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Enantioselective Palladium-Catalyzed Decarboxylative Allylation of β-Keto Esters Assisted by a Thiourea

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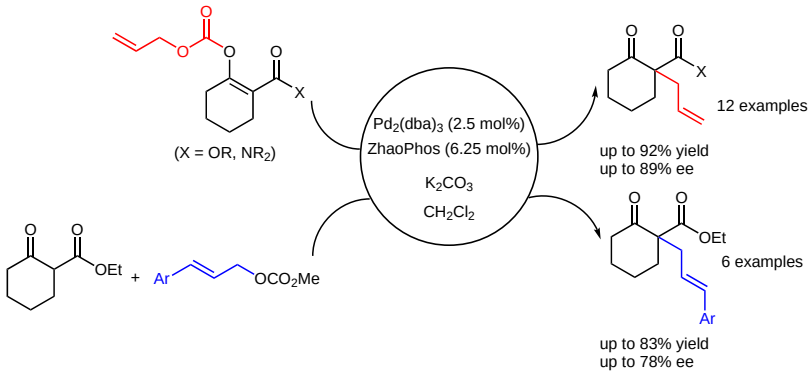

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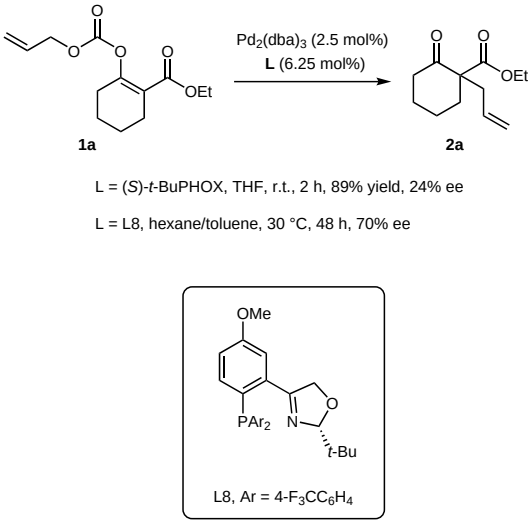
Abstract Enantioselective intramolecular decarboxylative allylation of β-keto esters catalyzed by a palladium bis(phosphine)-thiourea complex is reported. This procedure is not only effective for β-keto esters, but also effective for β-keto amides. An intermolecular variant of the asymmetric decarboxylative allylation is also established. DFT calculations indicate that an outer-sphere mechanism is viable for the decarboxylative allylation of β-keto esters.

Key words asymmetric synthesis, β-keto esters, decarboxylative allylation, thioureas, palladium catalysis

The enantioselective formation of all-carbon quaternary stereocenters remains an interesting but challenging topic in synthetic organic chemistry.[1] For the past two decades, transition-metal-catalyzed decarboxylative asymmetric allylation of prochiral enolates (the Tsuji allylation reaction) has emerged as a powerful tool for the synthesis of enantioenriched quaternary stereocenters.[2]

Although tremendous efforts have been devoted to the development of the Tsuji allylation reaction,[3–8] the intramolecular decarboxylative asymmetric allylation of β-keto esters remains problematic.[9] For example, the Stoltz group reported an elegant example of a palladium-catalyzed protocol for the asymmetric Tsuji allylation;[9a] however, this allylation reaction was primarily effective for the allylation of unstabilized ketone enolates. For the allylation of stabilized allyl enol carbonates such as **1a**, the ee of the allylation product **2a** was only 24% (Scheme 1). Later, the ee of **2a** was improved to 70% through high-throughput screening of ligands and solvents.[9c] Nevertheless, new methods are still needed for enantioselective intramolecular decarboxylative allylation of β-keto esters.[10]



Scheme 1 Enantioselective allylation of β-keto esters developed by Stoltz

The combination of a transition-metal catalyst and an organocatalyst through a covalent bond into one bifunctional molecule provides unprecedented opportunities to achieve challenging transformations.[11] Recently, we have discovered that bis(phosphine)-thiourea (ZhaoPhos) ligated metal complexes efficiently catalyzed the asymmetric hydrogenation of imines and pyridines,[12] nitroalkenes,[13] α,β-unsaturated compounds,[14] and maleic acid derivatives.[15] The hydrogen bonding between the substrate and the thiourea moiety of the ligand was believed to be crucial for achieving high enantioselectivity. As part of our continued effort to extend the application of ZhaoPhos, we propose that this bis(phosphine)-thiourea ligand can also promote the enantioselective allylation of β-keto esters (Figure 1).

Herein, we report the enantioselective allylation of β-keto esters catalyzed by a palladium(0) bis(phosphine)-thiourea complex.

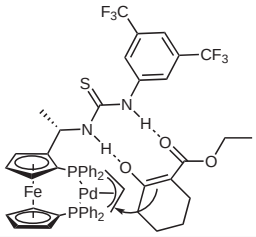
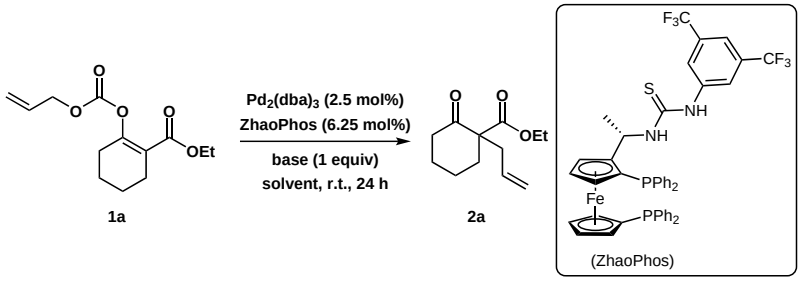


Figure 1 Proposed interaction of a β-keto ester with Pd-ZhaoPhos

We commenced our study by examining substrate **1a** as a model substrate catalyzed by a 1:2.5 mixture of $Pd_2(dba)_3$ (2.5 mol %) and ZhaoPhos in various solvents at room temperature. Substrates **1a–l** can be synthesized by deprotonation of β-keto esters with potassium *tert*-butoxide in tetrahydrofuran (THF) at room temperature followed by nucleophilic substitution with allyl chloroformate. Initially, ethereal solvents and halogenated solvents were tested, but no or trace amount of product **2a** was formed. Full conversion was achieved by using nonpolar solvent *n*-hexane as the solvent, whereas the ee of **2a** turned out to be negligible (Table 1, entry 1). Addition of one equivalent of K_2CO_3 to the reaction solution proved to be beneficial to the enantioselectivity (32% ee; entry 2). Subsequently, different solvents were screened for the allylation of **1a**. Ethereal solvents such as THF and 1,2-dimethoxyethane (DME) provided **2a** with 83% ee (entries 3 and 4). Diethyl ether, methyl *tert*-butyl ether (MTBE) and 1,4-dioxane gave **2a** with low enantioselectivity (25–73% ee; entries 5–7). Use of toluene as the solvent formed the desired product **2a** in 44% ee (entry 8). Halogenated solvents were also tested and CH_2Cl_2 turned out to be the choice of solvent, providing **2a** with 89% ee (entry 9). Polar solvents such as ethanol, acetonitrile, and ethyl acetate gave **2a** with low ee (15–66%; entries 13–15). Among the bases examined, K_3PO_4 gave an ee comparable to that with K_2CO_3 (entry 16). Triethylamine and BSA did not promote the reaction at all (entries 18 and 19). The addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 1,4-diazabicyclo[2.2.2]octane (DABCO) as base gave **2a** with 84% ee (entries 20 and 21). Overall, these experiments demonstrated that the use of CH_2Cl_2 as the solvent and K_2CO_3 as the base provided the best results (92% yield, 89% ee; entry 9).

Table 1 Screening of Solvents and Bases[a]



Entry	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	*n*-hexane	none	67	2
2	*n*-hexane	K_2CO_3	78	32
3	THF	K_2CO_3	95	83
4	DME	K_2CO_3	92	83
5	Et_2O	K_2CO_3	87	73
6	MTBE	K_2CO_3	81	68
7	1,4-dioxane	K_2CO_3	97	25
8	toluene	K_2CO_3	94	44
9	CH_2Cl_2	K_2CO_3	92	89
10	DCE	K_2CO_3	84	86
11	DCE/THF (1:1)	K_2CO_3	84	84
12	DCE/DME (1:1)	K_2CO_3	81	84
13	EtOH	K_2CO_3	71	15

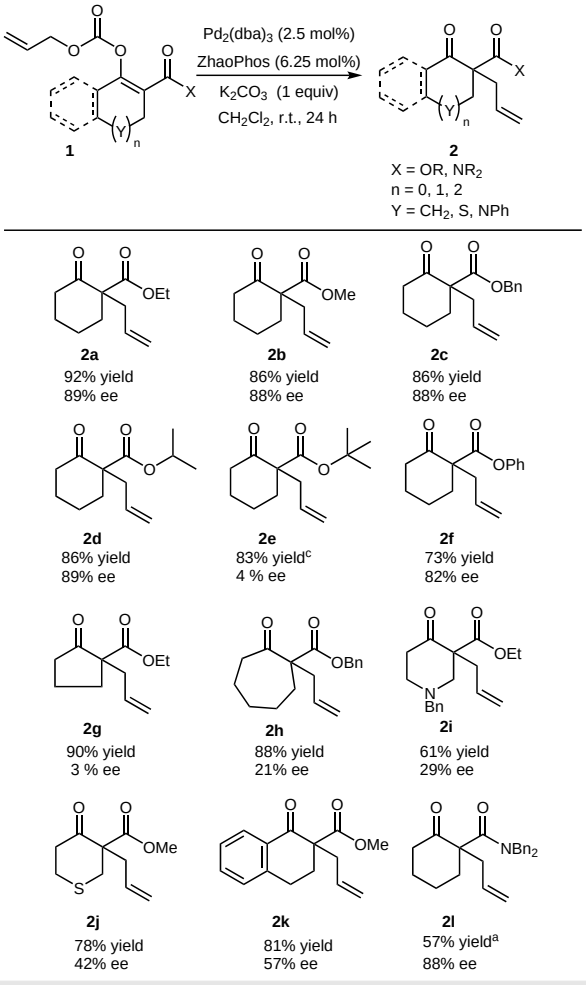
Table 1 (continued)

Entry	Solvent	Base	Yield (%)[b]	ee (%)[c]
14	MeCN	K_2CO_3	63	48
15	EtOAc	K_2CO_3	90	66
16	CH_2Cl_2	K_3PO_4	82	88
17	CH_2Cl_2	TBD	61	42
18	CH_2Cl_2	BSA	N.R.	N.A.
19	CH_2Cl_2	Et_3N	N.R.	N. A.
20	CH_2Cl_2	DBU	68	84
21	CH_2Cl_2	DABCO	71	84

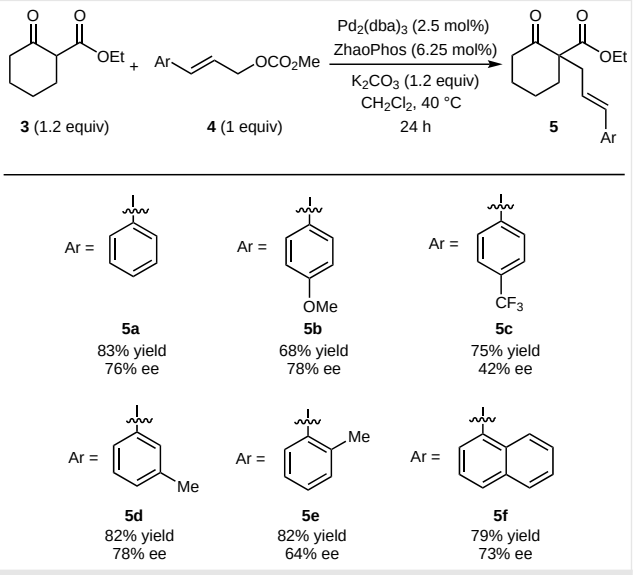
[a] Reaction conditions: substrate 0.30 mmol, $Pd_2(dba)_3$ (0.0075 mmol), ZhaoPhos (0.019 mmol), solvent (5 mL), base (0.30 mmol), r.t., 24 h. TBD = 1,5,7-Triazabicyclo-[4.4.0]dec-5-ene. BSA = N,O-Bis(trimethylsilyl)acetamide. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. DABCO = 1,4-Diazobicyclo(2.2.2)octane. N.R. = no reaction. N.A.= not available.
[b] Isolated yield.
[c] The ee was determined by HPLC using a chiral stationary phase.

With the optimized conditions in hand, we sought to study the substrate scope.[16] As summarized in Scheme 2, substrates containing a six-membered ring with ester functionality such as ethyl (**2a**), methyl (**2b**), benzyl (**2c**), and isopropyl (**2d**) esters provided the products in good yield with high enantioselectivity (88–89% ee). When the ester functionality was changed to phenyl ester, 82% ee was achieved for the desired allylation product (**2f**). However, when the ester group was switched to *tert*-butyl ester, the ee of the desired product (**2e**) turned out to be negligible. In addition, β-keto esters containing a five-membered ring (**2g**) or a seven-membered ring (**2h**) provided the allylation product with low enantioselectivity. Meanwhile, the incorporation of a heteroatom such as nitrogen (**2i**) and sulfur (**2j**) into the cyclohexanone ring had a detrimental effect on the ee of the allylation product. Substrate containing a tetralone moiety (**2k**) provided the desired product with diminished ee (57%) under the optimized conditions. Finally, β-keto amide worked well for the asymmetric decarboxylative allylation reaction, rendering the allylation product **2l** in 57% yield and 88% ee.

We also sought to study the intermolecular decarboxylative asymmetric allylation of β-keto esters.[17,18] To this end, treatment of ethyl 2-cyclohexanonecarboxylate (**3**; 1.2 equiv) and cinnamyl methyl carbonate (**4a**; 1 equiv) with a catalytic amount of $Pd_2(dba)_3$ (2.5 mol%) and ZhaoPhos (6.25 mol%) in the presence of a stoichiometric amount of K_2CO_3 (1.2 equiv) in CH_2Cl_2 at 40 °C for 24 h provided the desired allylation product **5** in 83% isolated yield and 76% ee (**5a**; Scheme 3).[19] As summarized in Scheme 3, a variety of cinnamyl methyl carbonates were tested and moderate to good enantioselectivities were observed. Substrates with electron-donating substituents (**4b** and **4d**) furnished the products with good ee values. Electron-withdrawing (**4c**) and sterically demanding (**4e**) substituents on the aromatic



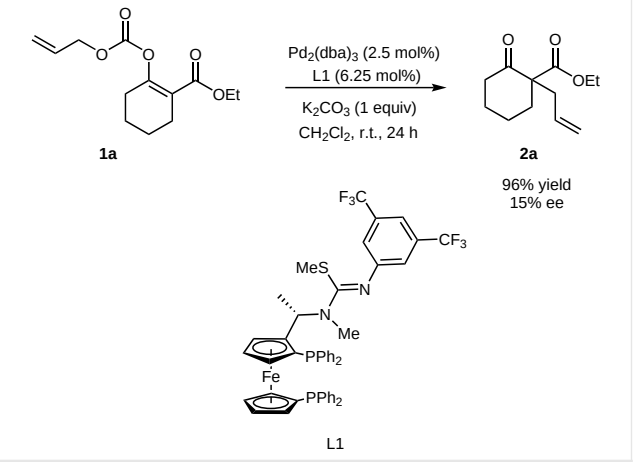
Scheme 2 Substrate Scope. *Reagents and conditions*: substrate (0.30 mmol), $Pd_2(dba)_3$ (0.0075 mmol), ZhaoPhos (0.019 mmol), solvent (5 mL), r.t. The ee was determined by HPLC using a chiral stationary phase.
[a] Reaction run for 48 h.



Scheme 3 Intermolecular asymmetric allylation of β-keto ester. *Reagents and conditions*: substrate (0.30 mmol), $Pd_2(dba)_3$ (0.0075 mmol), ZhaoPhos (0.019 mmol), K_2CO_3, solvent (1 mL), 40 °C. The ee was determined by HPLC using a chiral stationary phase.

ring led to a decrease of the enantioselectivity for the corresponding products.

To gain insight into the mechanism of the intramolecular asymmetric allylation reaction, a control experiment was conducted (Scheme 4). Subjecting **1a** to a catalytic 1:2.5 mixture of $Pd_2(dba)_3$ and ZhaoPhos-Me_2 (**L1**) in CH_2Cl_2 at r.t. for 24 h led to the formation of allylated product **2a** in 96% isolated yield with 15% ee. This result highlights the key role of the hydrogen bonding donor in the catalyst to achieve high enantioselectivity.



Scheme 4 Control experiment

According to previous computational studies,[2b,20] the enantioselectivity should be determined by the reductive elimination step. A mechanistic study on the enantioselectivity of this Pd-catalyzed allylation was performed by DFT (M06) calculations. Three mechanisms were considered: inner-sphere, outer-sphere, and three-membered-ring reductive elimination pathways (see the Supporting Information for details). **TS-RE-O2-*Si*** is the most favorable transition state for the *Si*-face of the enolate, which is lower in free energy than that for the *Re*-face manifold via **TS-RE-O1-*Re*** by 2.3 kcal/mol (Figure 2, and Figure X1 in the Supporting Information). These computational results are in good agreement with the experimental observations. Both transition states can be regarded as following the outer-sphere pathway.[21] **TS-RE-O2-*Si*** is an earlier transition state than **TS-RE-O1-*Re***, due to the longer C–C bond forming in the former case (2.36 Å). Furthermore, the enolate substrate forms stronger interactions with the catalyst, and strong stacking between the thiourea part and one phenyl on the P ligand were found in **TS-RE-O2-*Si***. Our distortion/interaction analysis[22] further supports the conclusion that larger interaction stabilization between the substrate and catalyst (18.3 kcal/mol) in **TS-RE-O2-*Si*** is a major factor in the observed enantioselectivity.

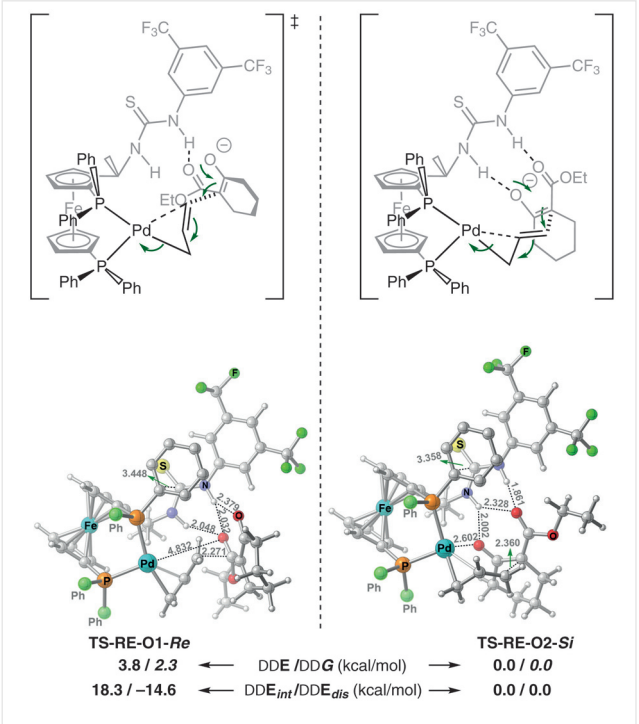


Figure 2 Computed structures for the most favorable reductive elimination transition state for the *Re*-and *Si*-face of the enolate at the M06/6-31G(d)+SDD level with relative energies and key structural parameters. The three Ph groups attached to the phosphines are simplified as green balls and hydrogen atoms on one phenyl ring linked to P are omitted for clarity.

In summary, we have developed a new protocol for the asymmetric allylation of β-keto esters catalyzed by a palladium bis(phosphine)-thiourea complex. This protocol works well with both β-keto esters and amides that contain six-membered rings. An intermolecular variant of this decarboxylative allylation is also reported. DFT calculations indicate that an outer-sphere mechanism is operative for the allylation of β-keto esters. Further studies to explain the role of K_2CO_3 on enantioselectivity, as well as improving the enantioselectivity and expanding the substrate scope of the enantioselective decarboxylative allylation, is under way in our laboratory.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1590869.

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(16) **General procedure for decarboxylative allylation of β-keto esters**: A Schlenk tube containing $Pd_2(dba)_3$ (7 mg, 0.0076 mol), ZhaoPhos (16 mg, 0.0184 mmol) and K_2CO_3 (42 mg, 0.30 mmol) in degassed anhyd CH_2Cl_2 (5 mL) was stirred for 15 min under Ar. Substrate (0.30 mmol) was added last. The resulting mixture was stirred at r.t. under Ar for 24 h and was concentrated under vacuum. The residue was then purified by chromatography with petroleum ether/EtOAc to afford enantioenriched product. For **2a**: Yield: 58 mg (92%); colorless oil; 89% ee. ^{1}H NMR: δ = 5.83–5.67 (m, 1 H), 5.04 (d, *J* = 13.3 Hz, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.61 (dd, *J* = 14.0, 6.9 Hz, 1 H), 2.47 (dt, *J* = 14.9, 4.3 Hz, 3 H), 2.34 (dd, *J* = 14.0, 7.8 Hz, 1 H), 2.07–1.97 (m, 1 H), 1.82–1.71 (m, 3 H), 1.50–1.43 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 3 H). ^{13}C{^{1}H} NMR: δ = 207.5, 171.4, 133.3, 118.2, 61.2, 60.8, 41.1, 39.3, 35.7, 27.5, 22.4, 14.1. HPLC (Daicel Chiralpak) AD-H column; hexanes/*i*-PrOH = 99.5:0.5; flow rate = 0.5 mL/min; UV detection at 210 nm): t_R = 10.512 (t_{minor}), 12.371 (t_{major}) min.

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