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Palladium/Zinc Co-Catalyzed Asymmetric Hydrogenation of γ-Keto Carboxylic Acids

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Abstract: A palladium-catalyzed asymmetric hydrogenation of levulinic acid has been successful developed by using $Zn(OTf)_2$ as co-catalyst. The present method not only has provided a strategy in the palladium-catalyzed asymmetric hydrogenation of ketone, but also allowed the preparation of a wide range of chiral γ-valerolactones in good yields with excellent enantioselectivities.

Transitional metal-catalyzed asymmetric hydrogenation reaction is one of the most fundamental reactions and widely used in the organic synthetic industry due to its high efficiency in the preparation of enantiomerically pure compounds. The asymmetric hydrogenation of ketones has provided a powerful synthetic route with 100% atom efficiency to chiral alcohols.[1] Since the first-generation of Ru-Binap catalysts have been developed in 1987, the ruthenium catalysts have become the dominant choice.[2] In the past three decades, chiral Rh,[3] and Ir[4] complexes were also extensively investigated, benefited from the successful development of new chiral ligands. On the contrary, although palladium is relatively cost-effective among the noble metals and successfully used in other enantioselective transformations, palladium-catalyzed homogeneous asymmetric hydrogenation of ketones is relatively less developed. In this context, the group of Zhou has reported the first example of highly enantioselective palladium-catalyzed asymmetric hydrogenation of functionalized ketones with (*R*,*R*)-Me-Duphos as chiral ligand (Figure 1).[5a] They have explored this kind of reactions thereafter by the strategies such as dynamic kinetic resolution, desymmetrization, and the employing of Brønsted acids.[5b–d] Zhang and co-workers have studied the palladium-catalyzed asymmetric hydrogenation of α-acyloxy-1-arylethanones and α-phthalimide ketones with excellent results.[6] Despite the advantages,[7] the palladium-catalyzed asymmetric hydrogenation of ketone is still less developed, and effective reduction of other valuable substrates is still in demand.

The γ-valerolactone (GVL) moiety is ubiquitous substructure in natural products and biologically active moleculars, such as harzialactone A,[8] paraconic acids,[9] steganacin,[10] cardanolide[11] and others[12] (Figure 2). It has also been frequently used as intermediate for the synthesis of many valuable products in this kind.[13] Therefore, it is not strange that many effective methods were developed for its preparation from levulinic acid (LA), a cellulose waste used as a low cost biosourced platform chemical.[14] However, the asymmetric hydrogenation of levulinic acid with palladiumcatalyst has not been explored so far. Our group has a continuous interest in the transition metal/Lewis acid co-catalysts, which had been proved as powerful catalysts in many important transformations.[15] Recently, we have reported the Pd/Zn co-catalyzed chemo-selective hydrogenation of α-methylene-γ-keto carboxylic acids.[16] In connection with our previous investigations in the transition metal/Lewis acid co-catalysis, we here in report a palladium/zinc co-catalyzed asymmetric hydrogenation of levulinic acid.

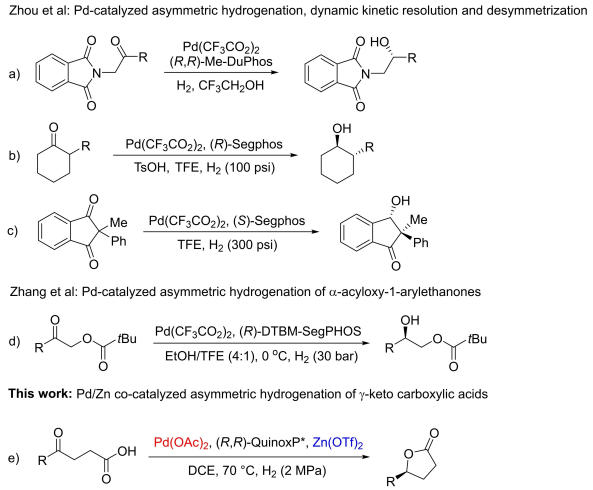

Figure 1. Represented Pd-catalyzed asymmetric hydrogenation of ketones.

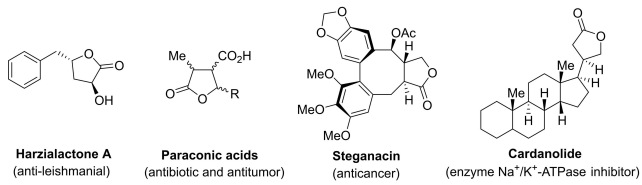

Figure 2. Represented biologically active γ-valerolactones.

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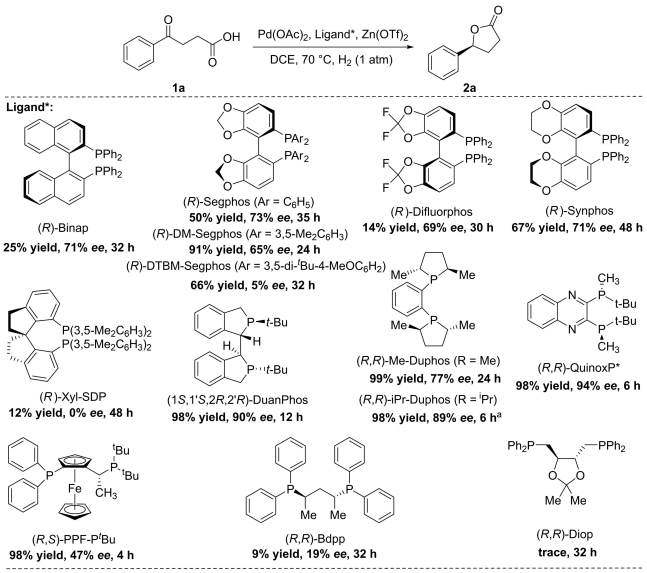
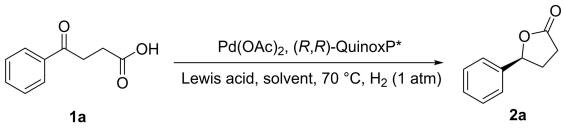
Initially, a range of chiral ligands were investigated in the hydrogenation of levulinic acid (**1 a**) with $Pd(OAc)_2/Zn(OTf)_2$ co-catalytic system (Scheme 1). By using (*R*)-Binap, γ-valerolactone **2 a** was obtained in 25% yield with 71% *ee* under normal presure of hydrogen gas. Then, some other biphenylbisphosphine ligands were screened. Among them, (*R*)-DM-Segphos performed well than the others to give **2 a** in excellent yield but with moderate *ee*. The chiral spiro bidentate ligand (*R*)-Xyl-SDP gave poor result. To our delight, (1*S*,1′*S*,2*R*,2′*R*)-DuanPhos and (*R*,*R*)-QuinoxP* won out with excellent results in view of both yield and enantioselectivity. (*R*,*R*)-Me-Duphos and (*R*,*R*)-iPr-Duphos also afforded the desired product with excellent yields albeit with inferior enantioselectivities. Although quantitative yield was obtained by (*R*,*S*)-PPF-P^{t}Bu, the *ee* of the products was low. Other chiral ligands such as (*R*,*R*)-Bdpp and (*R*,*R*)-Diop were not suitable for the present reaction due to their poor catalytic activities. Therefore, (*R*,*R*)-QuinoxP* was selected as the chiral ligand for further study.



Scheme 1. Chiral ligand screening for the asymmetric hydrogenation reaction of **1 a**. Reaction conditions: **1 a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), Ligand* (6 mol%), and $Zn(OTf)_2$ (10 mol%) in DCE (2.0 mL) at 70 °C for the time indicated. [a] **2 a** was obtained with *S*-configuration.

Table 1. Optimization of the reaction conditions.[a]

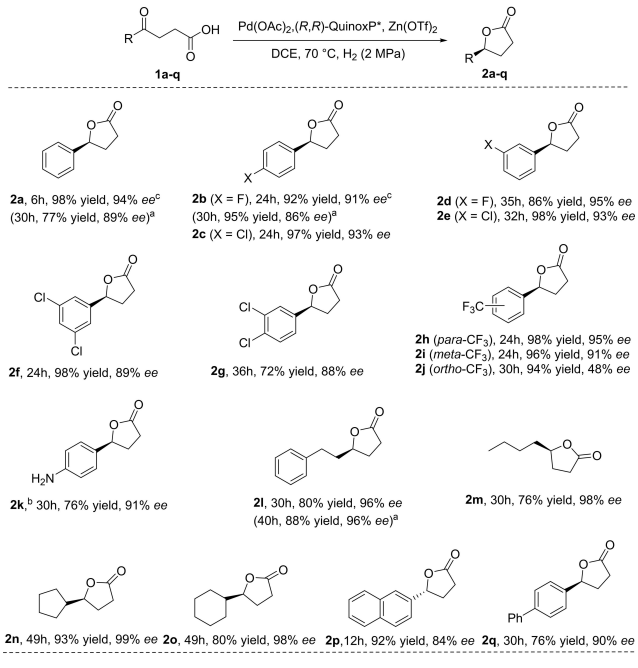


entry	solvent	additive	time [h]	yield[b] [%]	ee[c] [%]
1	DCE	$Zn(OTf)_2$	6	98	94
2	DCE	–	48	NR	–
3[d]	DCE	–	48	NR	–
4	DCE	AgOTf	48	Trace	–
5	DCE	$Cu(OTf)_2$	48	19	10
6	DCE	$Fe(OTf)_2$	30	82	93
7	DCE	$Fe(OTf)_3$	18	93	90
8	DCE	$ZnCl_2$	48	11	83
9	DCE	$Zn(OAc)_2$	48	21	77
10	DCE	$Fe(OAc)_2$	30	NR	–
11	toluene	$Zn(OTf)_2$	12	91	83
12	TFE	$Zn(OTf)_2$	12	98	37
13	THF	$Zn(OTf)_2$	36	90	87
14	1,4-dioxane	$Zn(OTf)_2$	24	97	89
15	MeOH	$Zn(OTf)_2$	24	32	85

[a] Reaction conditions: **1 a** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), (*R*,*R*)-QuinoxP* (6 mol%), and additive (10 mol%) in DCE (2.0 mL) at 70 °C for the time indicated. [b] Yield of the isolated product. [c] *ee*s were determined by chiral-phase HPLC. [d] Reacted under 2 Mpa.

Next, the reaction conditions were studied by surveying the Lewis acids and solvents (Table 1). The control experiment has verified the necessary of the Lewis acid as the reaction failed to give any product in its absence whether under normal pressure or 2 Mpa H_2 (Table 1, entries 2–3). By using other trifluoromesylates instead, AgOTf failed to promote the reaction (Table 1, entry 4), and $Cu(OTf)_2$ led to a poor result (Table 1, entry 5). Although $Fe(OTf)_2$ and $Fe(OTf)_3$ were suitable additives, the reaction outcomes were inferior to that of $Zn(OTf)_2$ (Table 1, entries 6&7 vs entry 1). Other Lewis acids, such as $ZnCl_2$, $Zn(OAc)_2$, and $Fe(OAc)_2$ were not efficient (Table 1, entries 8–10). In the solvent investigations, DCE was still the optimal solvent despite THF and 1,4-dioxane were also suitable (Table 1, entries 11–15).

With the optimized conditions in hand, we investigated the scope of present protocol for different γ-keto carboxylic acids (Scheme 2). γ-Keto carboxylic acids with fluoro and chloro substituents on the *para* and *meta* positions of the phenyl ring were well tolerated to give the corresponding chiral γ-valerolactones (**2 b**–**e**) in excellent results. And the substrates with di-chloro substituents also reacted well, thus allowing the



Scheme 2. Reaction scope investigation. Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol%), (*R*,*R*)-QuinoxP* (6 mol%), and $Zn(OTf)_2$ (10 mol%) in DCE (2.0 mL) at 70 °C for the time indicated. [a] Results in the brackets were obtained by using the corresponding ethyl esters of **1** as reactant. [b] Obtained by using 4-(4-nitrophenyl)-4-oxobutanoic acid as reactant. [c] Reacted under normal pressure.

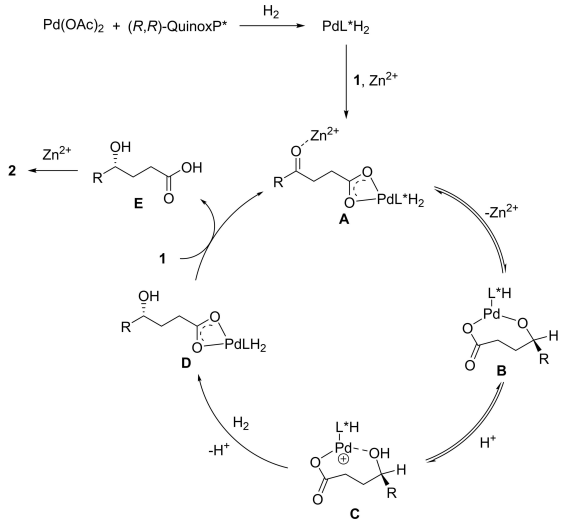
further elaborations of the product *via* the cross coupling reactions. The reaction performed well with CF_3 group on the phenyl ring (**2h**–**i**), but only 48% *ee* was observed by that on the *ortho* position (**2j**). The present protocol is effective for the hydrogenation of nitro group on the phenyl ring as indicated by **2k**. Moreover, the present methodology is applicable for the alkyl levulinic acids to afford the chiral γ-valerolactones (**2l**–**n**) in good yields with excellent optical purities. And the corresponding ethyl ester of **1l** was hydrogenated smoothly. Besides, the γ-keto carboxylic acids with naphthyl and biphenylyl groups were also applicable (**2p**–**q**).

According to the related literatures of transitional metal catalyzed hydrogenation of γ-keto carboxylic acids,[14b,17] a proposed reaction mechanism is shown in Scheme 3. Firstly, the reaction of chiral palladium complex with hydrogen affords the chiral palladium dihydride, which coordinates with **1** to give intermediate **A**. Subsequently, **A** is transferred to **B** by migratory insertion of the Pd–H into the keto group. Then, **B** has attracted a proton to generate intermediate **C**. Next, C is hydrogenated and depronated to give intermediate D. And the ligand-exchange reaction of intermediate **D** with the **1** affords **E** and regenerates **A**. Finally, the lactonization of **E** results chiral γ-valerolactone **2**.

In summary, a powerful asymmetric hydrogenation method of various γ-keto carboxylic acids was developed successfully. The catalytic system constituted of Pd(OAc)/(*R*,*R*)-QuinoxP* complex and $Zn(OTf)_2$ as Lewis acid co-catalyst, which allowed the preparation of a wide range of chiral γ-valerolactones. Further synthetic applications of this methodology for the valuable molecules are ongoing in our laboratory.

Experimental Section

Typical procedure for the asymmetric hydrogenation of γ-keto carboxylic acids. Under an argon atmosphere, to a flame dried reaction flask were added $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), 2,3-bis((*R*)-*tert*-butyl(methyl)phosphino)quinoxaline (4 mg, 0.012 mmol), and DCE (1 mL). After stirring 30 min, $Zn(OTf)_2$ (7.3 mg, 0.02 mmol) and 4-oxo-4-phenylbutanoic acid (35.6 mg, 0.2 mmol) were added, then dry DCE (1.0 mL) was added to the reaction mixture by using a syringe. Then after replacing nitrogen with hydrogen for three times, hydrogen was continuously injected into the reaction in 0.1 MPa. Finally, after stirred at 70 °C (oil bath) for 6 h, the reaction mixture was purified by silica gel chromatography (PE/EA = 6:1) to give product **2a** (98%).



Scheme 3. Proposed Mechanism.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: palladium · hydrogenation · ketone · valerolactone · levulinic acid

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