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Catalytic asymmetric conjugate reduction with ethanol: A more reactive system Pd(II)–^{i}Pr-DUPHOS complex with molecular sieves 4A

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Abstract

We describe herein the catalytic asymmetric conjugate reduction of α,β-unsaturated carbonyl compounds using a novel cationic Pd–^{i}Pr-DUPHOS complex. In this reaction, EtOH worked well as a solvent and a reducing agent, and the reaction was completed within several hours in most cases to afford the reduced compounds almost quantitatively with modest to good enantioselectivity (up to 72% ee). It was found that the Pd–^{i}Pr-DUPHOS complex was more reactive than the previously reported Pd–BINAP complex when molecular sieves 4A was added as an additive. Based on an X-ray structural analysis of [Pd{(*S*,*S*)-^{i}Pr-duphos}](OTf)$_2$ complex, a working hypothesis of the reaction mechanism is also described.

Keywords: Palladium; Asymmetric catalysis; Conjugate reduction; Ethanol; DUPHOS; Molecular sieves 4A

1. Introduction

Catalytic asymmetric conjugate reduction of β,β-disubstituted electron-deficient olefins is an efficient method for the construction of tertiary stereogenic carbon centers. Great efforts have been devoted to the development of practical asymmetric reactions, and excellent enantioselectivity was achieved with the development of Cu-bisphosphine and Rh-Phebox complexes [1–3]. In addition, chiral secondary amines were reported to be excellent catalysts for asymmetric conjugate reduction of α,β-unsaturated aldehydes and ketones [4]. These reactions normally require a more-than-stoichiometric amount of reducing agents such as hydrosilane, $NaBH_4$, and Hantzsch ester, and thus a large amount of co-products are formed, which should be removed as a waste. In terms of atom economy and environmental concerns, replacement of metal hydrides and dihydropyridine derivatives by more environmentally benign and atom-economical reducing agents is in high demand.

We recently reported an efficient catalytic asymmetric conjugate reduction of enones using cationic Pd complexes **1a** and **2a** (Fig. 1 and Scheme 1) [5,6]. This reaction can be carried out in EtOH at room temperature to give the corresponding reduced products in high chemical yield with good to excellent enantioselectivity. Importantly, safe and clean EtOH is used not only as a solvent but also as a hydride source. In addition, the only co-product in this reaction is acetaldehyde diethylacetal, which can be readily removed under reduced pressure. Regardless of these advantages, the scope of the Pd–BINAP system is limited: (1) reduction of specific enones was sluggish as discussed later in Table 1 and (2) additionally, less reactive α,β-unsaturated esters could not be used in the Pd–BINAP-catalyzed conjugate reduction. Therefore, the development of a more highly reactive Pd catalyst is extremely desirable. In this article, we have developed a novel cationic Pd–^{i}Pr-DUPHOS complex as a promising catalyst for catalytic

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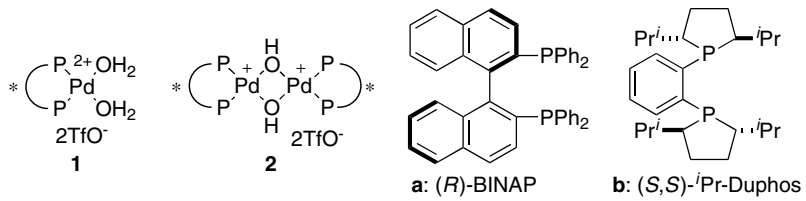
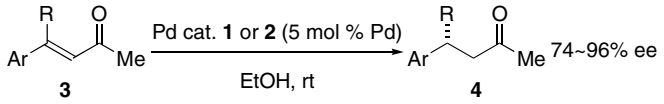
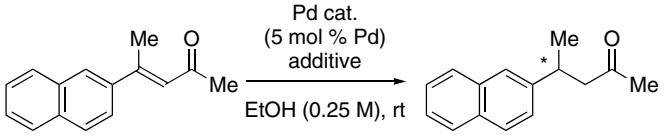


Fig. 1. Chiral Pd complexes used in this work.



Scheme 1.

Table 1
Optimization of the reaction conditions



Entry	Pd cat.	Additive	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a**	–	20	9	82
2	**2a**	–	20	21	80
3	**1b**	–	20	29	15[c]
4	**1b**	**MS4A**	20	**95**	21[c]
5	**1a**	MS4A	60	35	69

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] The absolute stereochemistry of the product was opposite to that from Pd–BINAP complexes.

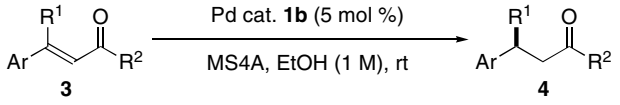
asymmetric conjugate reduction. This complex in combination with molecular sieves 4A showed much higher reactivity than the Pd–BINAP systems, being applicable to the efficient reduction of even α,β-unsaturated esters. The reaction mechanism is also discussed based on an X-ray structural analysis of an anhydrous Pd-DUPHOS complex.

2. Results and discussion

We chose **3a** as a model compound, because the Pd–BINAP complexes were less effective for this substrate. The reaction of **3a** was carried out in the presence of 5 mol% of Pd in ethanol at room temperature (Table 1). When **1a** was used as a catalyst, the reaction was slow. The reduced product **4a** was obtained in only 9% yield after 20 h, although the ee was high (entry 1). The Pd μ-hydroxo complex **2a** slightly improve the chemical yield to give **4a** in 16% yield (entry 2). It is likely that the poor chemical yield in these reactions might be due to insufficient nucleophilicity of a putative palladium hydride (Pd-H) intermediate. Therefore, we envisaged that the reactivity of the Pd-H species would be enhanced if a more electron-donating bisphosphine ligand was used. Thus, the use of alkyl-substituted bisphosphine ligand DUPHOS was next examined [7]. As we expected, a better chemical yield (29%) was observed when **1b** was used as a catalyst (entry 3). To improve the reaction rate, we planned to examine the use of Pd μ-hydroxo complex **2b**, expected to facilitate the formation of a Pd-ethoxide intermediate as a result of hydroxide and alkoxide exchange reaction (vide infra). Unfortunately, however, all attempts to obtain pure **2b** were unsuccessful. According to our previous observation that molecular sieves 4A acts as a weak base and dehydrating agent to facilitate the formation of **2a** from **1a** [6a], we next examined the in situ formation of the Pd μ-hydroxo complex **2b** or its equivalent from the aqua-type complex **1b**. To our delight, the reaction proceeded very smoothly when **1b** was used in combination with molecular sieves 4A, and complete consumption of **3a** was observed after 20 h. The corresponding product **4a** was isolated in 95% yield with 21% ee (entry 4). In contrast, the reaction with **1a** under identical reaction conditions yielded **4a** in only 35% yield after even 60 h (entry 5). These results clearly indicate that **1b** is superior to **1a** in terms of the reaction rate, when they were used in combination with molecular sieves 4A. Even though improvement of the enantioselectivity is necessary, this higher reactivity achieved with an alkyl-substituted electron-rich bisphosphine prompted us to examine the scope and limitations of this catalytic system.

With the more reactive catalytic system in hand, we first applied this system to other enone substrates (Table 2). All reactions conducted in Table 2 were complete within several hours. In the case of substrates having a less bulky alkyl-substituent at the β-position (**3b**, **3c**), the enantioselectivity was poor (entries 1 and 2). Interestingly, as the bulkiness of the β-substituent was increased (**3d** and **3e**), the enantioselectivity was improved (entries 3 and 4). In particular, the substrate bearing ^{i}Pr group at the β-position was converted to **4e** in 98% yield with 70% ee. In addition, enones with a substituent at the ortho position of the aromatic ring were also good substrates. The reactions of **3f** and **3g** having an electron-donating group gave the products in good yield with high enantioselectivity (56% ee and 72% ee, respectively) (entries 5 and 6). Finally, Br-substituted substrate **3h** also underwent the conjugate reduction without difficulty to afford **4h** in 83% yield with 64% ee (entry 7). In this reaction, the Br group was completely intact, and no debrominated compounds were formed. It should be noted that all products obtained in this work have the absolute configuration opposite to those

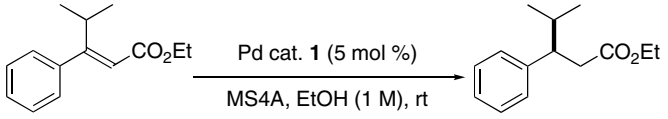
Table 2
Catalytic asymmetric conjugate reduction of enones



Entry	Ar	R^1	R^2	Substrate	Product	Time (h)	Yield[a] (%)	ee[b] (%)
1	Ph	Me	Me	**3b**	**4b**	2	96	16 (*S*)[c]
2	Ph	Me	Ph	**3c**	**4c**	14	95	26 (*S*)[d]
3	Ph	Et	Me	**3d**	**4d**	2	84	32 (*S*)[c]
4	Ph	^{i}Pr	Me	**3e**	**4e**	5	98	70 (*R*)[c]
5	2-$MeOC_6H_4$	Me	Me	**3f**	**4f**	2	91	56[e]
6	2-MeC_6H_4	Me	Me	**3g**	**4g**	2	85	72[e]
7	2-BrC_6H_4	Me	Me	**3h**	**4h**	7	83	64 (*S*)[f]

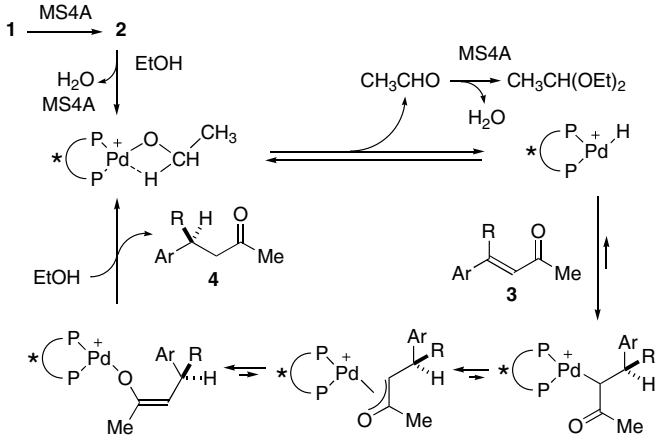
[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] See Ref. [5].
[d] See Ref. [2b].
[e] The absolute configuration of the product has not been determined.
[f] See Section 4.

Table 3
Catalytic asymmetric conjugate reduction of an ester



Entry	Pd cat.	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1b**	4	95	35 (*R*)[c]
2	**1a**	40	69	49 (*R*)[c]

[a] Isolated yield.
[b] Determined by chiral HPLC.
[c] See Ref. [2b].



Scheme 2. Proposed catalytic cycle.

observed when the Pd-(*R*)-BINAP complex **2a** was used, even though both catalysts constitute a similar chiral environment around Pd with ^{i}Pr groups and Ph groups at the upper-left and lower-right corners, respectively (vide infra) [5].

Considering the higher reactivity of **1b** with molecular sieves 4A, the catalytic asymmetric conjugate reduction of α,β-unsaturated ester was examined under identical conditions. (*E*)-Ethyl 4-methyl-3-phenylpent-2-enoate **5** was chosen as a substrate, and two Pd complexes derived from BINAP and ^{i}Pr-DUPHOS, **1a** and **1b**, were compared (Table 3). The reaction catalyzed by **1b** was complete after 4 h in the presence of molecular sieves 4A, affording **6** in 95% yield with 35% ee (entry 1). In contrast, the reaction with **1a** was slow and did not reach completion even after 40 h (entry 2). Interestingly, in contrast to the reactions of enones, the same sense of enantioselection was observed in these reactions.

A proposed catalytic cycle is outlined in Scheme 2. First, the Pd aqua complex **1b** may be transformed to **2b** or a similar hydroxo complex with the aid of molecular sieves 4A, and the generated Pd-OH acts as a Brønsted base to form a Pd-ethoxide complex. Subsequent β-hydride elimination affords a Pd-H intermediate. The enones **3** coordinating to the Pd complex would undergo hydride transfer, and the resulting Pd enolate is protonated by ethanol to complete the catalytic cycle. Acetaldehyde formed during the oxidation step is converted to diethylacetal. It is likely that molecular sieves 4A promotes acetal formation and the generation of the Pd-ethoxide intermediate from **2b** by removing water molecules produced in these steps. In addition, the electron-rich phosphine ligand might enhance the nucleophilicity of the Pd-H intermediate, thereby the less reactive substrates, in particular, enoate **5** could undergo the conjugate reduction smoothly. Additionally, DUPHOS may also increase the reactivity of the resulting Pd enolate, and the final protonation is accelerated. These factors can explain the higher reactivity of the present catalytic system.

To obtain more insight into the reaction mechanism, structural determination of the Pd–^{i}Pr-DUPHOS complex was examined. Unfortunately, all attempts to obtain a single crystal of **1b** under usual vapor diffusion method were unsuccessful. But concentration of a hexane–CH_2Cl_2 (1: 1) solution of **1b** under reduced pressure afforded an anhydrous complex **1b′**. This yellow crystalline was apt to absorb water molecules and change to the original **1b** as yellow oil when it was left in the solvent at room temperature for several hours. To our delight, however, we succeeded in determining the structure of **1b′** unequivocally by X-ray analysis (Fig. 2). The molecular structure displays a square-planar coordination for palladium (II) ligated with two phosphorous atoms of DUPHOS and two oxygen atoms of trifluormethanesulfonyl group. Two trifluoromethansulfonyl groups are positioned in the open

space (upper-left and lower-right corners), avoiding unfavorable interaction with the ^{i}Pr group on the ligand (side-view).

A simplified model of the putative Pd-H intermediate **8** is shown in Scheme 3. As viewed side-on, the ^{i}Pr group of the (*S*,*S*)-DUPHOS occupies the upper-left side of the open space around the coordination site for the enone. Therefore, a favorable complex between **3** and **8** would be the model **A** shown in Scheme 4. In contrast, the model **B** would suffer from steric repulsion between the methyl ketone moiety of the substrate and the ^{i}Pr group of the ligand. Even though the ee depends on the nature of the substrate, the sense of enantioselection can be explained by using the model **A** on the assumption that enantioselection is mainly determined in the hydride transfer step. In contrast, this idea was not applicable to the Pd-(*R*)-BINAP-catalyzed conjugate reduction of the enones, where the observed stereochemistry was opposite to the prediction based on similar models depicted in Scheme 4 [8]. We speculate that enantio-determining step in these two reactions may be different: the hydride transfer step in the reaction catalyzed by **2a** would be reversible because the final protonation step is not fast enough [9], and protonation of the Pd enolate intermediate might determine the final absolute stereochemistry of the product. In the case of Pd-DUPHOS system, the putative Pd enolate having an electron-rich phosphine ligand would undergo the final protonation smoothly, since the nucleophilicity of the enolate is increased. Consequently, reversible reactions going back to **8** would be retarded, making the insertion step a major enantio-determining step. Such a reverse of the stereochemistry was not observed in the case of **5** (Table 3). This is probably because the smooth protonation occurred, since the corresponding enolate of esters should be more reactive. Therefore, it seems that the absolute stereochemistry was determined in the insertion step even in the case of the Pd–BINAP system, which is in accord with the prediction. The models of the complex of **3** and **8** were constructed with a parallel alignment between the C=C bond and the Pd–H bond. Other skewed coordination modes should be considered to understand the β-substituent effect of the enones. Although the story is not so simple, the working hypothesis discussed here would be useful for further improvement.

3. Conclusions

We have developed a catalytic asymmetric conjugate reduction with EtOH using a novel Pd–^{i}Pr-DUPHOS complex combined with molecular sieves 4A. This catalyst sys-

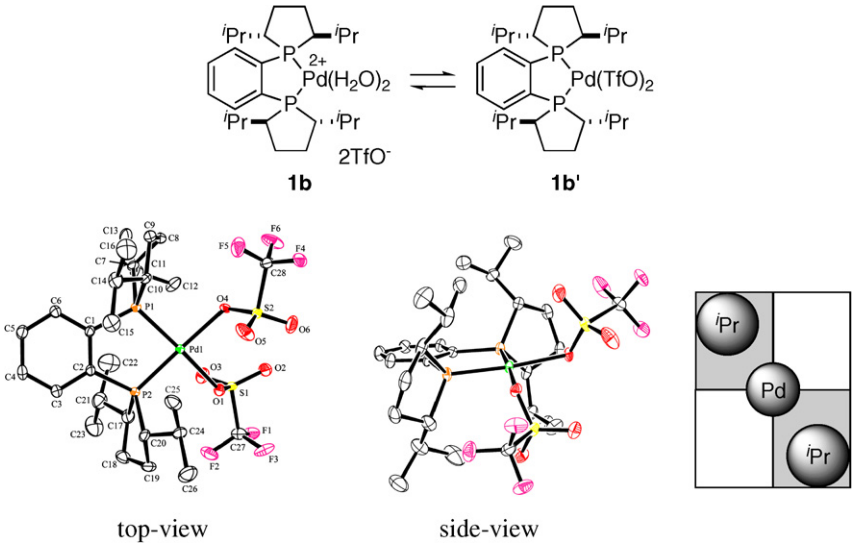
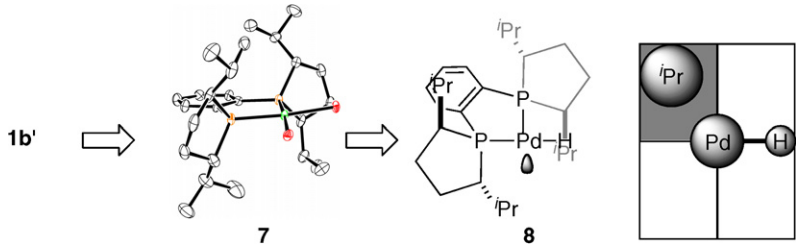
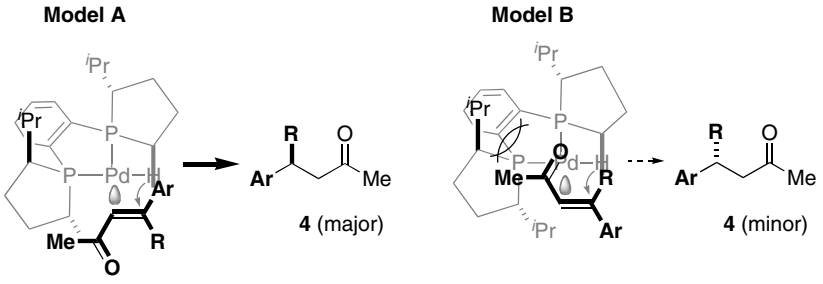


Fig. 2. X-ray structure of **1b′**.



Scheme 3.



Scheme 4. A possible mechanism for asymmetric induction.

tem shows greater reactivity than the previous Pd–BINAP system, and the reduction of enones and enoates proceeded smoothly. Even though the enantioselectivity observed in the present work varied depending on the substrate, we believe that the present results would provide a guide for a better understanding of the reaction. Systematic tuning of the catalyst using various known alkyl-substituted bisphosphine ligands based on our hypothesis will lead to great improvement of the reaction efficiency. Further investigations into the improvement of the reaction efficiency and to confirm our proposed reaction mechanism are underway in our laboratory.

4. Experimental

All asymmetric reactions were carried out without precaution to exclude air and moisture. NMR spectra were recorded on a JEOL-LA 300 or 400 spectrometer, operating at 300 or 400 MHz for ^{1}H NMR, 75.0 or 100 MHz for ^{13}C NMR. Chemical shifts were reported downfield from TMS (=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used an internal reference. IR was measured on Thermo Nicolet AVATAR 370 FT-IR equipped with DuraScope™. Optical rotations were measured on a JASCO DIP-370 polarimeter. Column chromatography was performed with silica gel 60 (40–100 μm) purchased from Kanto Chemical Co. The enantiomeric excesses (ees) were determined by HPLC analysis using JASCO Borwin Ver.1.5 systems consisting of the following; pump, JASCO PU-2080 plus; detector, JASCO CD-2095 plus measured at 254 nm or 280 nm; column, DAICEL CHIRALPAK AS-H, and CHIRALCEL OJ-H; mobile phase, hexane/2-propanol (IPA). Commercially available dehydrated EtOH was used directly. Molecular sieves 4A 1/16 purchased from Wako Pure Chemical Industries, Ltd. was used after drying at 150 °C for 20 h under reduced pressure.

4.1. Preparation of palladium aqua complex (*1b*)

[Pd{(*S*,*S*)-^{i}Pr-duphos}]Cl_2 was prepared according to the reported procedure [7a]. To a solution of [Pd{(*S*,*S*)-^{i}Pr-duphos}]Cl_2 (87 mg, 0.15 mmol) in CH_2Cl_2 (4 mL) was added AgOTf (75.3 mg, 0.29 mmol), H_2O (10 μL) at room temperature. The mixture was stirred at room temperature for 2 h. The precipitated AgCl was filtered off through Celite, and the filtrate was evaporated under reduced pressure to afford **1b** (113 mg, 0.13 mmol) in 90% yield.

1b: ^{1}H NMR (400 MHz, $CDCl_3$, TMS) $\delta = 0.81$ (d, 6H, $J = 6.6$ Hz), 0.86 (d, 6H, $J = 6.6$ Hz), 1.15 (d, 6H, $J = 6.8$ Hz), 1.26 (d, 6H, $J = 6.8$ Hz), 1.66–1.69 (m, 2H), 1.78–1.82 (m, 2H), 1.99–2.03 (m, 2H), 2.30–2.49 (m, 4H), 2.51–2.54 (m, 4H), 3.10–3.30 (m, 2H), 4.49 (br-s, 4H, H_2O), 7.79 (br-s, 2H), 7.87 (br-s, 2H); ^{31}P NMR (160 MHz, $CDCl_3$, 85% H_3PO_4) $\delta = -71.4$: $[\alpha]_D = -16.5$ (29 °C, $c = 1.3$, $CHCl_3$).

4.2. X-ray crystal structure analysis of *1b′*

Crystal data: $C_{28}H_{44}F_6O_6P_2PdS_2 \cdot CH_2Cl_2 \cdot H_2O$, FW = 926.03, hexagonal $P6_1$, $a = 17.3064(4)$ Å, $c = 26.4722(6)$ Å, $V = 6866.5(3)$ Å^3; $D_X = 1.344$ Mg m^{-3}; $Z = 6$; μ(Mo Kα) = 0.743 mm^{-1}, $T = 100$ K. Block shaped colorless crystals were grown under reduced pressure from a hexane–CH_2Cl_2 solution of **1b**. A single crystal with the dimensions of $0.48 \times 0.25 \times 0.19$ mm was mounted on a glass capillary and set on a Rigaku RAXIS-RAPID diffractometer. The diffraction data were collected using graphite-monochromated Mo Kα radiation. The unit cell dimensions were determined using 70265 reflections with $6° \leqslant 2\theta \leqslant 60°$. The diffraction data of 76918 within $6° \leqslant 2\theta \leqslant 60°$ were collected and merged to give 13002 unique reflections with R_{int} of 0.0628. The structure was solved by a direct method and refined on F^2 by a least-squares method by the programs SIR2004 and SHELXL97, respectively. The crystal showed twinning by merohedry. To merge the intensities of the equivalent reflections from each of two components, the data were processed by the TWIN 0 1 0 1 0 0 0 0 −1 command in the SHELXL97 program on the refinements. The final *R* values against 6868 unique reflections ($2\theta_{max} = 60°$) with $I > 2\sigma(I)$ are 0.0472 and 0.1218 for $R(F)$ and $wR(F^2)$, respectively. The absolute structure of the crystal was determined by anomalous dispersion effects; the resulted configuration of the **1b′** agrees with the (*S*,*S*) configuration of the ^{i}Pr-DUPHOS ligand. Programs used: SIR2004: M.C. Burla, R. Caliandro, M. Camalli, B. Carrozzini, G.L. Cascarano, L. De Caro, C. Giacovazzo, G. Polidori, R. Spagna, J. Appl. Cryst. 38

(2005) 381–388; SHELXL97: G.M. Sheldrick, University of Göttingen, Germany, 1997.

Selected distances (Å) and angles (°) are as follows: Pd(1)–O(4) 2.165(3), Pd(1)–O(1) 2.171(4), Pd(1)–P(2) 2.2181(13), Pd(1)–P(1) 2.2293(12), O(4)–Pd(1)–O(1) 89.56(13), O(4)–Pd(1)–P(2) 174.83(11), O(1)–Pd(1)–P(2) 90.86(10), O(4)–Pd(1)–P(1) 93.37(10), O(1)–Pd(1)–P(1) 175.88(11), P(2)–Pd(1)–P(1) 86.47(4), C(1)–P(1)–Pd(1) 109.47(16), C(7)–P(1)–Pd(1) 115.55(17), C(10)–P(1)–Pd(1) 114.76(15), C(2)–P(2)–Pd(1) 109.51(16), C(20)–P(2)–Pd(1) 113.92(17), C(17)–P(2)–Pd(1) 116.7(2), S(1)–O(1)–Pd(1) 118.9(2), S(2)–O(4)–Pd(1) 119.7(2), P(1)–C(10)–H(10) 107.6, P(2)–C(17)–H(17) 107.3.

4.3. Preparation of starting materials

Starting materials **3a**, **3f**, and **3g** were synthesized according to the procedure described in Supporting Information of our previous paper [5]. Other compounds are known in the literature [2b,5].

(E)-4-(naphthalen-3-yl)-3-penten-2-one (**3a**): Amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 2.33$ (s, 3H), 2.65 (d, $J = 1.1$ Hz, 3H), 6.66 (br-s, 1H), 7.48–7.53 (m, 2H), 7.60 (dd, $J = 1.8$, 8.3 Hz, 1H), 7.82–7.88 (m, 3H), 7.96 (br-s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 198.9$, 153.6, 139.6, 133.5, 133.1, 128.5, 128.2, 127.6, 126.7, 126.5, 126.2, 124.8, 124.0, 32.3, 18.3; IR (solid) ν 1673, 1583, 1385, 1359, 1280, 1232, 1174, 1009, 957 cm^{-1}.

(E)-4-(2-methoxyphenyl)-3-penten-2-one (**3f**): Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.25$ (s, 3H), 2.45 (s, 3H), 3.83 (s, 3H), 6.27 (s, 1H), 6.89–6.96 (m, 2H), 7.13 (d, $J = 8.0$ Hz, 1H), 7.28–7.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 198.7$, 156.3, 154.8, 133.1, 129.4, 128.6, 126.5, 120.4, 111.0, 55.5, 32.2, 20.4; IR (neat) ν 1680, 1596, 1487, 1434, 1353, 1259, 1231, 1178, 1025 cm^{-1}.

(E)-4-(2-methylphenyl)-3-pentene-2-one (**3g**): Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 2.25$ (s, 3H), 2.28 (s, 3H), 2.41 (d, $J = 1.6$ Hz, 3H), 6.15 (br-s, 1H), 7.06 (d, $J = 6.8$ Hz, 1H), 7.14–7.26 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 198.7$, 156.4, 143.9, 133.8, 130.3, 127.6, 126.9, 126.5, 125.6, 32.1, 21.3, 19.8; IR (neat) ν 1684, 1610, 1598, 1485, 1425, 1353, 1259, 1174, 961 cm^{-1}.

4.4. General procedure for the catalytic asymmetric conjugate reduction (Table 2)

A solution of **1b** (4.4 mg, 0.005 mmol), **3 g** (17 mg, 0.1 mmol), and molecular sieves 4A (20 mg) in ethanol (0.1 mL) was stirred at ambient temperature for 2 h. Evaporation of the solvent, following by silica gel column chromatography hexane/AcOEt (9/1, $R_f = 0.3$) gave **4g** in 85% yield (14.9 mg, 0.085 mmol) with 72% ee. The ee was determined by chiral HPLC analysis. For compounds **4b**, **4d**, **4e**, and **4h**, see Ref. [5]. For compounds **4c** and **6**, see [2b].

4-(Naphthalen-3-yl)pentan-2-one (**4a**): Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.35$ (d, $J = 7.0$ Hz, 3H), 2.07 (s, 3H), 2.70–2.90 (m, 2H), 3.47 (tdd, $J = 6.6$, 6.6, 6.6 Hz, 1H), 7.34–7.48 (m, 3H), 7.63 (br-s, 1H), 7.78 (d, $J = 8.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 207.7$, 143.6, 133.6, 132.3, 128.2, 127.6, 127.5, 126.0, 125.5, 125.4, 124.9, 51.9, 35.5, 30.6, 22.0; IR (neat) ν 2962, 1712, 1600, 1506, 1357, 1271, 1161, 1128 cm^{-1}; HPLC (DAICEL CHIRALCEL OJ-H, *n*-hexane/IPA = 99/1, flow rate: 0.5 mL/min, UV: 254 nm, τ_{major} 21.2 min, τ_{minor} 24.3 min for **4a** from **1b**); $[\alpha]_D = +8.93$ (28 °C, $c = 0.5$, 21% ee from **1b**, $CHCl_3$), $[\alpha]_D = -31.3$ (28 °C, $c = 0.14$, 69% ee from **1a**, $CHCl_3$).

4-(2-Methoxyphenyl)pentan-2-one (**4f**): Viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 1.25$ (d, $J = 6.7$ Hz, 3H), 2.08 (s, 3H), 2.61 (dd, $J = 8.3$, 15.8 Hz, 1H), 2.78 (dd, $J = 5.6$, 15.1 Hz, 1H), 3.66–3.70 (m, 1H), 3.73 (s, 3H), 6.85–6.94 (m, 2H), 7.15–7.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 20.1$, 29.0, 30.1, 50.8, 55.3, 110.5, 120.6, 126.8, 127.2, 134.1, 156.7, 208.5; IR (neat) ν 2962, 1711, 1599, 1491, 1461, 1355, 1239, 1161, 1123, 1025 cm^{-1}; HPLC (DAICEL CHIRALPAK AS-H, *n*-hexane/IPA = 99/1, flow rate: 1.0 mL/min, UV: 254 nm, τ_{minor} 12.1 min, τ_{major} 14.1 min); $[\alpha]_D = +8.46$ (26 °C, $c = 0.2$, 56% ee, $CHCl_3$).

4-(2-Methylphenyl)pentan-2-one (**4g**): Viscous oil. ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 1.23$ (d, $J = 6.8$ Hz, 3H), 2.09 (s, 3H), 2.37 (s, 3H), 2.63–2.79 (m, 2H), 3.56 (tdd, $J = 6.8$, 6.8, 6.8 Hz, 1H), 7.07–7.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 207.6$, 144.2, 135.1, 130.4, 126.2, 125.9, 124.9, 51.3, 30.6, 30.4, 21.5, 19.5; IR (neat) ν 2964, 2926, 2873, 1712, 1490, 1456, 1354, 1292, 1260, 1161, 1029 cm^{-1}; HPLC (DAICEL CHIRALCEL OJ-H, *n*-hexane/IPA = 200/1, flow rate: 0.5 mL/min, UV: 254 nm, τ_{major} 23.5 min, τ_{minor} 29.4 min); $[\alpha]_D = +21.43$ (26 °C, $c = 0.6$, 72% ee, $CHCl_3$).

4.5. Determination of absolute configuration of *4h*

A solution of **4h** (11 mg, 0.046 mmol, 64% ee) and 10% Pd/C (2 mg) in ethanol (0.1 mL) was stirred at ambient temperature under hydrogen atmosphere (1 atm) for 2 h. Evaporation of the solvent, following by silica gel chromatography hexane/AcOEt (3/1, $R_f = 0.3$) gave **4b** in 83% yield (6.2 mg, 0.038 mmol) with 57% ee. The absolute configuration were determined by comparing retention times of each isomer on chiral HPLC: DAICEL CHIRALPAK AS-H, *n*-hexane/IPA = 98/2, flow rate: 0.5 mL/min, UV = 254 nm, $\tau_{major} = 14.9$ min (*S*), $\tau_{minor} = 17.6$ min (*R*).

5. Supplementary material

CCDC 657104 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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