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CATALYTIC ASYMMETRIC INTERMOLECULAR C–H INSERTION OF 1,4-CYCLOHEXADIENE WITH α-ALKYL-α-DIAZOESTERS USING CHIRAL DIRHODIUM(II) CARBOXYLATES†

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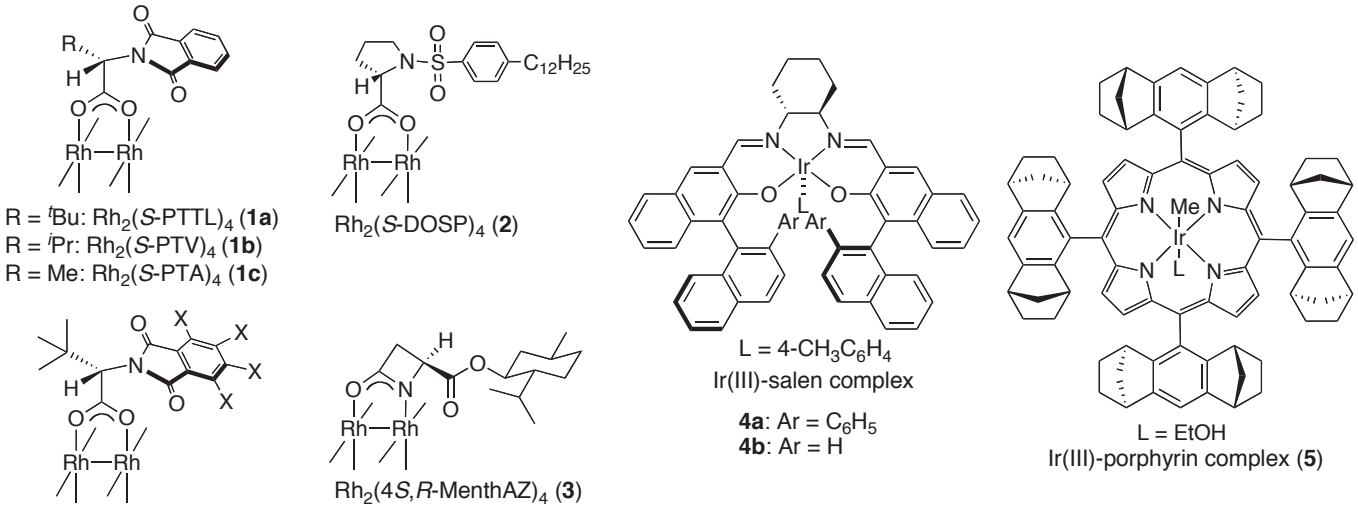
Abstract – The first example of dirhodium(II) complex-catalyzed asymmetric intermolecular C–H insertion with α-alkyl-α-diazoesters is described. The reaction of 1,4-cyclohexadiene with 2,4-dimethyl-3-pentyl α-alkyl-α-diazoacetates under catalysis by dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, or dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-TFPTTL)$_4$, gave the corresponding C–H insertion products with enantioselectivities of up to 86% ee, albeit in low to modest yields.

Catalytic functionalization of unactivated C–H bonds represents one of the most powerful strategies for C–C bond formation, and the development of asymmetric variants would be one of the ultimate goals in organic synthesis.[1] In this context, C–H insertion of diazo compounds catalyzed by chiral dirhodium(II) complexes has been recognized as an efficient means for enantioselective functionalization of C(sp^3)–H bonds.[2] In 1997, Davies and Hansen made a major breakthrough in this field when they achieved intermolecular C–H insertion reactions with high yield and excellent enantiocontrol.[3a] Donor/acceptor rhodium carbenes derived from the combination of aryldiazoacetates or arylvinyldiazoacetates with Rh_2(*S*-DOSP)$_4$ (**2**) as a chiral catalyst are capable of effective asymmetric C–H insertions with a diverse array of substrates, including alkanes (up to 96% ee),[3a,c] tetrahydrofuran (up to 60% de and 98% ee),[3a,c]

† Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

N-Boc-protected amines (up to 94% de and 97% ee),[3b] allylic alkenes (up to 88% de and 95% ee),[3c,e] silyl ethers (up to >90% de and 95% ee),[3d] silyl enol ethers (up to >90% de and 97% ee),[3f] ethylbenzenes (up to 68% de and 94% ee),[3g] and *N*,*N*-dimethylanilines (up to 95% ee).[3h] The power of this strategy[3–10] has been verified by the synthesis of a variety of natural products and pharmaceutical agents.[4a–c,11–13] However, catalytic asymmetric intermolecular C–H insertion with α-alkyl-α-diazoesters[14,15] remains a significant challenge because of the propensity to form α,β-unsaturated esters via a 1,2-hydride shift in metal-carbene intermediates.[16] A notable exception is the recent work of Katsuki and Suematsu in which highly diastereo- and enantioselective C–H insertions with *tert*-butyl α-diazopropionate were achieved by using Ir(III)-salen complexes **4**.[7]



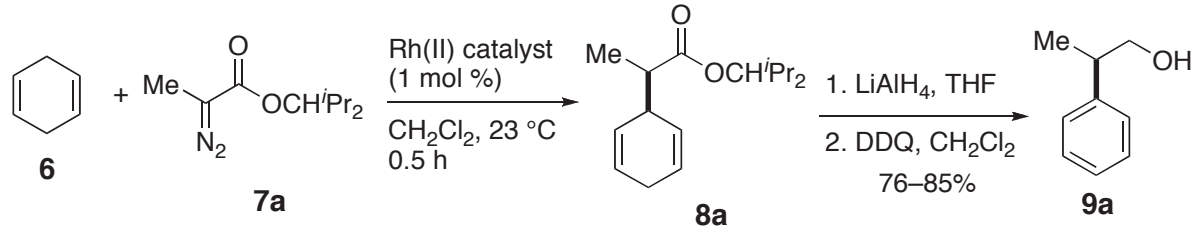
The intermolecular C–H insertion reaction of 1,4-cyclohexadiene with diazocarbonyl compounds under the influence of chiral catalysts represents the bench mark reaction in this area.[4–8,13,17] In 1999, Davies and co-workers were the first to demonstrate asymmetric induction (up to 95% ee) in the reaction with aryldiazoacetates using Rh_2(*S*-DOSP)$_4$ (**2**).[4,5] Thereafter, Doyle and co-workers reported the reaction with vinyldiazolactone, in which Rh_2(4*S*,*R*-MenthAZ)$_4$ (**3**) provided the corresponding C–H insertion product in up to 80% ee.[6] As touched on above, Katsuki and Suematsu recently disclosed that Ir(III)-salen catalyst **4a** is highly exceptional for reactions with aryldiazoacetates (up to 99% ee) or *tert*-butyl α-diazopropionate (up to >99% ee).[7] More recently, Che and co-workers explored the reaction with aryldiazoacetates in the presence of iridium(III)-porphyrin catalyst **5**, in which high levels of asymmetric induction (up to 98% ee) were achieved.[8]

In recent years, we have achieved high levels of enantiocontrol in a range of catalytic metal carbene transformations of α-alkyl-α-diazoesters, including intramolecular C–H insertion,[18] cyclopropenation,[19] cyclopropanation,[20] and C–H functionalization of indole,[21] by using dirhodium(II) carboxylate catalysts,

which incorporate *N*-phthaloyl- or *N*-tetrahalophthaloyl-(*S*)-amino acids as bridging ligands. In a continuation of our work, we addressed the issue of enantiocontrol in intermolecular C–H insertion reactions of 1,4-cyclohexadiene with α-alkyl-α-diazoesters.

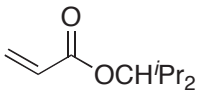
At the outset, we explored the reaction of 2,4-dimethyl-3-pentyl α-diazopropionate (**7a**) with 4 equiv of 1,4-cyclohexadiene (**6**) in dichloromethane at room temperature using 1 mol % of Rh_2(*S*-PTTL)$_4$ (**1a**),[15d,18,22] the most generally efficient catalyst of our dirhodium(II) carboxylate catalysts (Table 1, entry 1). The reaction proceeded to completion within 0.5 h and gave the C–H insertion product **8a** in 61% yield with no signs of the formation of α,β-unsaturated ester **10a**. In order to determine the sense and extent of asymmetric induction, **8a** {$[\alpha]_D^{23}$ +25.5 (*c* 1.36, $CHCl_3$)} was converted by reduction with $LiAlH_4$ and subsequent oxidation with DDQ into the known 2-phenyl-1-propanol (**9a**).[23] The enantiomeric excess of **9a** was determined to be 62% by HPLC using a Daicel Chiralcel OB-H column. The absolute stereochemistry of **9a** was established as *R* by comparison of the sign of optical rotation {$[\alpha]_D^{23}$ +9.1 (*c* 0.77, $CHCl_3$) for 62% ee; lit.,[23] $[\alpha]_D^{23}$ +14.3 (*c* 1.65, $CHCl_3$) for 95% ee of

Table 1. Enantioselective C–H Insertion of 1,4-Cyclohexadiene (**6**) with 2,4-Dimethyl-3-pentyl α-Diazopropionate (**7a**) Catalyzed by Chiral Dirhodium(II) Carboxylates[a]



6 **7a** **8a** **9a**

		C–H Insertion product **8a**	
Entry	Rh(II) catalyst	Yield (%)[b]	Ee (%)[c]
1	Rh_2(*S*-PTTL)$_4$ (**1a**)	61	62
2[d]	Rh_2(*S*-PTTL)$_4$ (**1a**)	63	61
3	Rh_2(*S*-PTV)$_4$ (**1b**)	66	25
4	Rh_2(*S*-PTA)$_4$ (**1c**)	72	3
5	Rh_2(*S*-TFPTTL)$_4$ (**1d**)	72	71
6	Rh_2(*S*-TCPTTL)$_4$ (**1e**)	73	61



10a
not detected

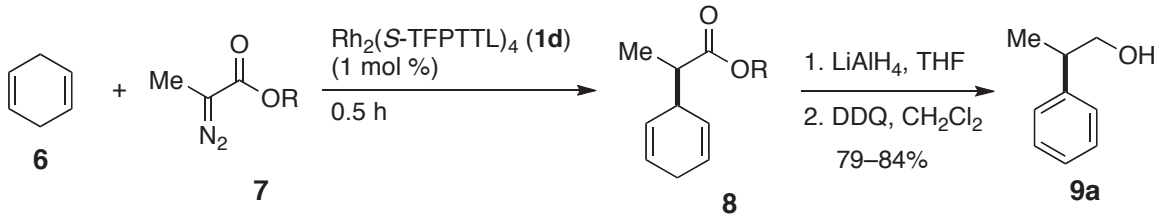
[a] All reactions were carried out as follows: Rh(II) catalyst (1 mol %) was added in one portion to a solution of **6** (2 mmol) and **7a** (0.5 mmol) in CH_2Cl_2 (1.5 mL). [b] Isolated yield. [c] Determined by HPLC after transformation of **8a** to (*R*)-2-phenyl-1-propanol (**9a**). [d] 10 equiv of **6** was used.

(*R*)-enantiomer}. The reaction with 10 equiv of **6** showed little variation in either yield or enantioselectivity (entry 2). Although Rh_2(*S*-PTV)$_4$ (**1b**) and Rh_2(*S*-PTA)$_4$ (**1c**) provided **8a** in good yields with the same sense of asymmetric induction as that observed with **1a**, poor enantioselectivities were

obtained (25% and 3% ee, entries 3 and 4). We then evaluated the performance of Rh_2(*S*-TFPTTL)$_4$ (**1d**)[24]and Rh_2(*S*-TCPTTL)$_4$ (**1e**),[25,26] fluorinated and chlorinated analogues of Rh_2(*S*-PTTL)$_4$ (**1a**). Catalysis with Rh_2(*S*-TFPTTL)$_4$ was found to provide **8a** in 72% yield with 71% ee (entry 5), while Rh_2(*S*-TCPTTL)$_4$ displayed modest enantioselectivity (61% ee, entry 6).

Using Rh_2(*S*-TFPTTL)$_4$ (**1d**) as a catalyst, the effects of solvents on the enantioselectivity were examined (Table 2, entries 1–4). The use of α,α,α-trifluorotoluene, hexanes, and 2,2-dimethylbutane in place of CH_2Cl_2 produced good levels of asymmetric induction, in which 2,2-dimethylbutane exhibited the highest enantioselectivity (80% ee, entry 4). The effect of the ester moiety was also evaluated. Reactions with *tert*-butyl ester **7b** and ethyl ester **7c** resulted in only modest enantioselectivity (45% ee, entries 5 and 6). These results clearly show that the use of 2,4-dimethyl-3-pentyl ester moiety[19,21,27] is crucial for a good degree of enantioselection. An examination of the temperature profile demonstrated that lowering the reaction temperature to 0 or –20 °C had only a marginal effect on the enantioselectivity (82% and 80% ee), though a sharp drop in product yield was observed (50% and 48%, entries 7 and 8).

Table 2. Enantioselective C–H Insertion of 1,4-Cyclohexadiene (**6**) with α-Diazopropionates **7** Catalyzed by Rh_2(*S*-TFPTTL)$_4$ (**1d**)[a]



6 + **7** → **8** → **9a**

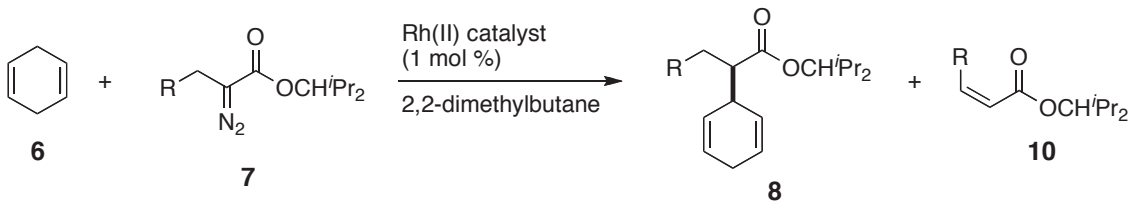
					C–H Insertion product **8**		
Entry		R	Solvent	Temp, °C		Yield (%)[b]	Ee (%)[c]
1	**7a**	*i*Pr$_2$CH	CH_2Cl_2	23	**8a**	72	71
2	**7a**	*i*Pr$_2$CH	$CF_3C_6H_5$	23	**8a**	63	77
3	**7a**	*i*Pr$_2$CH	hexanes	23	**8a**	60	79
4	**7a**	*i*Pr$_2$CH	2,2-dimethylbutane	23	**8a**	66	80
5	**7b**	*t*Bu	2,2-dimethylbutane	23	**8b**	55	45
6	**7c**	Et	2,2-dimethylbutane	23	**8c**	73	45
7	**7a**	*i*Pr$_2$CH	2,2-dimethylbutane	0	**8a**	50	82
8	**7a**	*i*Pr$_2$CH	2,2-dimethylbutane	–20	**8a**	48	80

[a] All reactions were performed on 0.5 mmol scale with 4 equiv of **6**. [b] Isolated yield. [c] Determined by HPLC after transformation of **8** to (*R*)-2-phenyl-1-propanol (**9a**).

We next turned our attention to C–H insertion with 2,4-dimethyl-3-pentyl α-diazobutanoate (**7d**) bearing more reactive β-C–H bonds than the methyl C–H bonds of α-diazopropionates (Table 3). The reaction

with **7d** using 1 mol % of Rh_2(*S*-TFPTTL)$_4$ (**1d**) or Rh_2(*S*-PTTL)$_4$ (**1a**) resulted in complete conversion within 0.5 h at room temperature, but formation of the desired C–H insertion product **8d** was not observed by ^{1}H-NMR analysis of the crude reaction mixture (entries 1 and 2). Instead (*Z*)-alkene **10d** via a 1,2-hydride shift was isolated in 76% and 71% yields, respectively. It has been shown that low reaction temperatures are the key to suppression of the 1,2-hydride shift.[15b–g,18] Thus, we conducted the reaction at –60 °C. Although Rh_2(*S*-TFPTTL)$_4$ produced almost none of **8d** (entry 3), catalysis with Rh_2(*S*-PTTL)$_4$ furnished **8d** with 83% ee, albeit in 12% yield (entry 4).[28] These results are consistent with Taber's speculation that a rhodium carbene intermediate bearing more electron-withdrawing ligands is more strongly positive at the carbene carbon and favors the less entropically demanding 1,2-hydride shift via an early transition state.[15a,g,16b,d,19] Under the same conditions, the reaction with α-diazopentanoate **7e** gave the C–H insertion product **8e** in 20% yield with 86% ee, along with 22% of (*Z*)-alkene **10e** (entry 5).[29]

Table 3. Enantioselective C–H Insertion of 1,4-Cyclohexadiene (**6**) with α-Alkyl-α-diazoesters **7** Catalyzed by Chiral Dirhodium(II) Carboxylates[a]



Entry		R	Rh(II) catalyst	Temp (°C)	Time (h)	C–H Insertion product **8**			Alkene **10**	
							Yield (%)[b]	Ee (%)		Yield (%)[b]
1	**7d**	Me	Rh_2(*S*-TFPTTL)$_4$ (**1d**)	23	0.5	**8d**	–	–	**10d**	76
2	**7d**	Me	Rh_2(*S*-PTTL)$_4$ (**1a**)	23	0.5	**8d**	–	–	**10d**	71
3	**7d**	Me	Rh_2(*S*-TFPTTL)$_4$ (**1d**)	–60	6	**8d**	–	–	**10d**	38
4	**7d**	Me	Rh_2(*S*-PTTL)$_4$ (**1a**)	–60	8	**8d**	12	83[c]	**10d**	26
5	**7e**	Et	Rh_2(*S*-PTTL)$_4$ (**1a**)	–60	12	**8e**	20	86[d]	**10e**	22

[a] All reactions were performed on 1 mmol scale with 4 equiv of **6**. [b] Isolated yield. [c] Determined by HPLC after transformation of **8d** to (*R*)-2-Phenyl-1-butanol. [d] Determined by HPLC after transformation of **8e** to (*R*)-2-Phenyl-1-pentanol.

In summary, we have reported that chiral dirhodium(II) carboxylate catalysts, Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-TFPTTL)$_4$, display a reasonable level of catalytic performance in intermolecular C–H insertion reactions of 1,4-cyclohexadiene (**6**) with 2,4-dimethyl-3-pentyl α-alkyl-α-diazoacetates **7**. This represents the first example of intermolecular C–H insertion with α-alkyl-α-diazocarbonyl compounds bearing longer-chain alkyl groups than a methyl substituent, though there is considerable room for improvement in terms of chemo- and enantioselectivity as well as product yield. Efforts toward such improvement are currently underway.

EXPERIMENTAL

General. IR spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on a JEOL JNM-AL 400 (400 MHz) spectrometer. Chemical shifts are reported relative to an internal standard (tetramethylsilane at δ_H 0.00 or $CDCl_3$ at δ_H 7.26). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant and integration. ^{13}C NMR spectra were recorded on a JEOL JNM-AL 400 (100 MHz) spectrometer. Chemical shifts are reported relative to an internal standard ($CDCl_3$ at δ 77.00). Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). ESI-MS spectra were obtained on a JEOL JMS-T100LP or Thermo Scientific Exactive. Column chromatography was carried out on Kanto silica gel 60 N (63–210 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet, anisaldehyde stain solution or phosphomolybdic acid stain solution. Analytical high-performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with a JASCO UV-1575 intelligent UV/VIS detector. Detection was performed at 254 nm. Chiralpak AD-H, Chiralpak IA, or Chiralcel OB-H columns (0.46 cm × 25 cm) from Daicel were used. Retention times (t_R) and peak ratios were determined with a JASCO-Borwin analysis system. All non-aqueous reactions were carried out in flame-dried glassware under an Ar atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated CH_2Cl_2 was purchased from Kanto Chemical Co., Inc. 2,2-Dimethylbutane and α,α,α-trifluorotoluene were distilled from calcium hydride prior to use. 1,4-Cyclohexadiene (**6**) and hexanes were purchased from Aldrich, Inc. Chiral dirhodium(II) carboxylates **1a**–**e**[22c,24a,25a] and α-alkyl-α-diazoesters **7**[19] were prepared according to the literature procedures.

General procedure for enantioselective intermolecular C–H insertion (Table 1, entry 1): (*R*)-2,4-Dimethyl-3-pentyl 2-(2,5-cyclohexadienyl)propionate (8a). Rh_2(*S*-PTTL)$_4$·2AcOEt (**1a**) (7.1 mg, 0.005 mmol) was added in one portion to a solution of **6** (160.3 mg, 2.0 mmol) and **7a**[19] (99.1 mg, 0.50 mmol) in CH_2Cl_2 (1.5 mL) at room temperature. After stirring for 0.5 h at this temperature, the mixture was concentrated in vacuo. The ratio of **8a**/**10a** was determined to be >99:1 by ^1H NMR analysis of the crude reaction mixture. The crude product was purified by column chromatography (silica gel, 25:1 hexane/EtOAc) to provide **8a** (76.5 mg, 61%) as a colorless oil; TLC R_f = 0.39 (10:1 hexane/EtOAc); $[\alpha]_D^{23}$ +25.5 (*c* 1.36, $CHCl_3$) for 62% ee; IR (neat) ν 2934, 2877, 1730, 1464, 1387, 1176 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86–0.90 (m, 12H, CH(C*H*$_3$)$_2$), 1.09 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.87–1.94 (m, 2H, C*H*(CH$_3$)$_2$), 2.52–2.57 (m, 1H, C*H*CO), 2.64 (m, 2H, C*H*$_2$CH=CH), 3.28 (m, 1H, C*H*CH=CH), 4.63 (t, *J* = 6.0 Hz, 1H, OC*H*), 5.56–5.64 (m, 2H, CH$_2$C*H*=CH), 5.80–5.85 (m, 2H, CH$_2$CH=C*H*); ^{13}C NMR (100

MHz, $CDCl_3$) δ 12.0 (CH_3), 17.3 (CH_3), 17.4 (CH_3), 19.4 (CH_3), 19.5 (CH_3), 26.4 (CH_2), 29.3 (CH), 29.4 (CH), 37.4 (CH), 52.5 (CH), 83.8 (CH), 127.7 (CH), 129.3 (CH), 133.9 (CH), 133.9 (CH), 175.9 (C=O); HRMS (EI) calcd for $C_{16}H_{27}O_2$ $(M + H)^+$ 251.2006, found 251.2005. The absolute configuration of **8a** was determined to be *R* by chemical correlation (*vide infra*).

General procedure for reduction with $LiAlH_4$ and oxidation with DDQ (Table 1, entry 1): (*R*)-2-Phenyl-1-propanol (9a). A solution of **8a** (62.6 mg, 0.25 mmol) in THF (0.5 mL) was added dropwise to a stirred suspension of $LiAlH_4$ (19.0 mg, 0.50 mmol) in THF (0.5 mL) at 0 °C. After stirring for 1 h, 1 M hydrochloric acid (1 mL) was added at 0 °C and the whole mixture was extracted with EtOAc (15 mL). The organic layer was washed with water (2 mL) and brine (2 mL) and then dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished crude 2-(2,5-cyclohexadienyl)-1-propanol (35.1 mg) as a colorless oil, which was used without purification. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (113.5 mg, 0.50 mmol) was added to a stirred solution of 2-(2,5-cyclohexadienyl)-1-propanol in CH_2Cl_2 (2 mL) at room temperature. After stirring for 1 h at this temperature, the reaction mixture was quenched with saturated aqueous Na_2CO_3 (2 mL). The mixture was extracted with EtOAc (15 mL). The organic layer was washed with water (2 mL) and brine (2 mL) and then dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (35 mg), which was purified by column chromatography on silica gel (7:3 hexane/Et_2O) to afford **9a** (28.3 mg, 83%) as a colorless oil; TLC R_f = 0.35 (3:1 hexane/EtOAc); $[\alpha]_D^{23}$ +9.1 (*c* 0.77, $CHCl_3$) [lit.,[23] $[\alpha]_D^{23}$ +14.3 (*c* 1.65, $CHCl_3$) for 95% ee of (*R*)-enantiomer]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (d, *J* = 7.2 Hz, 3H, CHC*H*$_3$), 2.94–3.00 (m, 1H, C*H*CH_3), 3.71 (d, *J* = 6.8 Hz, 2H, C*H*$_2$OH), 7.22–7.26 (m, 3H, *Ar*), 7.32–7.36 (m, 2H, *Ar*). The enantiomeric excess of **9a** was determined to be 62% by HPLC with a Chiralpak OB-H column (100:1 hexane/*i*PrOH, 1.0 mL/min): t_R (minor) = 16.5 min; t_R (major) = 17.7 min.

(*R*)-*tert*-Butyl 2-(2,5-cyclohexadienyl)propionate (8b).[7] According to the general procedure for intermolecular C–H insertion, **8b** was prepared from **6** (160.3 mg, 2.0 mmol) and **7b** (78.1 mg, 0.50 mmol) using Rh_2(*S*-TFPTTL)$_4$·2AcOEt (**1d**) (8.6 mg, 0.005 mmol). The crude product was purified by column chromatography (silica gel, 25:1 hexane/EtOAc) to provide **8b** (57.3 mg, 55%) as a colorless oil; TLC R_f = 0.39 (10:1 hexane/EtOAc); $[\alpha]_D^{25}$ +13.0 (*c* 1.41, $CHCl_3$) for 45% ee [lit.,[7] $[\alpha]_D^{21}$ +29.1 (*c* 1.1, $CHCl_3$) for >99% ee of (*R*)-enantiomer]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$), 1.45 (s, 9H, C(C*H*$_3$)$_3$), 2.33–2.44 (m, 1H, C*H*CO), 2.62 (m, 2H, C*H*$_2$CH=CH), 3.19 (m, 1H, C*H*CH=CH), 5.49–5.59 (m, 2H, CH_2C*H*=CH), 5.73–5.84 (m, 2H, CH_2CH=C*H*). The enantiomeric excess of **8b** was determined to be 45% after conversion to **9a**.

(*R*)-Ethyl 2-(2,5-cyclohexadienyl)propionate (8c).[7] According to the general procedure for intermolecular C–H insertion, **8c** was prepared from **6** (160.3 mg, 2.0 mmol) and **7c** (64.1 mg, 0.50 mmol) using Rh_2(*S*-TFPTTL)$_4$·2AcOEt (**1d**) (8.6 mg, 0.005 mmol). The crude product was purified by column chromatography (silica gel, 25:1 hexane/EtOAc) to provide **8c** (65.9 mg, 73%) as a colorless oil; TLC R_f = 0.36 (10:1 hexane/EtOAc); $[\alpha]_D^{25}$ +15.8 (*c* 1.28, $CHCl_3$) for 45% ee [lit.,[7] $[\alpha]_D^{23}$ +27.4 (*c* 1.1, $CHCl_3$) for 83% ee of (*R*)-enantiomer]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, *J* = 6.8 Hz, 3H, CHC*H*$_3$), 1.26 (t, *J* = 6.9 Hz, 3H, OCH$_2$C*H*$_3$), 2.50 (m, 1H, C*H*CO), 2.66 (m, 2H, C*H*$_2$CH=CH), 3.16–3.27 (m, 1H, C*H*CH=CH), 4.04–4.22 (m, 2H, OC*H*$_2$CH$_3$), 5.51–5.64 (m, 2H, CH$_2$C*H*=CH), 5.77–5.88 (m, 2H, CH$_2$CH=C*H*). The enantiomeric excess of **8c** was determined to be 45% after conversion to **9a**.

(*R*)-2,4-Dimethyl-3-pentyl 2-(2,5-cyclohexadienyl)butanoate (8d). According to the general procedure for intermolecular C–H insertion, **8d** was prepared from **6** (320.1 mg, 4.0 mmol) and **7d**[19] (212.3 mg, 1.0 mmol) using Rh_2(*S*-PTTL)$_4$·2AcOEt (**1a**) (14.2 mg, 0.01 mmol). The crude product was purified by column chromatography (silica gel, 9:1 hexane/benzene) to give **8d** (31.7 mg, 12%) as a colorless oil and **10d**[19] (47.9 mg, 26%) as a colorless oil; Data for **8d**: TLC R_f = 0.38 (15:1 hexane/EtOAc); $[\alpha]_D^{25}$ +23.3 (*c* 0.67, $CHCl_3$) for 83% ee; IR (neat) ν 2965, 2876, 1730, 1464, 1388, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.7 Hz, 6H, CH(C*H*$_3$)$_2$), 0.89 (d, *J* = 6.7 Hz, 6H, CH(C*H*$_3$)$_2$), 0.91 (t, *J* = 7.4 Hz, 3H, CH$_2$C*H*$_3$), 1.48 (m, 1H, CHC*H*$_2$), 1.66 (m, 1H, CHC*H*$_2$), 1.85-1.95 (m, 2H, C*H*(CH$_3$)$_2$), 2.35 (dt, *J* = 3.8, 10.5 Hz, 1H, C*H*CO), 2.64 (m, 2H, C*H*$_2$CH=CH), 3.28 (m, 1H, C*H*CH=CH), 4.64 (t, *J* = 6.1 Hz, 1H, OC*H*), 5.59–5.67 (m, 2H, CH$_2$C*H*=CH), 5.76–5.82 (m, 2H, CH$_2$CH=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.6 (CH_3), 17.2 (CH_3), 17.5 (CH_3), 19.6 (CH_3), 19.7 (CH_3), 20.7 (CH_2), 26.3 (CH_2), 29.4 (CH), 29.4 (CH), 37.4 (CH), 52.5 (CH), 82.4 (CH), 125.7 (CH), 125.9 (CH), 125.9 (CH), 127.5 (CH), 174.4 (C=O); HRMS (ESI) calcd for $C_{17}H_{28}O_2Na$ $(M+Na)^+$ 287.1987, found 287.1987. Data for **10d**: TLC R_f = 0.41 (15:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, *J* = 6.8 Hz, 6H, CH(C*H*$_3$)$_2$), 0.89 (d, *J* = 7.2 Hz, 6H, CH(C*H*$_3$)$_2$), 1.88–1.96 (m, 2H, C*H*(CH$_3$)$_2$), 2.14 (dd, *J* = 1.8, 7.2 Hz, 3H, C*H*$_3$CH=CH), 4.65 (t, *J* = 6.3 Hz, 1H, OC*H*), 5.83 (dq, *J* = 1.8, 11.3 Hz, 1H, CH$_3$CH=C*H*), 6.32 (dq, *J* = 7.2, 11.8 Hz, 1H, CH$_3$C*H*=CH). The absolute configuration of **8d** was determined to be *R* by chemical correlation (*vide infra*).

(*R*)-2-Phenyl-1-butanol.[28] According to the general procedure for preparation of **9a**, 2-phenyl-1-butanol was prepared from **8d** (26.4 mg, 0.10 mmol). The crude product was purified by column chromatography on silica gel (7:3 hexane/Et_2O) to afford 2-phenyl-1-butanol (11.9 mg, 79%) as a colorless oil; TLC R_f = 0.35 (3:1 hexane/EtOAc); $[\alpha]_D^{23}$ –15.3 (*c* 0.35, $CHCl_3$) [lit.,[28] $[\alpha]_D^{25}$ –21.1 (*c* 1.00, $CHCl_3$) for (*R*)-enantiomer]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (t, *J* = 7.5 Hz, 3H, CH$_2$C*H*$_3$), 1.52 (m, 1H, CHC*H*$_2$),

1.68 (m, 1H, CHCH_2), 2.62 (m, 1H, CHCH_2), 3.64–3.71 (m, 2H, CH_2OH), 7.10–7.20 (m, 3H, *Ar*), 7.22–7.39 (m, 2H, *Ar*). The enantiomeric excess of 2-phenyl-1-butanol was determined to be 83% by HPLC with a Chiralpak AD-H column (300:1 hexane/*i*PrOH, 1.0 mL/min): t_R (minor) = 54.6 min; t_R (major) = 59.0 min.

(*R*)-2,4-Dimethyl-3-pentyl 2-(2,5-cyclohexadienyl)pentanoate (8e). According to the general procedure for intermolecular C–H insertion, **8e** was prepared from **6** (320.6 mg, 4.0 mmol) and **7e**[19] (226.3 mg, 1.0 mmol) using Rh_2(*S*-PTTL)$_4$·2AcOEt (**1a**) (14.2 mg, 0.01 mmol). The crude product was purified by column chromatography (silica gel, 9:1 hexane/benzene) to provide **8e** (55.7 mg, 20%) as a colorless oil and **10e**[19] (43.6 mg, 22%) as a colorless oil; Data for **8e**: TLC R_f = 0.39 (15:1 hexane/EtOAc); $[\alpha]_D^{23}$ +24.7 (*c* 1.10, $CHCl_3$) for 86% ee; IR (neat) ν 2962, 2874, 1730, 1465, 1388, 1176 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.7 Hz, 6H, CH(CH_3)$_2$), 0.88 (d, *J* = 6.7 Hz, 6H, CH(CH_3)$_2$), 0.90 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.19–1.41 (m, 3H, CH_2), 1.60–1.69 (m, 1H, CHCH_2), 1.85–1.95 (m, 2H, CH(CH_3)$_2$), 2.42–2.45 (m, 1H, CHCO), 2.63–2.65 (m, 2H, CH_2CH=CH), 3.16–3.20 (m, 1H, CHCH=CH), 4.63 (t, *J* = 6.1 Hz, 1H, OCH), 5.58–5.67 (m, 2H, CH_2CH=CH), 5.78–5.82 (m, 2H, CH_2CH=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 17.2 (CH_3), 17.5 (CH_3), 19.6 (CH_3), 19.7 (CH_3), 21.2 (CH_2), 26.3 (CH_2), 29.4 (CH_2), 29.4 (CH), 29.6 (CH_2), 37.5 (CH), 50.4 (CH), 82.4 (CH), 125.7 (CH), 126.0 (CH), 126.0 (CH), 127.5 (CH), 174.6 (C=O); HRMS (ESI) calcd for $C_{18}H_{30}O_2Na$ $(M+Na)^+$ 301.2138, found 301.2136. Data for **10e**: TLC R_f = 0.42 (15:1 hexane/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (d, *J* = 6.8 Hz, 6H, CH(CH_3)$_2$), 0.89 (d, *J* = 6.8 Hz, 6H, CH(CH_3)$_2$), 1.07 (t, *J* = 7.7 Hz, 3H, CH_2CH_3), 1.87–1.96 (m, 2H, CH(CH_3)$_2$), 2.66 (dd, *J* = 7.7, 7.7 Hz, 2H, CH_2CH_3), 4.65 (t, *J* = 6.3 Hz, 1H, OCH), 5.78 (dt, *J* = 1.8, 11.3 Hz, 1H, CH_2CH=CH), 6.21 (dt, *J* = 7.2, 11.3 Hz, 1H, CH_2CH=CH). The absolute configuration of **8e** was determined to be *R* by chemical correlation (*vide infra*).

(*R*)-2-Phenyl-1-pentanol.[29] According to the general procedure for preparation of **9a**, 2-phenyl-1-pentanol was prepared from **8e** (50.1 mg, 0.18 mmol). The crude product was purified by column chromatography on silica gel (7:3 hexane/Et_2O) to give 2-phenyl-1-pentanol (23.7 mg, 80%) as a colorless oil; TLC R_f = 0.35 (3:1 hexane/EtOAc); $[\alpha]_D^{23}$ –9.9 (*c* 0.71, MeOH) for 86% ee [lit.,[29] $[\alpha]_D^{23}$ –12 (*c* 3.76, MeOH) for (*R*)-enantiomer]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.2 Hz, 3H, CH_2CH_3), 1.15–1.26 (m, 2H, CH_2CH_3), 1.53–1.67 (m, 2H, CHCH_2), 2.73 (m, 1H, CHCH_2), 3.65–3.76 (m, 2H, CH_2OH), 7.19–7.33 (m, 5H, *Ar*). The enantiomeric excess of 2-phenyl-1-pentanol was determined to be 86% by HPLC with a Chiralpak IA column (300:1 hexane/*i*PrOH, 1.0 mL/min): t_R (minor) = 23.4 min; t_R (major) = 26.6 min.

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