Pd-Catalyzed Asymmetric Hydrogenation of C=C Bond of α,β-Unsaturated Ketones

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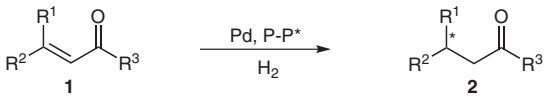
Abstract: Homogenous palladium-catalyzed asymmetric hydrogenation of C=C double bond of α,β-unsaturated ketones has been developed by using palladium(II) trifluoroacetate/(*S*)-7,7′-bis-[di(4-methoxyphenyl]phosphino)-1,1′-spirobiindane complex [$Pd(OCOCF_3)_2$–(*S*)-An-SDP] as the catalyst under ambient hydrogen pressure and room temperature with up to 89% ee.

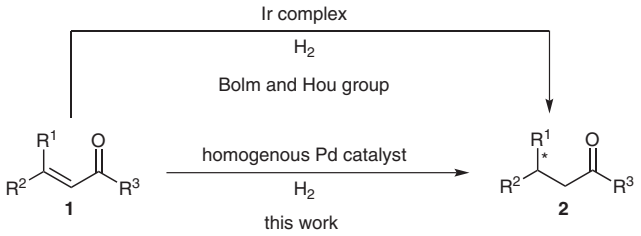
Key words: palladium, hydrogenation, unsaturated ketones, SDP ligand

Transition-metal-catalyzed asymmetric hydrogenation is one of the most powerful tools for the synthesis of optically active compounds and occupied a venerable position in organic synthesis.[1] Although chiral Ru, Rh, and Ir complexes have been extensively employed in asymmetric hydrogenation reactions, it was not until the past few years that homogenous palladium catalysts were successfully introduced for this process.[2,3] In 2001, Uneyama and co-workers reported the first homogenous Pd-catalyzed asymmetric hydrogenation of α-fluorinated iminoesters with up to 91% ee.[2a] Subsequently, Pd catalysts were applied to the asymmetric hydrogenation of a series of activated imines, such as *N*-diphenylphosphinyl and *N*-tosylimines, and cyclic *N*-sulfonylimines by us and other groups, respectively.[2d,3b–e] In 2005, this catalytic system was extended to the asymmetric hydrogenation of functionalized ketones by our group with high enantioselectivity.[3a] Very recently, Pd-catalyzed asymmetric hydrogenation of simple indoles and ketimines was developed by our group successively.[3f,h] It was also found to be effective in the asymmetric hydrogenation of *N*-PMP-protected fluorinated imines for the synthesis of the corresponding chiral fluorinated amines.[3g] Despite the progress achieved, to the best of our knowledge, homogenous Pd-catalyzed asymmetric hydrogenation of carbon–carbon double bond has never been realized and attracted our attention (Scheme 1).

The selective asymmetric hydrogenation of C=C bond of α,β-unsaturated ketones is one of the most straight access to ketones with a chiral center at the α- or β-position, which are important groups of compounds in organic synthesis.[4] Nevertheless, it has long been a challenge issue.[5] For the successful examples, it was mainly focused on cyclic substrates,[6] and the corresponding linear analogues were usually overlooked. In 2008, the asymmetric hydrogenation of linear unsaturated ketones achieved a breakthrough with Ir complexes by the groups of Bolm and Hou, respectively (Scheme 2).[7] As our ongoing work on Pd-catalyzed asymmetric hydrogenation reactions, we tried this kind of substrates.



Scheme 1 Pd-catalyzed asymmetric hydrogenation of C=C bond



Scheme 2 Asymmetric hydrogenation of linear α,β-unsaturated ketones

In 2006, Sodeoka and co-workers reported the asymmetric conjugate reduction of unsaturated ketones catalyzed by palladium complex with EtOH as hydride source.[8] This result promoted us to envision that Pd hydride species generated under hydrogen atmosphere may provide an alternative approach to reduce unsaturated ketones to saturated ones. Herein, we depicted the first example of homogenous Pd-catalyzed enantioselective hydrogenation of unsaturated ketones with specific chemoselectivity using $Pd(OCOCF_3)_2$–(*S*)-An-SDP as catalyst.

In our primary exploratory studies, different types of unsaturated ketones were tested, and the linear β,β-disubstituted 1,3-diphenyl-2-butenone [(*E*)-**1a**] showed the best result in terms of enantioselectivity. Therefore, it was selected as a model substrate for further studies.

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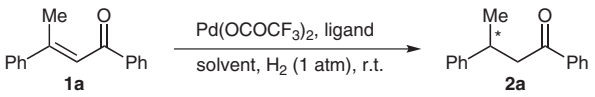
Table 1 Optimization of Reaction Conditions[a]



Entry	Ligand	Solvent	Time (h)	Conv. (%)[b]	ee (%)[c]
1	**L1**	TFE	38	>95	61
2[d]	**L1**	TFE	8	<5	–
3	**L1**	THF	16	68	4
4	**L1**	acetone	14	52	5
5	**L1**	toluene	13	<5	–
6	**L1**	CH_2Cl_2	14	<5	–
7	**L2**	TFE	33	>95	58
8	**L3**	TFE	24	>95	70
9	**L4**	TFE	33	>95	61
10	**L5**	TFE	24	>95	60
11	**L6a**	TFE	21	>95	74
12	**L6b**	TFE	31	>95	83
13	**L6c**	TFE	12	>95	86
14	**L6d**	TFE	39	>95	30
15	**L6e**	TFE	31	>95	13

[a] Conditions: **1a** (0.25 mmol), $Pd(OCOCF_3)_2$ (0.005 mmol), ligand (0.006 mmol), solvent (2 mL).
[b] Determined by GC or ^1H NMR.
[c] Determined by HPLC.
[d] Without H_2.

Initially, the reaction was carried out in 2,2,2-trifluoroethanol (TFE) with $Pd(OCOCF_3)_2$–(*S*)-SynPhos as catalytic system. The reaction occurred smoothly with saturated ketone **2a** as the sole product with 61% ee after 38 hours at room temperature under ambient pressure of hydrogen (Table 1, entry 1). The reaction was monitored by GC and ^1H NMR analysis, no allylic alcohol or excess hydrogenated product saturated alcohol appeared during this process. Subsequently, a control experiment was carried out to distinguish our catalytic system from Sodeoka's.[8] No conversion occurred when the reaction was performed in TFE without hydrogen (Table 1, entry 2), suggesting that hydrogen rather than TFE itself acts as hydride source; thus, this reaction is a hydrogenation process. Subsequently, the effect of solvent was investigated (Table 1, entries 1 and 3–6). It was found that this reaction was strongly solvent-dependent. As shown in our previous work, TFE is most effective in terms of both activity and enantioselectivity.[3] Other alcoholic solvents such as ethanol and isopropyl alcohol were excluded as they could serve as hydride sources.

Various commercially available ligands were then screened for high enantioselectivity. With axially chiral bisphosphine ligands **L1**–**5** (Figure 1), the reactions occurred smoothly, 58–70% ee were obtained (Table 1, entries 7–10). Finally, a series of chiral spiro bisphosphine ligands SDP (**L6a**–**e**), which was developed by Zhou group and successfully applied in asymmetric transformations,[9] were examined (entries 11–15). Ligand **L6c** (An-SDP) gave high activity and best enantioselectivity (Table 1, entry 13, 86% ee). Therefore, the optimal conditions were established as: $Pd(OCOCF_3)_2$, An-SDP, H_2 (1 atm), TFE, room temperature.

With the optimized reaction conditions in hand, the scope of substrate was explored (Table 2). Generally, the reactions completed within 12 hours with good to excellent enantioselectivity. The phenyl group R^2 was necessary for high activity and ee values, and if both R^1 and R^2 are alkyl groups the reaction proceeded slowly and with poor enantioselectivity. The length and steric property of R^1 displayed little effect to the enantioselectivity (Table 2, entries 1, 2, 4, and 9, 86–88% ee). Changing the substitution pattern on the ketonic phenyl group affected the activity and enantioselectivity variationally within a small range. For the isopropyl-substituted unsaturated ketones (*E*)-**1d**–**h**, the enantioselectivity varied from 85% to 89% (Table 2, entries 4–8). The highest ee was obtained for **2h** with methoxy substituent at the 4-position (Table 2, entry 8, 89% ee). Gratifyingly, this catalytic system was also ef-

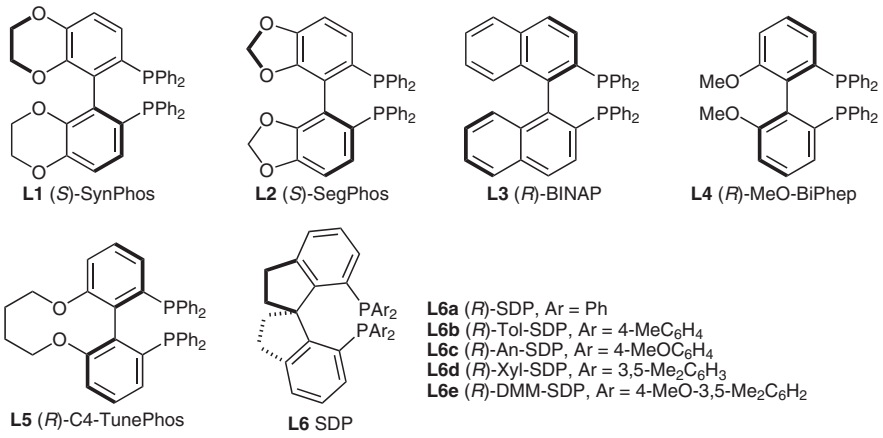
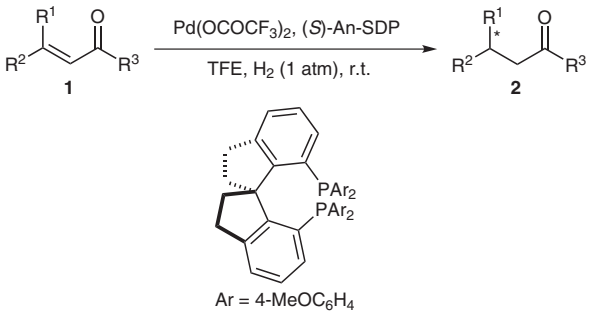


Figure 1

fective for alkyl ketones though the enantioselectivity was a little lower than the corresponding aryl ketones. In this case, the steric effect of the alkyl group (R^1) at the β-position on the enantioselectivity was more obvious. For the methyl ketone **1j**, the reaction complete within 26 hours and with only 78% ee (Table 2, entry 10). In contrast, the reaction was completed within 8 hours when the substrate bearing *i*-Pr or *c*-Hex, affording the products **2k** and **2l** in higher enantioselective manner (83% ee for both). In order to test the geometry of the enone whether it will have significant effect on the activity and enantioselectivity of the reaction, (*Z*)-**1d** with inverse geometry of the enone (*E*)-**1d**, gave **2d** with the same stereochemical outcome but much lower ee value (Table 2, entry 13, 34% ee) under otherwise identical reaction conditions. Notably, the hydrogenation of enone **2e** with 4-chloro substituent on the benzene ring afforded the corresponding product with full conversion and 88% ee (Table 2, entry 5). No other byproduct was observed, suggesting that no Pd(0) species is involed in the reaction. It is noteworthy that this is the first example with a Pd/bisphosphine complex as a homogenous asymmetric hydrogenation catalyst of unsaturated ketones.

In conclusion, we have developed the asymmetric hydrogenation of C=C bond of linear β,β-disubstituted unsaturated ketones with specific chemoselectivity and high enantioselectivity by using $Pd(OCOCF_3)_2$–(*S*)-An-SDP complex as the catalyst under mild conditions.[10] Our ongoing experiments are focused on the asymmetric hydrogenation of other types of substrates with C=C and on disclosure of the mechanism of Pd-catalyzed asymmetric hydrogenation reaction.

Table 2 Asymmetric Hydrogenation of Unsaturated Ketone **1** by $Pd(OCOCF_3)_2$–(*S*)-An-SDP System[a]



Entry	R^1	R^2	R^3	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	Me	Ph	Ph	12	**2a** 95	86 (*S*)
2	Et	Ph	Ph	36	**2b** 93	86 (*R*)
3	Et	Ph	4-MeC_6H_4	8	**2c** 88	86 (+)
4	*i*-Pr	Ph	Ph	8	**2d** 97	88 (–)
5	*i*-Pr	Ph	4-ClC_6H_4	8	**2e** 89	88 (+)
6	*i*-Pr	Ph	4-$MeOC_6H_4$	10	**2f** 89	89 (+)
7	*i*-Pr	Ph	2-$MeOC_6H_4$	6	**2g** 86	86 (+)
8	*i*-Pr	Ph	3-$MeOC_6H_4$	70	**2h** 89	85 (–)
9	Cy	Ph	Ph	4	**2i** 86	87 (–)
10	Me	Ph	Me	26	**2j** 70	78 (*R*)
11	*i*-Pr	Ph	Me	8	**2k** 71	83 (*S*)
12	Cy	Ph	Me	5	**2l** 90	83 (–)
13	Ph	*i*-Pr	Ph	12	**2d** 99	34 (–)

[a] Conditions: **1** (0.125 mmol), $Pd(OCOCF_3)_2$ (0.0025 mmol), (*S*)-An-SDP (0.003 mmol), TFE (2 mL).
[b] Isolated yields.
[c] Determined by HPLC.
[d] Conditions: **1a** (0.25 mmol), $Pd(OCOCF_3)_2$ (0.005 mmol), (*R*)-An-SDP (0.006 mmol), TFE (2 mL).

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(10) **Typical Procedure for the Asymmetric Hydrogenation of β,β-Disubstituted Unsaturated Ketones**

(*S*)-An-SDP (4.2 mg, 0.006 mmol) and $Pd(OCOCF_3)_2$ (1.7 mg, 0.005 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhyd acetone was added. The mixture was stirred at r.t. for 1 h. The solvent was removed under vacuum to give the catalyst. To this catalyst was added substrate **1a** (0.25 mmol) and dry TFE (2 mL) under a hydrogen atmosphere, then the mixture was stirred at r.t. After confirmation of consumption of substrate by GC, the hydrogen gas was slowly released from the reaction vessel. The ee was determined by HPLC after purification on silica gel using PE and EtOAc.

(*S*)-1,3-Diphenylbutan-1-one (2a)

Yield 95%, 86% ee; $[\alpha]_D^{r.t.}$ +0.70 (*c* 1.87, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ =1.36 (d, *J* = 6.9 Hz, 3 H), 3.21 (dd, *J* = 16.4, 8.2 Hz, 1 H), 3.32 (dd, *J* = 16.5, 5.8 Hz, 1 H), 3.49–3.58 (m, 1 H), 7.20–7.24 (m, 1 H), 7.28–7.36 (m, 4 H), 7.42–7.50 (m, 2 H), 7.53–7.56 (m, 1 H), 7.93–7.96 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.1, 35.7, 47.2, 126.5, 127.0, 128.2, 128.5, 128.7, 133.1, 137.4, 146.7, 199.2. HPLC (AD-H, eluent: hexanes–*i*-PrOH = 95:5, detector: 230 nm, flow rate: 0.8 mL/min), t_{R1} (*S*) = 7.6 min (major); t_{R2} (*R*) = 8.7 min.