e]	97	10	Na	Cs_2CO_3	−	−
4	NH_4	$KHCO_3$	−	−	11	Na	K_2HPO_4	37	83
5	K	$KHCO_3$	49	84	12	Na	Li_2CO_3	44	85
6	Cs	$KHCO_3$	−	−	13	Na	NaOTs[f]	57	79
7	Na	K_2CO_3	25	87	14	K	$NaHCO_3$	53	91

[a] Conditions: 0.5 mmol of **1a**, 5 mol % $Pd(OAc)_2$, 10 mol % **L1**, 5 mol % BQ, 0.5 equiv of base, and 1 atm O_2 in 3 mL of *tert*-amyl alcohol at 90 °C for 48 h. [b] Determined by ^1H NMR analysis using CH_2Br_2 as a calibrated internal standard. [c] Determined by chiral HPLC analysis. [d] Using 2 equiv of $KHCO_3$. [e] Isolated yield. [f] Using 1 equiv of NaOTs.

Table 2. Evaluation of Amino Acids[a]

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



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

We next proceeded to establish the scope of the styrene coupling partner. Styrenes with para and meta alkyl substitutents gave high enantioselectivity (92−97% ee; Table 3, entries 2, 3, and 7) while

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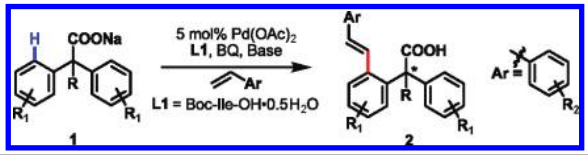
o-methyl-substituted styrene gave only 81% ee (entry 4). *p*-Chlorostyrene afforded both high enantioselectivity (96% ee) and reactivity (74% yield); however, *p*-fluorostyrene gave both decreased yield and enantioselectivity (entry 6).

Different carboxylic acid substrates were also subjected to this reaction protocol. Alkyl-substituted sodium carboxylates **1h**−**k** were converted to the corresponding products with good to high enantioselectivity (entries 8−11). Boc-Tyr(*t*-Bu)-OH was found to be a 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 and 18). Unfortunately, the reaction of α-hydrogen-containing **1s** gave only 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).

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*-Cl	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*-Cl	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 were identical to those described in Table 1. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration was determined by analysis of the X-ray crystal structure. [e] Boc-Tyr(*t*-Bu)-OH was used as the ligand. [f] Racemization occurred during the reaction.

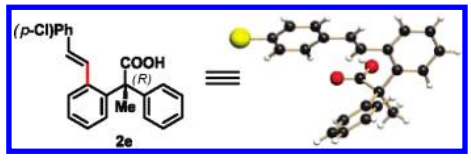
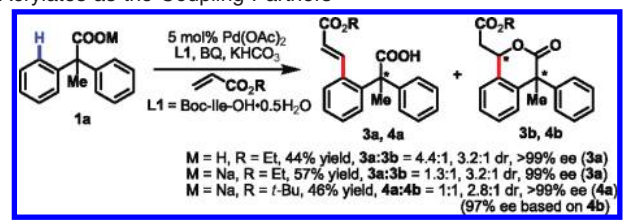


Figure 2. Absolute configuration of olefination product **2e**.

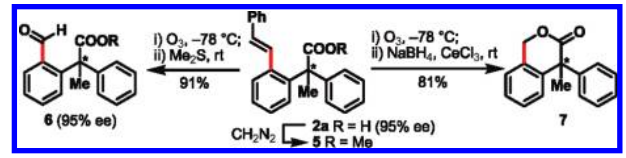
Acrylates were also found to be efficient coupling partners under these conditions, affording 99% ee. However, a mixture of the desired olefination product and the corresponding conjugated addition product was obtained (Scheme 1). The use of sodium carboxylate salt also improved the yield.

Scheme 1. Enantioselective C−H Activation/Olefination Using Acrylates as the Coupling Partners[a,b]



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

Scheme 2. Derivatization of the Olefination Products



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 monoprotected 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.

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

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