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Highly enantioselective 1,4-addition of arylzinc reagents to 3-arylpropenals catalyzed by a rhodium–binap complex in the presence of chlorotrimethylsilane

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Abstract—Asymmetric 1,4-addition of arylzinc chlorides to (*E*)-3-arylpropenals proceeded with high enantioselectivity in the presence of a rhodium/(*R*)-binap catalyst and chlorotrimethylsilane to give, after hydrolysis, high yields of the corresponding 3,3-diarylpropanals of 98–99% ee. The presence of the chlorosilane is essential for high yields of the 1,4-addition products.

1. Introduction

Catalytic asymmetric 1,4-addition of organometallic reagents to electron-deficient olefins is a powerful tool for asymmetric carbon–carbon bond formation.[1] Among the olefins activated by electron-withdrawing groups, α,β-unsaturated aldehydes are one of the most challenging substrates, because the aldehyde carbonyls are so reactive that undesired 1,2-addition takes place. In the rhodium-catalyzed asymmetric 1,4-addition, which has been growing very rapidly,[2,3] aryl- and alkenylboronic acids have been widely used for various types of electron-deficient olefins, but the reaction systems, which realize both high chemoselectivity and enantioselectivity in the asymmetric addition of boronic acids to α,β-unsaturated aldehydes have not been reported,[4,5] until very recently. One solution to this problem is to use chiral diene ligands for the rhodium-catalyzed 1,4-addition of arylboronic acids,[6–8] where exclusive 1,4-addition was observed although the enantioselectivity was not always high (around 90% ee). Herein, we report another approach to the asymmetric 1,4-addition to α,β-unsaturated aldehydes. High enantioselectivity of not lower than 98% ee was realized by use of arylzinc reagents and chlorotrimethylsilane in the rhodium-catalyzed asymmetric 1,4-addition to 3-arylpropenals.

2. Results and discussion

Several phenyl-metal reagents were examined for the asymmetric addition to (*E*)-3-(4-methoxyphenyl)propenal **1a** in the presence of a rhodium catalyst coordinated with (*R*)-binap. The best result was obtained with PhZnCl in the presence of $ClSiMe_3$ (Scheme 1). Thus, to a solution of **1a**, $ClSiMe_3$ (1.3 equiv to **1a**), and $[RhCl((R)\text{-binap})]_2$ (3 mol % Rh) in THF was added PhZnCl (1.1 equiv to **1a**), which was generated from PhLi and $ZnCl_2$, and the mixture stirred at 20 °C for 1 h. Volatile materials were removed under reduced pressure, and then the mixture hydrolyzed by addition of a solution of potassium carbonate in methanol and water. Silica gel chromatography gave 80% yield of 1,4-addition product, (*S*)-3-(4-methoxyphenyl)-3-phenylpropanal **2a** together with 17% yield of 1,2-addition product, (*E*)-3-(4-methoxyphenyl)-1-phenyl-2-propenol **3a** (Table 1, entry 1). NMR analysis of the reaction mixture before hydrolysis showed that the primary 1,4-addition product is silyl enol ether **4a**, consisting of *Z*- and *E*-isomers in a ratio of 7:1. The enantiomeric purity of **2a** was determined to be 99% ee by HPLC analysis of 3-(4-methoxyphenyl)-3-phenyl-1-propanol, which was obtained by reduction with $NaBH_4$. The reaction in the absence of $ClSiMe_3$[9] did not provide the 1,4-addition product **2a**, starting enal **1a** being recovered in a high yield (entry 2). The high performance of the zinc reagent in combination with $ClSiMe_3$ has been observed in the asymmetric 1,4-addition to 4-quinolones[10] and 1,6-addition to dienones.[11] Other phenyl-metal reagents, which

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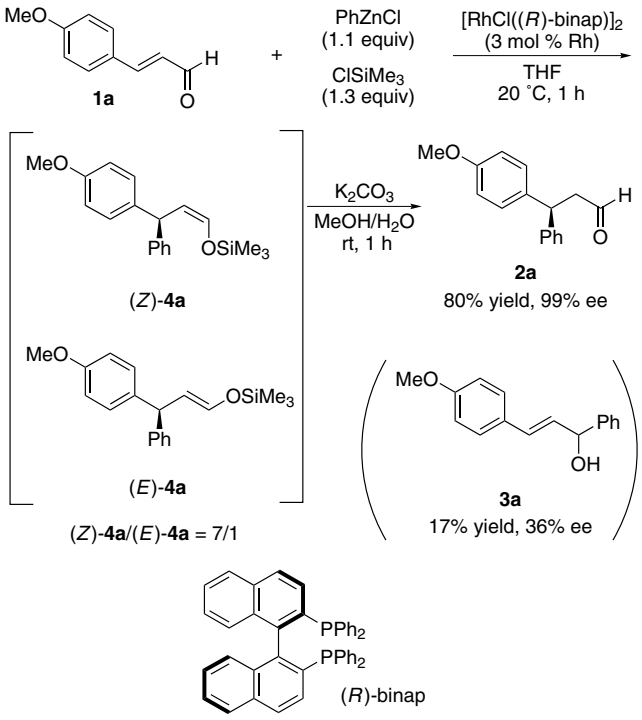


Scheme 1.

have successfully been used for the rhodium-catalyzed asymmetric 1,4-addition to some other electron-deficient olefins,[2] were much less reactive or selective for the present 1,4-addition to α,β-unsaturated aldehydes. The reaction conditions and results obtained are included in Table 1. Phenylboronic acid, which is a standard phenyl-metal reagent for the rhodium-catalyzed 1,4-addition,[2] was not reactive towards enal **1a** resulting in a low yield of the 1,4-addition product **2a**. Thus, the reaction of $PhB(OH)_2$ catalyzed by a rhodium–binap complex at 50 °C for 3 h only gave 19% yield of **2a** (90% ee), 67% of enal **1a** being recovered (entry 3). Titanium reagents, either $PhTi(O\textit{i}\text{-}Pr)_3$[12] or $PhTi(O\textit{i}\text{-}Pr)_4Li/ClSiMe_3$[13] were not suitable for the present substrate **1a**. Selective 1,2-addition giving allylic alcohol **3a** was observed with $PhTi(O\textit{i}\text{-}Pr)_3$ (entry 4), and $PhTi(O\textit{i}\text{-}Pr)_4Li/ClSiMe_3$ gave a low yield (9%) of 1,4-addition product **2a** in addition to 28% yield of **3a** (entry 5).

Table 2 illustrates the scope of the present asymmetric 1,4-addition to α,β-unsaturated aldehydes containing aryl substituents at β-position. In general, the 1,4-addition proceeded with very high enantioselectivity (98–99% ee) via the use of a combination of arylzinc reagents (1.1 equiv) and $ClSiMe_3$ (1.3 equiv), although the yields of 1,4-addition products **2** are not always high (55–80% yield) due to competitive 1,2-addition giving allylic alcohols. The enantioselectivity was high for the addition of PhZnCl to cinnamaldehydes substituted on the phenyl group at the β-position (entries 1–4) and in the addition of substituted arylzinc reagents to unsubstituted cinnamaldehyde (entries 5–10). Various aryl groups possessing both electron-donating and -withdrawing groups were introduced in a 1,4-fashion into cinnamaldehyde with high enantioselectivity to give 3,3-diaryl-substituted propanals of 98–99% ee. Both enantiomers can be obtained with a single enantiomer of the binap ligand by varying the zinc reagent and cinnamaldehyde (entries 1 and 5). It should be noted that the aryl moieties with electron-withdrawing groups can be used for this asymmetric 1,4-addition process, because their introduction is difficult in the amine-catalyzed reactions.[14]

The stereochemical outcome of the 1,4-addition reaction catalyzed by Rh/(*R*)-binap can be rationalized by the α*si* face attack of the enal to avoid a steric repulsion between the phenyl group on the phosphorous atom of (*R*)-binap and the carbonyl group of the enal (Fig. 1).[3b]

The role of chlorotrimethylsilane in the present asymmetric 1,4-addition remains to be clarified. It is likely that the chlorosilane activates the enone as a Lewis acid to facilitate the insertion step.

Table 1. Rhodium-catalyzed asymmetric 1,4-addition to enal **1a**[a]

Entry	[Ph–M] (equiv)	Conditions[b]	Yield (%) of **2a**[c]	ee (%) of **2a**[d]
1	$PhZnCl$[e]/$ClSiMe_3$ (1.1/1.3)	A	80[f]	99 (*S*)
2	$PhZnCl$[e] (1.1)	B	0[g]	
3	$PhB(OH)_2$ (5.0)	C	19[h]	90 (*S*)
4	$PhTi(O\textit{i}\text{-}Pr)_3$ (1.1)	D	0[i]	
5	$PhTi(O\textit{i}\text{-}Pr)_4Li/ClSiMe_3$ (1.1/1.3)	E	9[j]	82 (*S*)

[a] The reaction was carried out with 0.20 mmol of **1a** in the presence of 3 mol % of the rhodium catalyst.

[b] Condition A: $[RhCl((R)\text{-binap})]_2$, THF, 20 °C, 1 h; then hydrolysis with K_2CO_3 in $MeOH/H_2O$. Condition B: $[RhCl((R)\text{-binap})]_2$, THF, 20 °C, 1 h; then hydrolysis with H_2O. Condition C: $[RhCl(C_2H_4)]_2$/(*R*)-binap, KOH (10 mol %), $MeOH/THF/H_2O$ (12/3/2), 50 °C, 3 h. Condition D: $[Rh(OH)((R)\text{-binap})]_2$, THF, 20 °C, 1 h; then hydrolysis with H_2O. Condition E: $[RhCl((R)\text{-binap})]_2$, THF, 20 °C, 1 h; then hydrolysis with K_2CO_3 in $MeOH/H_2O$.

[c] Isolated yields by column chromatography on silica gel (hexane/Et_2O = 8/1–4/1).

[d] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AD-H: hexane/2-propanol = 90/10) after reduction into 3-(4-methoxyphenyl)-3-phenyl-1-propanol. The absolute configuration (*S*) was determined by comparison of its specific rotation with that of authentic sample (Ref. 7).

[e] Generated from PhLi and $ZnCl_2$.

[f] A 1,2-addition product **3a** was formed in 17% yield with 36% ee.

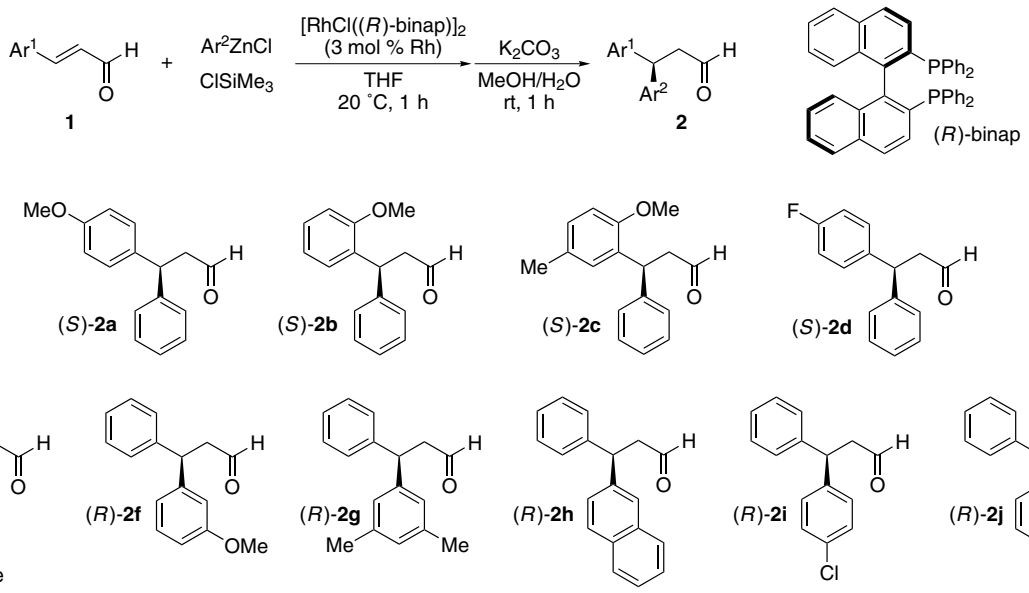
[g] Enal **1a** was recovered (63%).

[h] Enal **1a** was recovered (67%).

[i] A 1,2-addition product **3a** was formed in 70% yield with 0% ee, and enal **1a** was recovered (6%).

[j] A 1,2-addition product **3a** was formed in 28% yield with 0% ee, and enal **1a** was recovered (31%).

Table 2. Rhodium-catalyzed asymmetric 1,4-addition to enal **1**[a]



Entry	Ar^1 on substrate	Ar^2 on Zn	Yield (%) of **2**[b]	ee[c] (%) of **2**[d]
1[e]	4-$MeOC_6H_4$	C_6H_5	80 **2a**	99 (*S*)
2[e]	2-$MeOC_6H_4$	C_6H_5	74 **2b**	99 (*S*)
3[e]	2-MeO-5-MeC_6H_3	C_6H_5	66 **2c**	99 (*S*)
4[e]	4-FC_6H_4	C_6H_5	80 **2d**	98 (*S*)
5[f]	C_6H_5	4-$MeOC_6H_4$	55 **2e**	99 (*R*)
6[f]	C_6H_5	3-$MeOC_6H_4$	75 **2f**	99 (*R*)
7[f]	C_6H_5	3,5-$Me_2C_6H_3$	68 **2g**	99 (*R*)
8[f]	C_6H_5	2-Naphthyl	75 **2h**	99 (*R*)
9[f]	C_6H_5	4-ClC_6H_4	79 **2i**	99 (*R*)
10[f]	C_6H_5	3-ClC_6H_4	79 **2j**	98 (*R*)

[a] The reaction conditions: **1** (0.20 mmol), [RhCl((*R*)-binap)]$_2$ (3 mol % Rh), THF, 20 °C, 1 h; then hydrolysis with K_2CO_3 in MeOH/H_2O.
[b] Isolated yields by column chromatography on silica gel (hexane/Et_2O).
[c] Determined by HPLC analysis with a chiral stationary phase column Chiralpak AD-H (**2a**, **2b**, **2e**, **2f**, **2h**, **2i**), Chiralpak AS (**2c**, **2d**, **2g**), Chiralcel OD-H (**2j**) after reduction into the corresponding 3,3-diaryl-1-propanol.
[d] The absolute configuration was assigned by analogy with (*S*)-**2a**.
[e] Reaction with 0.22 mmol of ArZnCl and 0.26 mmol of $ClSiMe_3$.
[f] Reaction with 0.44 mmol of ArZnCl and 0.52 mmol of $ClSiMe_3$.

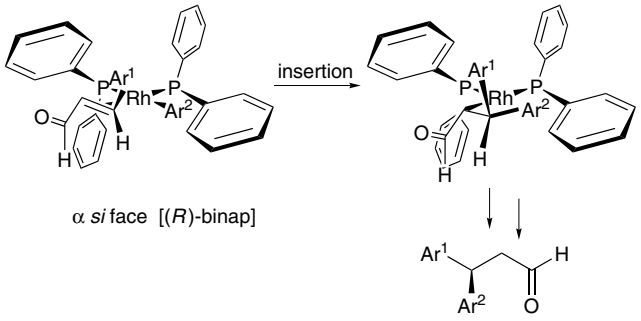


Figure 1. The stereochemical pathway in the rhodium-catalyzed asymmetric 1,4-addition.

3. Conclusions

We have demonstrated that the asymmetric 1,4-arylation of 3-arylpropenals can be efficiently catalyzed by a rhodium–binap complex by the combination of arylzinc reagents and chlorotrimethylsilane. The asymmetric addition proceeded with high enantioselectivity to give 1,3-diarylpropanals of 98–99% ee, some of which are key intermediates to pharmaceutically interesting compounds.[15]

4. Experimental

4.1. General

All anaerobic and moisture-sensitive manipulations were carried out with standard Schlenk techniques under predried nitrogen or glovebox techniques under prepurified argon. NMR spectra were recorded on a JEOL JNM LA-500 spectrometer (500 MHz for ^1H, and 125 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^1H NMR and chloroform-*d* (δ 77.05) for ^{13}C NMR. Optical rotations were measured on a JASCO DIP-370 polarimeter.

4.2. Materials

THF, Et_2O, dioxane, and benzene were distilled from benzophenone-ketyl under nitrogen prior to use. MeOH was distilled from Mg under nitrogen prior to use. DMF was distilled from CaH_2 under nitrogen prior to use. $[RhCl(C_2H_4)_2]_2$,[16] $[RhCl((S)\text{-binap})]_2$,[3b] ArZnCl,[9] PhTi(OPr-*i*)$_3$,[12] PhTi(OPr-*i*)$_4$Li,[13] were prepared according to the reported procedures.

4.3. Synthesis of (*E*)-3-(2-methoxy-5-methylphenyl)-propenal from 2-bromo-1-methoxy-4-methylbenzene

4.3.1. (*E*)-3-(2-Methoxy-5-methylphenyl)propenoic acid from 2-bromo-1-methoxy-4-methylbenzene. To Mg (0.38 g, 16 mg atom, dried by heat gun under vacuum) in THF (10 mL) was added dibromoethane (ca. 100 μL) as an activator. To the mixture was added dropwise at 0 °C, a solution of 2-bromo-1-methoxy-4-methylbenzene (2.0 mL, 14 mmol) in THF (10 mL). After 3.5 h stirring at room temperature, DMF (1.7 mL, 21 mmol) was added. This was stirred at room temperature for 14 h, before the mixture was quenched with 10% HCl aq and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give 2-methoxy-5-methylbenzaldehyde. The crude product was used for the next reaction without further purification (>95% pure, a quantitative yield).

A mixture of 2-methoxy-5-methylbenzaldehyde (ca. 14 mmol, a crude compound), malonic acid (2.89 g, 28 mmol), pyridine (5.4 mL, 67 mmol), and piperidine (0.21 mL, 2.0 mmol) was stirred at room temperature for 1 h and then at 160 °C for 3 h. After cooling to room temperature, 20% NaOH aq was added to the solution until pH 14. The mixture was washed with Et_2O, and the water layer was acidified with concd HCl until pH 1. The resulting water layer was extracted with Et_2O and the combined organic layers were dried over $MgSO_4$. Evaporation of the solvent gave 86% yield in two steps (2.37 mg, 12 mmol) of (*E*)-3-(2-methoxy-5-methylphenyl)propenoic acid as pale yellow solid. [CAS: 103986-76-1]: ^{1}H NMR ($CDCl_3$): δ 2.29 (s, 3H), 3.85 (s, 3H), 6.53 (d, $J = 16.0$ Hz, 1H), 6.81 (d, $J = 8.4$ Hz, 1H), 7.16 (d, $J = 8.4$ Hz, 1H), 7.32 (s, 1H), 8.07 (d, $J = 16.0$ Hz, 1H), 11.20 (br s, 1H).

4.3.2. (*E*)-3-(2-Methoxy-5-methylphenyl)propenal from (*E*)-3-(2-methoxy-5-methylphenyl)propenoic acid. A solution of (*E*)-3-(2-methoxy-5-methylphenyl)propenoic acid (1.20 g, 6.3 mmol) and $SOCl_2$ (0.64 mL, 8.7 mmol) in benzene (10 mL) was stirred at 120 °C for 10 h. Evaporation of the solvent gave the corresponding acyl chloride, which was used immediately for the next reduction step without further purification.

To a solution of the acyl chloride in THF (20 mL) was added dropwise a solution of LiAlH(OBu-*t*)$_3$ (1.59 g, 6.3 mmol) in THF (10 mL) at −78 °C. The mixture was stirred at the same temperature for 0.5 h and warmed to room temperature over a period of 1 h. After addition of crushed ice (ca. 30 g), the precipitates formed were filtered and washed with Et_2O. The filtrate was washed with 5% NaOH aq, and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by silica gel column chromatography (hexane/Et_2O = 2/1) gave 61% yield (0.67 g, 3.8 mmol) of (*E*)-3-(2-methoxy-5-methylphenyl)propenal as pale yellow oil.

^{1}H NMR ($CDCl_3$): δ 2.31 (s, 3H), 3.89 (s, 3H), 6.78 (dd, $J = 16.0$, 7.9 Hz, 1H), 6.85 (d, $J = 8.4$ Hz, 1H), 7.21 (d, $J = 8.4$ Hz, 1H), 7.35 (s, 1H), 7.81 (d, $J = 16.0$ Hz, 1H), 9.68 (d, $J = 7.9$ Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 20.42, 55.71, 111.32, 122.71, 128.97, 129.26, 130.14, 133.31, 148.37, 156.44, 194.61. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.90; H, 6.90.

4.4. Rhodium-catalyzed asymmetric 1,4-addition of PhZnCl to (4-methoxyphenyl)propenal 1a in the presence of chlorotrimethylsilane

To a solution of enal **1a** (32.4 mg, 0.20 mmol), $[RhCl((R)\text{-binap})]_2$ (4.6 mg, 0.0030 mmol, 3 mol % Rh), and $ClSiMe_3$ (33 μL, 0.26 mmol) in THF (0.50 mL) was added PhZnCl (0.44 mL, 0.22 mmol; 0.50 M in THF solution), and the mixture stirred at 20 °C for 1 h. Volatile materials were removed by evaporation, and ^{1}H NMR measurement of the residue indicated the formation of silyl enol ethers (*Z*)-**4a** and (*E*)-**4a** ((*Z*)-**4a**/(*E*)-**4a** = 7/1) as 1,4-addition products.

4.4.1. (*R*)-(*Z*)-3-(4-Methoxyphenyl)-3-phenyl-1-trimethylsilyloxy-1-propene (*Z*)-4a. ^{1}H NMR ($CDCl_3$): δ 0.15 (s, 9H), 3.77 (s, 3H), 5.01 (dd, $J = 9.6$, 5.8 Hz, 1H), 5.22 (d, $J = 9.6$ Hz, 1H), 6.30 (d, $J = 5.8$ Hz, 1H), 6.81 (d, $J = 8.7$ Hz, 2H), 7.12 (d, $J = 8.7$ Hz, 2H), 7.13–7.28 (m, 5H).

4.4.2. (*R*)-(*E*)-3-(4-Methoxyphenyl)-3-phenyl-1-trimethylsilyloxy-1-propene (*E*)-4a. ^{1}H NMR ($CDCl_3$): δ 0.17 (s, 9H), 3.77 (s, 3H), 4.56 (d, $J = 8.6$ Hz, 1H), 5.48 (dd, $J = 12.0$, 8.6 Hz, 1H), 6.19 (d, $J = 12.0$ Hz, 1H), 6.81 (d, $J = 8.7$ Hz, 2H), 7.12 (d, $J = 8.7$ Hz, 2H), 7.13–7.28 (m, 5H).

4.4.3. Hydrolysis of the silyl enol ethers 4. To the residue obtained above, which contained the silyl enol ethers **4** were added K_2CO_3 (276 mg, 2.0 mmol), MeOH (1.0 mL), and H_2O (0.70 mL). After 1 h stirring at 20 °C, the mixture was extracted with Et_2O three times, and the combined organic layers dried over $MgSO_4$. Evaporation of the solvent followed by silica gel column chromatography (hexane/Et_2O = 8/1–4/1) gave 80% yield (38.4 mg, 0.160 mmol) of **2a** as a 1,4-addition product and 17% yield (8.2 mg, 0.034 mmol) of **3a** as a 1,2-addition product. The enantiomeric excess of **2a** was 99% ee, which was determined by HPLC analysis with a chiral stationary column (Chiralpak AD-H, hexane/2-propanol = 90/10) after reduction into (*S*)-3-(4-methoxyphenyl)-3-phenyl-1-propanol (with $NaBH_4$ in CH_2Cl_2 and EtOH).

4.4.4. (*S*)-3-(4-Methoxyphenyl)-3-phenylpropanal 2a. [CAS:92804-32-5]: 80% Yield (colorless oil; column eluent: hexane/Et_2O = 8/1–4/1). $[\alpha]_D^{20} = +4.4$ (*c* 0.77,

$CHCl_3$) for (*S*) isomer of 99% ee {lit.[7] $[\alpha]_D^{20} = -3.1$ (*c* 0.88, $CHCl_3$) for (*R*) isomer of 90% ee}. ^1H NMR ($CDCl_3$): δ 3.11 (dd, $J = 7.7$, 1.9 Hz, 2H), 3.75 (s, 3H), 4.56 (t, $J = 7.7$ Hz, 1H), 6.82 (d, $J = 8.6$ Hz, 2H), 7.13 (d, $J = 8.6$ Hz, 2H), 7.16–7.22 (m, 3H), 7.28 (t, $J = 7.7$ Hz, 2H), 9.71 (t, $J = 1.9$ Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 44.23, 49.58, 55.23, 114.12, 126.61, 127.63, 128.70, 135.31, 143.62, 158.31, 201.19. The ee of 3-(4-methoxyphenyl)-3-phenyl-1-propanol was 99% ee (Chiralpak AD-H, hexane/2-propanol = 90/10, flow = 1.0 mL/min, wavelength = 224 nm. Retention times: 12.7 min [(*R*)-enantiomer], 14.3 min [(*S*)-enantiomer]).

4.4.5. (*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-ol 3a. [CAS:3906-07-8]: 17% Yield (colorless oil; column eluent: hexane/Et_2O = 8/1–4/1), 36% ee. The ee was determined on a Chiralcel OD-H, hexane/2-propanol = 80/20, flow = 0.5 mL/min, wavelength = 224 nm. Retention times: 18.8 min [minor enantiomer], 20.8 min [major enantiomer]. $[\alpha]_D^{20} = -7.7$ (*c* 0.25, $CHCl_3$) for 36% ee. ^1H NMR ($CDCl_3$): δ 2.18 (s, 1H), 3.78 (s, 3H), 5.33 (d, $J = 6.7$ Hz, 1H), 6.23 (dd, $J = 15.7$, 6.7 Hz, 1H), 6.60 (d, $J = 15.7$ Hz, 1H), 6.83 (d, $J = 8.8$ Hz, 2H), 7.28 (t, $J = 7.3$ Hz, 1H), 7.31 (d, $J = 8.8$ Hz, 2H), 7.35 (t, $J = 7.3$ Hz, 2H), 7.41 (d, $J = 7.3$ Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 55.29, 75.28, 114.01, 126.32, 127.69, 127.83, 128.58, 129.31, 129.45, 130.25, 143.04, 159.39.

4.5. General procedure for Table 2

The reaction conditions and results are summarized in Table 2. To a solution of enal **1** (0.20 mmol), $[RhCl((R)\text{-binap})]_2$ (4.6 mg, 0.0030 mmol, 3 mol % Rh), and $ClSiMe_3$ (33 μL, 0.26 mmol) in THF (0.50 mL) was added ArZnCl (0.22 mmol; THF solution), and the mixture was stirred at 20 °C for 1 h. To the reaction solution were added K_2CO_3 (276 mg, 2.0 mmol), MeOH (1.0 mL), and H_2O (0.70 mL). After 1 h stirring at 20 °C, the mixture was extracted with Et_2O three times. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/Et_2O) to give the 1,4-addition product. Enantiomeric excess of the product was determined by HPLC analysis with a chiral stationary column after reduction into the corresponding alcohol (with $NaBH_4$ in CH_2Cl_2 and EtOH).

4.5.1. (*S*)-3-(2-Methoxyphenyl)-3-phenylpropanal 2b. [CAS:92804-31-4]: 74% Yield (colorless oil; column eluent: hexane/Et_2O = 8/1–4/1). $[\alpha]_D^{20} = -54.3$ (*c* 1.4, $CHCl_3$) for (*S*) isomer of 99% ee. ^1H NMR ($CDCl_3$): δ 3.09 (dd, $J = 7.9$, 2.3 Hz, 2H), 3.79 (s, 3H), 5.02 (t, $J = 7.9$ Hz, 1H), 6.85 (d, $J = 8.2$ Hz, 1H), 6.88 (td, $J = 7.5$, 1.0 Hz, 1H), 7.07 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.15–7.21 (m, 2H), 7.23–7.29 (m, 4H), 9.69 (t, $J = 2.3$ Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 38.28, 48.45, 55.36, 110.79, 120.69, 126.41, 127.81, 128.04, 128.10, 128.45, 131.61, 142.85, 156.63, 201.78. The ee of 3-(2-methoxyphenyl)-3-phenyl-1-propanol was 99% ee (Chiralpak AD-H, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 224 nm. Retention times: 23.0 min [(*S*)-enantiomer], 26.5 min [(*R*)-enantiomer]).

4.5.2. (*S*)-3-(2-Methoxy-5-methylphenyl)-3-phenylpropanal 2c. [CAS:857288-55-2]: 66% Yield (colorless oil; column eluent: hexane/Et_2O = 16/1–8/1). $[\alpha]_D^{20} = -16.2$ (*c* 1.4, $CHCl_3$) for (*S*)-isomer of 99% ee. ^1H NMR ($CDCl_3$): δ 2.22 (s, 3H), 3.08 (dd, $J = 7.9$, 2.3 Hz, 2H), 3.76 (s, 3H), 4.99 (t, $J = 7.9$ Hz, 1H), 6.74 (d, $J = 8.3$ Hz, 1H), 6.86 (d, $J = 1.9$ Hz, 1H), 6.97 (dd, $J = 8.3$, 1.9 Hz, 1H), 7.18 (tt, $J = 8.5$, 1.8 Hz, 1H), 7.22–7.30 (m, 4H), 9.69 (t, $J = 2.3$ Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 20.68, 38.33, 48.50, 55.56, 110.87, 126.39, 128.02, 128.10, 128.47, 128.87, 129.88, 131.37, 142.99, 156.62, 201.95. The ee of 3-(2-methoxy-5-methylphenyl)-3-phenyl-1-propanol was 99% ee (Chiralpak AS, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 224 nm. Retention times: 14.1 min [(*S*)-enantiomer], 18.2 min [(*R*)-enantiomer]).

4.5.3. (*S*)-3-(4-Fluorophenyl)-3-phenylpropanal 2d. [CAS:86397-22-3]: 80% Yield (colorless oil; column eluent: hexane/Et_2O = 16/1–8/1). $[\alpha]_D^{20} = +3.3$ (*c* 1.8, $CHCl_3$) for (*S*) isomer of 98% ee. ^1H NMR ($CDCl_3$): δ 3.13 (ddd, $J = 17.1$, 7.9, 1.8 Hz, 1H), 3.17 (ddd, $J = 17.1$, 7.7, 1.8 Hz, 1H), 4.61 (t, $J = 7.7$ Hz, 1H), 6.97 (t, $J = 8.6$ Hz, 2H), 7.16–7.23 (m, 5H), 7.30 (t, $J = 7.8$ Hz, 2H), 9.73 (t, $J = 1.8$ Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 44.16, 49.53, 115.52 (d, $J = 21$ Hz), 126.82, 127.60, 128.80, 129.19 (d, $J = 7.8$ Hz), 139.01, 143.03, 161.56 (d, $J = 245$ Hz), 200.58. The ee of 3-(4-fluorophenyl)-3-phenyl-1-propanol was 98% ee (Chiralpak AS, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 224 nm. Retention times: 16.9 min [(*S*)-enantiomer], 19.1 min [(*R*)-enantiomer]).

4.5.4. (*R*)-3-(4-Methoxyphenyl)-3-phenylpropanal 2e. [CAS:92804-32-5]: the enantiomer of **2a**. 55% yield (colorless oil). $[\alpha]_D^{20} = -4.2$ (*c* 0.80, $CHCl_3$) for (*R*)-isomer of 99% ee. The ee of 3-(4-methoxyphenyl)-3-phenyl-1-propanol was 99% ee.

4.5.5. (*R*)-3-(3-Methoxyphenyl)-3-phenylpropanal 2f. Yield 75% (colorless oil; column eluent: hexane/Et_2O = 8/1–4/1). $[\alpha]_D^{20} = -0.5$ (*c* 1.9, $CHCl_3$) for (*R*) isomer of 99% ee. ^1H NMR ($CDCl_3$): δ 3.13 (ddd, $J = 17.3$, 7.8, 1.9 Hz, 1H), 3.15 (ddd, $J = 17.3$, 7.7, 1.9 Hz, 1H), 3.75 (s, 3H), 4.58 (t, $J = 7.8$ Hz, 1H), 6.73 (dd, $J = 8.2$, 2.5 Hz, 1H), 6.77 (t, $J = 1.8$ Hz, 1H), 6.82 (dt, $J = 7.7$, 1.0 Hz, 1H), 7.16–7.24 (m, 4H), 7.28 (t, $J = 7.2$ Hz, 2H), 9.72 (t, $J = 1.9$ Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 44.99, 49.32, 55.15, 111.60, 114.03, 120.06, 126.73, 127.69, 128.73, 129.72, 143.07, 144.84, 159.83, 200.96. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.69; H, 6.85. The ee of 3-(2-methoxyphenyl)-3-phenyl-1-propanol was 99% ee (Chiralpak AD-H, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 224 nm. Retention times: 35.7 min [(*R*)-enantiomer], 38.9 min [(*S*)-enantiomer]).

4.5.6. (*R*)-3-(3,5-Dimethylphenyl)-3-phenylpropanal 2g. Yield 68% (colorless oil; column eluent: hexane/Et_2O = 16/1–8/1). $[\alpha]_D^{20} = -6.2$ (*c* 1.6, $CHCl_3$) for (*R*)

isomer of 99% ee. ^{1}H NMR ($CDCl_3$): δ 2.26 (s, 6H), 3.10 (ddd, $J = 18.4$, 8.3, 1.8 Hz, 1H), 3.12 (ddd, $J = 18.4$, 7.7, 1.8 Hz, 1H), 4.52 (t, $J = 7.8$ Hz, 1H), 6.83 (s, 3H), 7.18 (t, $J = 7.3$ Hz, 1H), 7.22 (d, $J = 7.3$ Hz, 2H), 7.28 (t, $J = 7.3$ Hz, 2H), 9.70 (t, $J = 1.8$ Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 21.37, 44.99, 49.39, 125.55, 126.60, 127.70, 128.42, 128.70, 138.21, 143.07, 143.46, 201.29. Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.94; H, 7.90. The ee of 3-(2,6-dimethylphenyl)-3-phenyl-1-propanol was 99% ee (Chiralpak AS, hexane/2-propanol = 90/10, flow = 0.3 mL/min, wavelength = 224 nm. Retention times: 19.5 min [(*R*)-enantiomer], 21.2 min [(*S*)-enantiomer]).

4.5.7. (*R*)-3-(2-Naphthyl)-3-phenylpropanal 2h. Yield 75% (white solid; column eluent: hexane/Et_2O = 8/1–4/1). $[\alpha]_D^{20} = -36.9$ (*c* 2.0, $CHCl_3$) for (*R*) isomer of 99% ee. ^{1}H NMR ($CDCl_3$): δ 3.24 (ddd, $J = 17.0$, 7.8, 1.8 Hz, 1H), 3.27 (ddd, $J = 17.0$, 7.8, 1.8 Hz, 1H), 4.78 (t, $J = 7.8$ Hz, 1H), 7.18 (tt, $J = 6.8$, 1.6 Hz, 1H), 7.23–7.34 (m, 5H), 7.44 (quintd, $J = 6.8$, 1.0 Hz, 2H), 7.68 (s, 1H), 7.73–7.81 (m, 3H), 9.77 (t, $J = 1.8$ Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 45.05, 49.25, 125.80, 125.82, 126.25, 126.44, 126.78, 127.61, 127.79, 127.87, 128.54, 128.77, 132.31, 133.46, 140.61, 143.09, 200.93. Anal. Calcd for $C_{19}H_{16}O$: C, 87.66; H, 6.19. Found: C, 87.93; H, 6.46. The ee of 3-(2-naphthyl)-3-phenyl-1-propanol was 99% ee (Chiralpak AD-H, hexane/2-propanol = 90/10, flow = 0.3 mL/min, wavelength = 224 nm. Retention times: 39.8 min [(*R*)-enantiomer], 43.1 min [(*S*)-enantiomer]).

4.5.8. (*R*)-3-(4-Chlorophenyl)-3-phenylpropanal 2i. [CAS:13243-64-6]: 79% Yield (white solid; column eluent: hexane/Et_2O = 16/1–8/1). $[\alpha]_D^{20} = -5.7$ (*c* 2.0, $CHCl_3$) for (*R*) isomer of 99% ee. ^{1}H NMR ($CDCl_3$): δ 3.13 (ddd, $J = 17.2$, 8.1, 1.7 Hz, 1H), 3.15 (ddd, $J = 17.2$, 7.6, 1.7 Hz, 1H), 4.59 (t, $J = 7.7$ Hz, 1H), 7.15 (d, $J = 8.5$ Hz, 2H), 7.17–7.23 (m, 3H), 7.25 (d, $J = 8.5$ Hz, 2H), 7.29 (t, $J = 7.2$ Hz, 2H), 9.72 (t, $J = 1.7$ Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 44.26, 49.34, 126.92, 127.65, 128.86, 129.11, 132.51, 141.82, 142.75, 200.41. The ee of 3-(4-chlorophenyl)-3-phenyl-1-propanol was 99% ee (Chiralpak AD-H, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 224 nm. Retention times: 18.1 min [(*R*)-enantiomer], 19.2 min [(*S*)-enantiomer]).

4.5.9. (*R*)-3-(3-Chlorophenyl)-3-phenylpropanal 2j. Yield 79% (yellow oil; column eluent: hexane/Et_2O = 16/1–8/1). $[\alpha]_D^{20} = -4.9$ (*c* 1.6, $CHCl_3$) for (*R*) isomer of 98% ee. ^{1}H NMR ($CDCl_3$): δ 3.14 (ddd, $J = 17.4$, 7.7, 1.6 Hz, 1H), 3.16 (ddd, $J = 17.4$, 7.6, 1.6 Hz, 1H), 4.59 (t, $J = 7.7$ Hz, 1H), 7.11 (d, $J = 7.5$ Hz, 1H), 7.15–7.27 (m, 6H), 7.30 (t, $J = 7.8$ Hz, 2H), 9.72 (t, $J = 1.6$ Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$): δ 44.56, 49.21, 125.97, 126.94, 127.00, 127.70, 127.91, 128.89, 129.99, 134.56, 142.46, 145.39, 200.41. Anal. Calcd for $C_{15}H_{13}ClO$: C, 73.62; H, 5.35. Found: C, 73.87; H, 5.62. The ee of 3-(3-chlorophenyl)-3-phenyl-1-propanol was 98% ee (Chiralcel OD-H, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 224 nm. Retention times: 23.1 min [(*R*)-enantiomer], 27.5 min [(*S*)-enantiomer]).

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