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DIASTEREO- AND ENANTIOSELECTIVE CONSTRUCTION OF 6,7-DIOXABICYCLO[2.2.1]HEPTANE DERIVATIVES BY A DIRHODIUM(II)-CATALYZED INTRAMOLECULAR C–H INSERTION REACTION†

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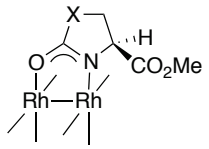
Abstract – The first diastereo- and enantioselective construction of bridged bicyclic ring systems by an intramolecular C–H insertion reaction is described. With dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, the C–H insertion of α-alkyl-α-diazoesters containing an ethylene ketal moiety at the γ-position provided methyl 6,7-dioxabicyclo[2.2.1]heptane-3-carboxylate derivatives with up to 95% ee and perfect diastereoselectivity.

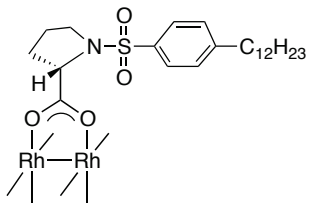
The development of catalytic asymmetric C–C bond forming reactions has been a subject of intensive investigation in the field of synthetic organic chemistry.[1] Among a wide variety of transition metal complexes used to catalyze a diverse array of transformations of α-diazocarbonyl compounds, dirhodium(II) complexes have distinguished themselves as superior catalysts in C–H insertion reactions that form C–C bonds in which a new stereogenic center is created at an unactivated carbon atom.[2,3] Over the past quarter-century, substantial progress has been made in the development of chiral dirhodium(II) carboxylate and carboxamidate complexes as catalysts for enantioselective intramolecular and intermolecular C–H insertion reactions via a dirhodium(II) carbene intermediate.[4] It is well known that the enantioselectivity of C–H insertion reactions depends on many factors including the type and structure of diazo compounds, substitution pattern at the C–H insertion site, polarity of the solvent, and nature of chiral dirhodium(II) catalysts, and thus each reaction system requires a different catalyst design. For example, the salient ability of Doyle's dirhodium(II) carboxamidate catalysts such as Rh_2(5*S*-MEPY)$_4$ (**1a**), Rh_2(4*S*-MEOX)$_4$ (**1b**), and Rh_2(4*S*-MPPIM)$_4$ (**1c**) is characteristic of enantioselective intramolecular

†Dedicated to Professor Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

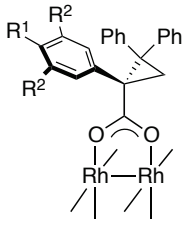
C–H insertion reactions of diazoacetates and diazoacetamides,[5] while Davies's dirhodium(II) carboxylate catalysts such as Rh_2(*S*-DOSP)$_4$ (**2**), Rh_2(*R*-BPCP)$_4$ (**3a**), and Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$ (**3b**) are highly exceptional for achieving site-selective, diastereoselective and enantioselective intermolecular C–H insertion reactions of aryl- or vinyldiazoacetates with relatively activated C–H bonds, such as those at benzylic and allylic positions and α to oxygen, as well as unactivated C–H bonds.[6,7] Our dirhodium(II) carboxylate catalysts that incorporate *N*-phthaloyl-(*S*)-amino acids as bridging ligands, such as Rh_2(*S*-PTTL)$_4$ (**4a**), Rh_2(*S*-PTPA)$_4$ (**4b**), Rh_2(*S*-PTA)$_4$ (**4c**), and Rh_2(*S*-PTV)$_4$ (**4d**), are especially well suited for intramolecular C–H insertion reactions of α-diazo-β-ketoesters,[8] α-methoxycarbonyl-α-diazoacetamides,[9] aryldiazoacetates,[10] and diaryldiazomethanes.[11] Of these catalysts, dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$ (**4a**), with a bulky *tert*-butyl group has proven to be the most generally effective catalyst for a range of diazo substrates.[12–14]



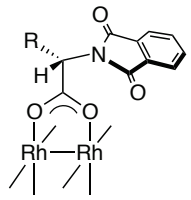
X = CH_2: Rh_2(5*S*-MEPY)$_4$ (**1a**)
X = O: Rh_2(4*S*-MEOX)$_4$ (**1b**)
X = $PhCH_2CH_2CON$: Rh_2(4*S*-MPPIM)$_4$ (**1c**)



Rh_2(*S*-DOSP)$_4$ (**2**)

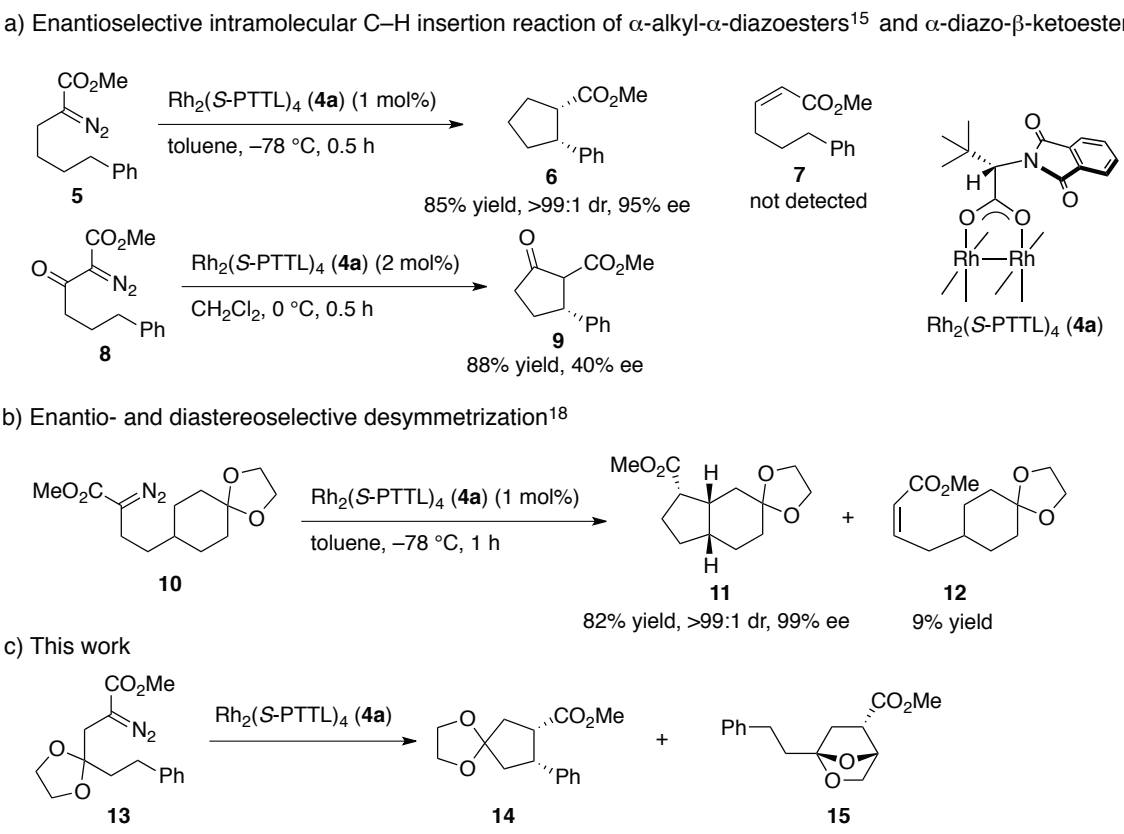


R^1 = Ph, R^2 = H: Rh_2(*R*-BPCP)$_4$ (**3a**)
R^1 = H, R^2 = 4-^{t}BuC$_6$H$_4$:
Rh_2[*R*-3,5-di(*p*-^{t}BuC$_6$H$_4$)TPCP]$_4$ (**3b**)



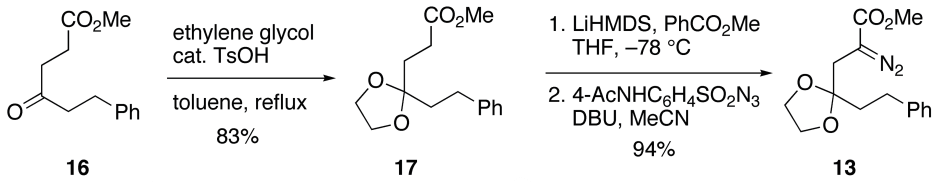
R = ^{t}Bu: Rh_2(*S*-PTTL)$_4$ (**4a**)
R = Bn: Rh_2(*S*-PTPA)$_4$ (**4b**)
R = Me: Rh_2(*S*-PTA)$_4$ (**4c**)
R = ^{i}Pr: Rh_2(*S*-PTV)$_4$ (**4d**)

Recently, we have demonstrated the first asymmetric intramolecular C–H insertion reaction of α-alkyl-α-diazoesters[15] using Rh_2(*S*-PTTL)$_4$ (**4a**) at –78 °C, in which even higher enantioselectivity (up to 95% ee) than that observed with the corresponding α-diazo-β-ketoesters[8a] as well as perfect *cis* diastereoselectivity was achieved with no evidence of the formation of α,β-unsaturated esters via a 1,2-hydride shift of dirhodium(II) carbene intermediates (Scheme 1a).[4p,16,17] This protocol has enabled the first diastereo- and enantioselective construction of fused bicyclic ring systems with three contiguous stereogenic centers via desymmetrization of σ-symmetric α-alkyl-α-diazoesters (Scheme 1b).[18] In continuation of our studies on dirhodium(II)-catalyzed asymmetric reactions with α-alkyl-α-diazoesters,[19–21] we investigated the intramolecular C–H insertion of α-alkyl-α-diazoester (**13**) containing a ketal moiety at the γ-position for the synthesis of a functionalized cyclopentane derivative (**14**), in which a transannular C–H insertion product (**15**) was obtained as the major product instead of **14** as discussed herein (Scheme 1c).



Scheme 1

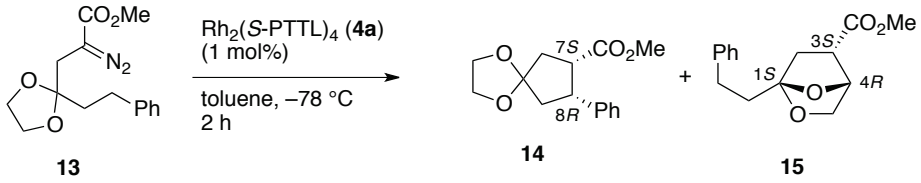
The requisite α-alkyl-α-diazoester (**13**) was prepared from the known γ-ketoester (**16**)[22] as shown in Scheme 2. Ketal formation of **16** with ethylene glycol gave ester (**17**) in 83% yield. After considerable experimentation, diazo transfer was accomplished by a modified Taber procedure.[23] Thus, addition of ester (**17**) to a mixture of LiHMDS and methyl benzoate in THF at –78 °C afforded an α-benzoylated ester, which, upon diazo transfer with *p*-acetamidobenzenesulfonyl azide and DBU, gave α-diazoester (**13**) in 94% yield over two steps.



Scheme 2

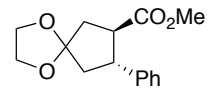
On the basis of our original work,[15] we initially explored the intramolecular C–H insertion of **13** in toluene at −78 °C using 1 mol% of Rh_2(*S*-PTTL)$_4$ (**4a**) (Table 1, entry 1). The reaction proceeded smoothly to completion within 2 h to give the expected *cis*-2-phenylcyclopentane-1-carboxylate derivative (**14**) via a benzylic C–H insertion with an exceptionally high enantioselectivity (97% ee), but the product yield was only 19%. No signs of trans isomer (**18**) or α,β-unsaturated ester (**19**) was detected

Table 1. Enantioselective Intramolecular C–H Insertion Reaction of α-Alkyl-α-diazoester **13** Catalyzed by Dirhodium(II) Carboxylates[a]



13 **14** **15**

entry	solvent	temp, °C	time h	**14** : **15**[b]	**14** % yield[c]	**14** % ee[d]	**15** % yield[c]	**15** % ee[d]
1	toluene	–78	2	22 : 78	19	97	76	95
2	toluene	–40	0.25	25 : 75	15	94	65	86
3	toluene	0	0.1	23 : 77	20	88	73	73
4	CH_2Cl_2	–78	2	8 : 92	6	80	81	81
5	Et_2O	–78	2	17 : 83	15	89	78	83



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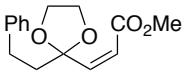


19

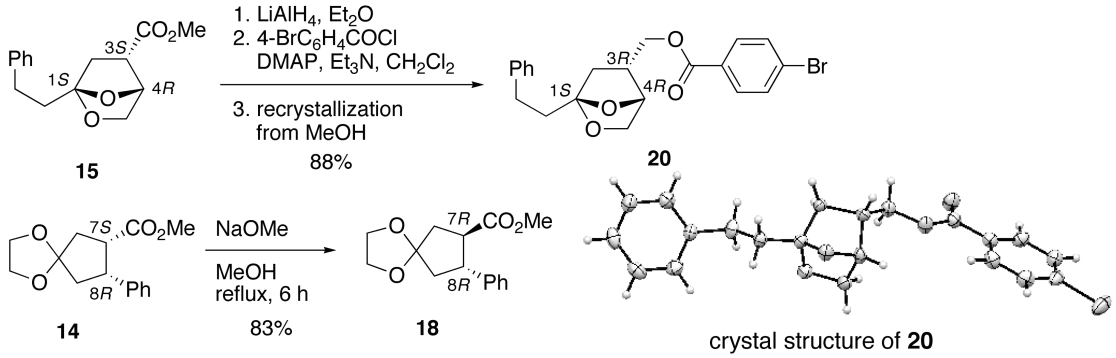
not detected

[a]Typical procedure for C–H insertion reaction (entry 1): Rh_2(*S*-PTTL)$_4$·2EtOAc (4.2 mg, 0.003 mmol) was added to a solution of **13** (87 mg, 0.3 mmol) in toluene (1.5 mL) at –78 °C. After 2 h, the mixture was concentrated and the residue was purified by column chromatography. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Isolated yield. [d]Determined by HPLC analysis.

in the crude reaction mixture by NMR spectroscopy. The major product was identified as 6,7-dioxabicyclo[2.2.1]heptane derivative (**15**) bearing three stereogenic centers, which was isolated as a single diastereomer in 76% yield and with a similarly high enantioselectivity (95% ee) as above. The unexpected and unprecedented result, which was probably because the insertion reaction into a C–H bond of the ethylene ketal moiety is activated by an adjacent ether oxygen[6c,24] with little deactivating effect of a β-alkoxy group,[25] was extremely interesting since this is the first example of a highly enantioselective construction of bridged bicyclic ring systems via intramolecular C–H insertion of σ-symmetric α-diazocarbonyl compounds.[26,27] Motivated by this encouraging result, we next examined the reaction conditions to further enhance site-selectivity. An examination of the temperature profile demonstrated that –78 °C was the temperature limit. Not unexpectedly, increasing the reaction temperature to −40 °C or 0 °C was accompanied by a significant decrease in enantioselectivity but, somewhat surprisingly, had little impact on site-selectivity (Entries 1–3). It is also noteworthy that not a trace of (*Z*)-alkene (**19**) was detected even at 0 °C, probably due to the inductively electron-withdrawing γ-alkoxy groups in the ketal moiety that make the β-C–H bond less electron-rich.[17f,28] A survey of solvents at –78 °C revealed that toluene was the optimal solvent for this transformation in terms of enantioselectivity (Entries 1 vs 4 and 5). Although dichloromethane greatly favored the formation of dioxabicyclo[2.2.1]heptane derivative (**15**),

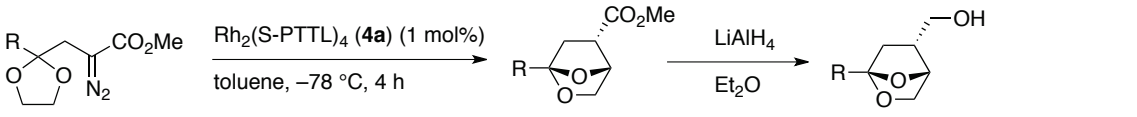
a sharp drop in enantioselectivity was observed. Ether had little impact on the site-selectivity but markedly reduced enantioselectivity.

The preferred absolute configuration of **15** was determined to be (1*S*,3*S*,4*R*) by single-crystal X-ray analysis of the corresponding *p*-bromobenzoate (**20**) (Scheme 3).[29] The absolute stereochemistry of **14** was established as 7*S*,8*R* by its conversion to the known *trans*-2-phenylcyclopentane-1-carboxylate (**18**), $[\alpha]_D^{23}$ –52.7 (*c* 1.33, $CHCl_3$) [lit.,[30] $[\alpha]_D^{23}$ +38.2 (*c* 2.2, $CHCl_3$) for the (7*S*,8*S*)-enantiomer], by epimerization using sodium methoxide in MeOH.



Scheme 3

Since both site-control and enantiocontrol in Rh_2(*S*-PTTL)$_4$-catalyzed reaction of α-diazoester (**13**) proved to be a formidable challenge,[31,32] we next investigated the reaction of α-alkyl-α-diazoesters (**21a,b**) that have no competitive insertion site on the side-chain at the 2-position of the 1,3-dioxolane ring (Scheme 4). The Rh_2(*S*-PTTL)$_4$-catalyzed reaction of **21a,b** in toluene at –78 °C was found to produce the desired transannular C–H insertion product (**22a,b**) as a single diastereomer along with an unidentified, inseparable impurity. No signs of α,β-unsaturated ester or cyclopentane derivative via electronically disfavored methyl C–H insertion was detected. Thus, dioxabicyclo[2.2.1]heptane derivatives (**22a,b**) were isolated as the corresponding alcohols (**23a,b**) after reduction with $LiAlH_4$. The enantiomeric excesses were determined by HPLC analysis of the corresponding benzoates, and the absolute configurations of these cyclization products were tentatively assigned by analogy. While a noticeable drop in enantioselectivity was observed with methyl-substituted α-diazoester (**21a**), high enantioselectivity (90% ee) was achieved with ethyl-substituted α-diazoester (**21b**).



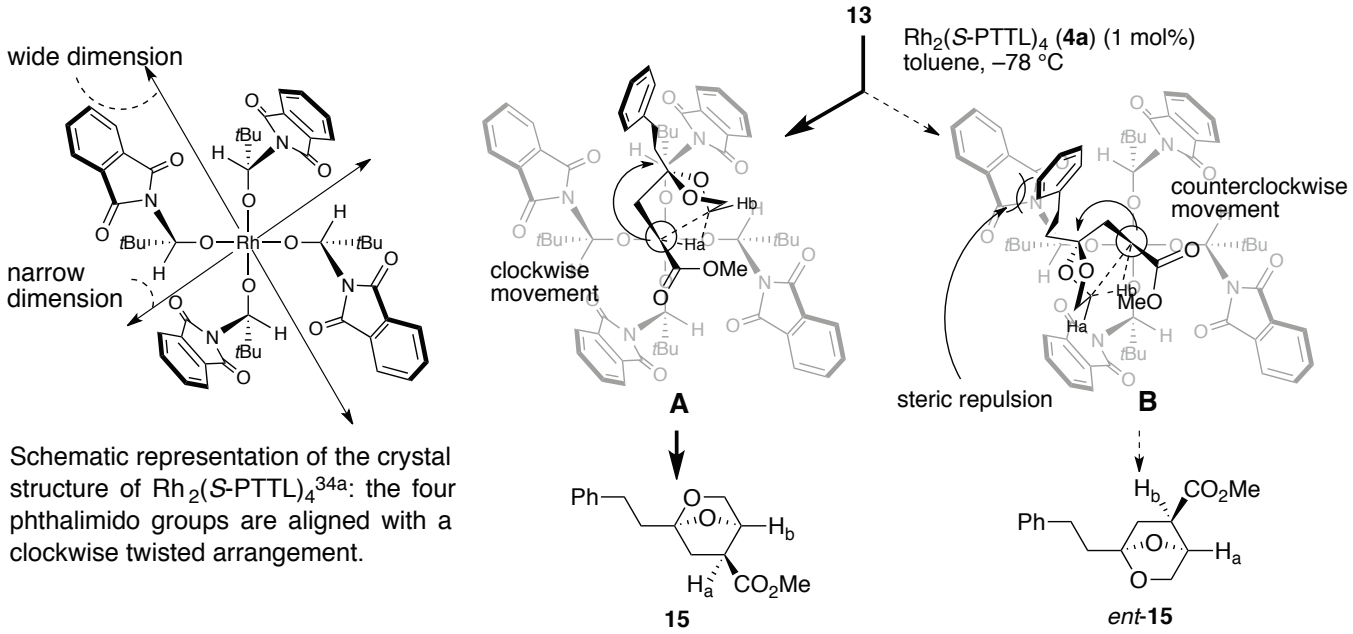
21a: R = Me
21b: R = Et

22a: R = Me
22b: R = Et

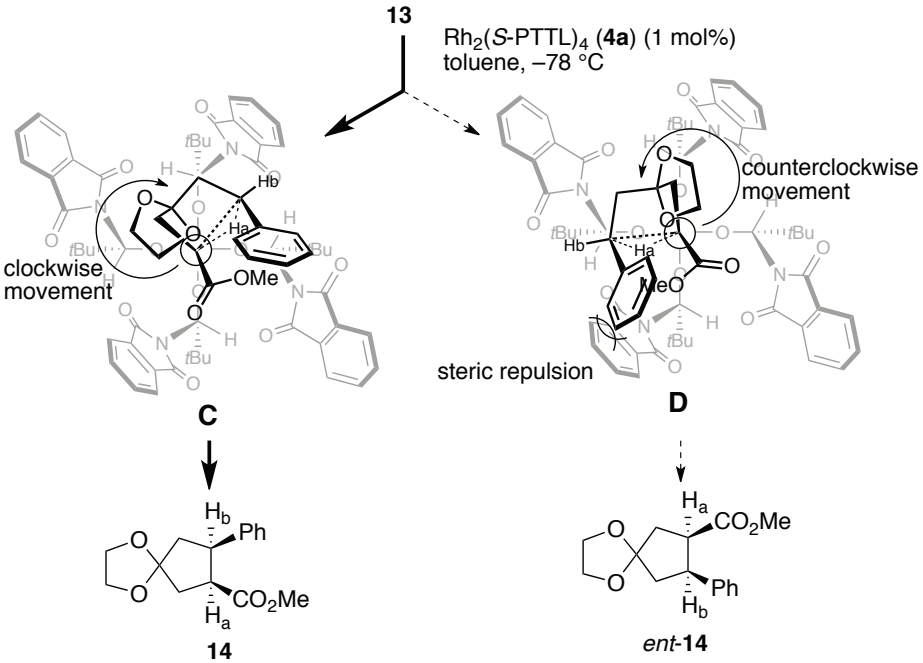
23a (R = Me): 66% yield (for 2 steps), 83% ee
23b (R = Et): 57% yield (for 2 steps), 90% ee

Scheme 4

Although the site-selectivity remains to be elucidated,[31] the stereochemical outcome of the C-H insertion of α-diazoester (**13**) can be explained on the basis of the crystal structure of Rh_2(*S*-PTTL)$_4$, which was determined by Fox et al.,[34a] coupled with Doyle–Taber's mechanistic hypothesis (Scheme 5).[35] Rh_2(*S*-PTTL)$_4$ was shown to adopt a C_2-symmetric "chiral crown" conformation,[4p,34,36] in which the four phthalimido groups are protruded with a clockwise twisted arrangement[37] on one face of the paddlewheel complex, and the four sterically demanding *tert*-butyl groups are oriented to block the reactivity on the opposite face. Provided that the chiral crown structure with wide and narrow dimensions of the C_2-symmetric cavity is available in solution,[34,37,38] there are two competing transition states, (**A**) and (**B**), in which the ester group is accommodated in the wide dimension of the chiral cavity in either case, and the carbon chain undergoing C–H insertion approaches the rhodium-bound carbene through a clockwise or counterclockwise movement, respectively. Transition state (**A)** is favored over transition state (**B**) because of the steric repulsion between the 2-phenylethyl moiety and the phthalimido group in **B**, directing the cyclization toward C–H_a bond in accord with the observed sense of asymmetric induction. A similar argument can be applied to the case of the formation of **14** (Scheme 6). There are two competing transition states, (**C**) and (**D**), in which the ester group and the ketal moiety are accommodated in the wide dimension of the chiral cavity in either case. Clearly, transition state (**C**) is preferred over transition state (**D**) due to the steric repulsion between the phenyl group and the phthalimido group in **D**, thereby leading to the formation of **14** as observed.



Scheme 5



Scheme 6

In summary, we have demonstrated a highly diastereo- and enantioselective construction of 6,7-dioxabicyclo[2.2.1]heptane-3-carboxylate derivatives bearing three stereogenic centers by Rh_2(*S*-PTTL)$_4$-catalyzed intramolecular C–H insertion of α-alkyl-α-diazoesters containing a ketal moiety at the γ-position. The work described herein represents the first successful example of asymmetric construction of bridged bicyclic ring systems via intramolecular C–H insertion of σ-symmetric α-diazocarbonyl compounds.[26,27]

EXPERIMENTAL

General. Melting points were determined on a Büchi 535 digital melting point apparatus and are uncorrected. IR spectra were recorded on a JASCO FT/IR-4100 spectrometer and absorbance bands are reported in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECX400P spectrometer, JEOL JNM-ECS400 spectrometer, or JEOL JNM-ECA500 spectrometer. Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). ESI-MS and APCI-MS spectra were obtained on a Thermo Scientific Exactive spectrometer. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575 intelligent UV/vis detector. Detection was performed at 254 nm. Chiralcel OD-H (0.46 cm × 25 cm), Chiralpak AD-H (0.46 cm × 25 cm), Chiralpak IB (0.46 cm × 25 cm), Chiralpak IC (0.46 cm × 25 cm), or Chiralpak ID (0.46 cm × 25 cm) from Daicel were used. Retention times (t_R) and peak ratios were determined with JASCO-ChromNAV analysis system. Single crystal X-ray analysis was performed on a Rigaku R-AXIS RAPID/S imaging plate area detector with graphite-monochromated Cu-Kα radiation.

All non-aqueous reactions were carried out in flame-dried glassware under an argon atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated stabilizer-free CH_2Cl_2, toluene, ether and THF were purchased from Kanto Chemical Co., Inc and purified by a solvent dispensing system supplied by Glass Contour (Nikko Hansen & Co., Ltd.).

Methyl 3-[2-(2-phenylethyl)-1,3-dioxolan-2-yl]propanoate (17). A solution of methyl 4-oxo-6-phenylhexanoate (**16**)[22] (3.28 g, 14.9 mmol), ethylene glycol (2.40 g, 38.7 mmol) and *p*-toluenesulfonic acid (28.3 mg, 0.15 mmol) in toluene (115 mL) was refluxed azeotropically for 4 h. The mixture was diluted with EtOAc (300 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 50 mL), water (2 × 50 mL) and brine (2 × 30 mL), and dried over Na_2SO_4. Filtration and evaporation followed by column chromatography (silica gel, hexane/EtOAc = 5:1) provided **17** (3.26 g, 83%) as a colorless oil; TLC R_f = 0.30 (5:1 hexane/EtOAc); IR (film) 1756, 1650, 1438, 1134, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89–1.94 (m, 2H, $PhCH_2CH_2$-), 2.06 (t, J = 7.7 Hz, 2H, C3-*H*), 2.41 (t, J = 7.7 Hz, 2H, C2-*H*), 2.67–2.71 (m, 2H, $PhCH_2CH_2$-), 3.68 (s, 3H, CO_2CH_3), 3.98 (s, 4H, OCH_2CH_2O), 7.17–7.19 (m, 3H, Ar*H*), 7.28–7.29 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6 (CH_2), 29.9 (CH_2), 32.1 (CH_2), 39.2 (CH_2), 51.5 (CH_3), 65.1 (CH_2), 110.3 (C), 125.7 (CH), 128.1 (CH), 128.3 (CH), 141.8 (C), 173.9 (C=O); ESI-HRMS *m/z* ca1cd for $C_{15}H_{20}O_4Na$ ($M+Na^+$) 287.1254, found 287.1251.

Typical procedure for the preparation of α-alkyl-α-diazoester. Methyl 2-diazo-3-[2-(2-phenylethyl)-1,3-dioxolan-2-yl]propanoate (13). A solution of **17** (360 mg, 1.36 mmol) in THF (0.8 mL) was added dropwise to a solution of LiHMDS (1.0 M solution in THF, 2.72 mL, 2.72 mmol) and methyl benzoate (370 mg, 2.72 mmol) in THF (4 mL) at –78 °C. After stirring at this temperature for 0.5 h, the reaction mixture was poured into saturated aqueous NH_4Cl (5 mL) and the whole was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (10 mL) and brine (2 × 10 mL), and dried over Na_2SO_4. Filtration and evaporation gave crude β-ketoester, which was used without further purification.

DBU (414 mg, 2.72 mmol) was added dropwise to a solution of crude β-ketoester and *p*-acetamidobenzenesulfonyl azide (490 mg, 2.72 mmol) in MeCN (5.5 mL) at 0 °C, and the mixture was stirred at room temperature for 5 h. The mixture was diluted with water (5 mL) and extracted with Et_2O (2 × 25 mL). The combined organic layers were washed with 10% aqueous NaOH (2 × 10 mL), water (10 mL) and brine (2 × 10 mL), and dried over Na_2SO_4. Filtration and evaporation followed by column chromatography (silica gel, hexane/EtOAc = 5:1) afforded **13** (370 mg, 94%) as a yellow oil; TLC R_f = 0.38 (3:1 hexane/EtOAc); IR (film) 2952, 2087, 1691, 1150, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.96–2.01 (m, 2H, $PhCH_2CH_2$-), 2.64 (s, 2H, C3-*H*), 2.07–2.74 (m, 2H, $PhCH_2CH_2$-), 3.77 (s, 3H, CO_2CH_3), 4.02 (s, 4H, -OCH_2CH_2O-), 7.16–7.20 (m, 3H, Ar*H*), 7.28–7.30 (m, 2H, Ar*H*); ^{13}C NMR (100

MHz, $CDCl_3$) δ 29.5 (CH_2), 30.4 (CH_2), 38.6 (CH_2), 51.7 (CH_3), 52.5 (C=N_2), 65.1 (CH_2), 110.8 (C), 125.5 (CH), 128.0 (CH), 128.1 (CH), 141.5 (C), 167.5 (C=O); ESI-HRMS *m/z* ca1cd for $C_{15}H_{18}N_2O_4Na$ (M+Na^+) 313.1159, found 313.1158.

Typical procedure for the enantioselective intramolecular C–H insertion reaction: (7*S*,8*R*)-Methyl *cis*-8-phenyl-1,4-dioxaspiro[4.4]nonane-7-carboxylate (14) and (1*S*,3*S*,4*R*)-methyl 1-(2-phenyethyl)-6,7-dioxabicyclo[2.2.1]heptane-3-carboxylate (15). Rh_2(*S*-PTTL)$_4$·2EtOAc (**4a**) (4.2 mg, 0.003 mmol, 1 mol%) was added to a solution of α-alkyl-α-diazoester **13** (87 mg, 0.30 mmol) in toluene (1.5 mL) at –78 °C. After stirring at this temperature for 2 h, the mixture was concentrated in vacuo and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 15:1) to give **14** (14.9 mg, 19%) as a colorless oil and **15** (59.7 mg, 76%) as a colorless oil.

Data for **14**: TLC R_f = 0.44 (3:1 hexane/EtOAc); $[\alpha]_D^{25}$ +32.5 (*c* 1.10, $CHCl_3$); IR (film) 2960, 2882, 1730, 1021 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 2.05–2.12 (m, 2H, C6-*H*, C9-*H*), 2.60 (dd, *J* = 12.0, 10.3 Hz, 1H, C6-*H*), 2.77 (dd, *J* = 14.0, 8.6 Hz, 1H, C9-*H*), 2.96 (s, 3H, CO_2CH_3), 3.23 (dd, *J* = 8.6, 8.2 Hz, 1H, C8-*H*), 3.42–3.51 (m, 4H, C2-*H*, C3-*H*), 3.61 (ddd, *J* = 16.6, 9.7 Hz, 1H, C7-*H*), 7.01–7.03 (m, 1H, Ar*H*), 7.08–7.11 (m, 2H, Ar*H*), 7.16–7.19 (m, 2H, Ar*H*); ^{13}C NMR (125 MHz, C_6D_6) δ 38.9 (CH_2), 40.9 (CH_2), 45.9 (CH), 47.5 (CH), 60.6 (CH_3), 64.0 (CH_2), 64.8 (CH_2), 116.7 (C), 128.23 (CH), 128.26 (CH), 128.33 (CH), 141.1 (C), 173.5 (C=O); ESI-HRMS *m/z* ca1cd for $C_{15}H_{18}O_4Na$ (M+Na^+) 285.1097, found 285.1095. The enantiomeric excess of **14** was determined to be 97% by HPLC with a Daicel Chiralcel OD-H (hexane/2-propanol = 9:1, 1.0 mL/min): t_R = 10.39 min for 7*S*,8*R* enantiomer; t_R = 16.91 min for 7*R*,8*S* enantiomer.

Data for **15**: TLC R_f = 0.47 (3:1 hexane/EtOAc); $[\alpha]_D^{25}$ +2.66 (*c* 1.03, C_6H_6); IR (film) 2953, 1739, 1202, 702 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 1.61 (dd, *J* = 12.6, 11.5 Hz, 1H, C2-*H*), 2.20 (dd, *J* = 9.5, 7.7 Hz, 2H, C1'-*H*), 2.37 (dd, *J* = 12.6, 5.2 Hz, 1H, C2-*H*), 2.85 (dddd, *J* = 11.5, 5.2, 5.2, 2.3 Hz, 1H, C3-*H*), 2.90–2.95 (m, 2H, C2'-*H*), 3.23 (s, 3H, CO_2CH_3), 3.46 (ddd, *J* = 7.4, 3.4, 2.3 Hz, 1H, C5-*H*), 3.77 (d, *J* = 7.4 Hz, 1H, C5-*H*), 4.51 (dd, *J* = 5.2, 3.4 Hz, 1H, C7-*H*), 7.05–7.07 (m, 3H, Ar*H*), 7.11–7.16 (m, 2H, Ar*H*); ^{13}C NMR (125 MHz, C_6D_6) δ 30.6 (CH_2), 34.7 (CH_2), 38.3 (CH_2), 46.4 (CH), 51.3 (CH_3), 67.6 (CH_2), 77.5 (CH), 111.1 (C), 126.1 (CH), 128.6 (CH), 128.7 (CH), 142.2 (C), 171.4 (C=O); ESI-HRMS *m/z* ca1cd for $C_{15}H_{18}O_4Na$ (M+Na^+) 285.1097, found 285.1096. The enantiomeric excess of **15** was determined to be 95% by HPLC with a Daicel Chiralpak AD-H (hexane/2-propanol = 19:1, 0.5 mL/min): t_R = 17.50 min for 1*S*,3*S*,4*R* enantiomer; t_R = 18.76 min for 1*R*,3*R*,4*S* enantiomer.

[(1*S*,3*R*,4*R*)-1-(2-Phenylethyl)-6,7-dioxabicyclo[2.2.1]heptan-3-yl]methyl 4-bromobenzoate (20). A solution of **15** (95% ee, 40.2 mg, 0.15 mmol) in THF (0.5 mL) was added dropwise to a solution of $LiAlH_4$ (38 mg, 1.0 mmol) in THF (1 mL) at 0 °C. After stirring at this temperature for 30 min, the

reaction was quenched by $Na_2SO_4 \cdot 10H_2O$, and the resulting mixture was stirred vigorously for an additional 1 h. The whole was filtered through a Celite pad, and the residue was washed with EtOAc (10 mL). The combined filtrates were concentrated to give the crude product, which was purified by column chromatography (silica gel, Et_2O/hexane/Et_3N = 66:33:1 → 83:16:1) to provide [(1*S*,3*R*,4*R*)-1-(2-phenylethyl)-6,7-dioxa-bicyclo[2.2.1]heptan-3-yl]methanol (34.3 mg, 96%) as a colorless oil; TLC R_f = 0.27 (1:5 hexane/Et_2O); $[\alpha]_D^{23}$ +41.4 (*c* 1.09, C_6H_6); IR (film) 3734, 2892, 1455, 979 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.17 (dd, *J* = 11.5, 5.4 Hz, 1H, C2-*H*), 1.55 (dd, *J* = 11.5, 11.5 Hz, 1H, C2-*H*), 2.23–2.27 (m, 3H, C1'-*H* and C3-*H*), 2.93–3.03 (m, 2H, C3-*H*), 3.17 (dd, *J* = 10.3, 10.3 Hz, 1H, CH_2OH), 3.30 (dd, *J* = 10.3, 6.3 Hz, 1H, CH_2OH), 3.49 (ddd, *J* = 7.4, 3.4, 1.7 Hz, 1H, C5-*H*), 3.77 (d, *J* = 7.4 Hz, 1H, C5-*H*), 4.48 (dd, *J* = 4.0, 3.4 Hz, 1H, C4-*H*), 7.03–7.07 (m, 1H, Ar*H*), 7.10–7.13 (m, 3H, Ar*H*); ^{13}C NMR (125 MHz, C_6D_6) δ 30.8 (CH_2), 35.1 (CH_2), 39.2 (CH), 42.7 (CH_2), 62.9 (CH_2), 65.7 (CH_2), 78.7 (CH), 110.4 (C), 126.1 (CH), 128.6 (CH), 128.7 (CH), 142.4 (C); ESI-HRMS *m/z* ca1cd for $C_{14}H_{18}O_3Na$ ($M+Na^+$) 257.1148, found 257.1149.

4-Bromobenzoyl chloride (35.4 mg, 0.16 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of the alcohol (31.5 mg, 0.13 mmol), 4-dimethylaminopyridine (1.64 mg, 0.013 mmol) and triethylamine (54.2 mg, 0.54 mmol) in CH_2Cl_2 (1 mL) at 0 °C, and the mixture was stirred at room temperature for 2 h. The reaction was quenched by crushed ice, and the whole was partitioned between EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (5 mL). The organic layer was washed with water (5 mL) and brine (2 × 5 mL) and dried over Na_2SO_4. Filtration and evaporation gave the crude product, which was purified by column chromatography (silica gel, hexane/EtOAc/Et_3N = 83:16:1) to provide **20** (51.7 mg, 92%) as a white solid; mp 70.5–71.0 °C (fine plates from MeOH); TLC R_f = 0.20 (4:1 hexane/Et_2O); $[\alpha]_D^{25}$ +14.1 (*c* 1.26, C_6H_6); IR (KBr) 3022, 2925, 1712, 1267 cm^{-1}; ^1H NMR (500 MHz, C_6D_6) δ 1.24 (dd, *J* = 11.8, 5.7 Hz, 1H, C2-*H*), 1.53 (dd, *J* = 11.8, 12.6 Hz, 1H, C2-*H*), 2.21–2.26 (m, 2H, C1'-*H*), 2.34–2.42 (m, 1H, C3-*H*), 2.90–3.01 (m, 2H, C2'-*H*), 3.43 (ddd, *J* = 7.4, 4.0, 1.7 Hz, 1H, C5-*H*), 3.71 (d, *J* = 7.4 Hz, 1H, C5-*H*), 4.04 (dd, *J* = 11.5, 9.2 Hz, 1H, CH_2O_2CAr), 4.13 (dd, *J* = 11.5, 6.3 Hz, 1H, CH_2O_2CAr), 4.30 (dd, *J* = 4.0, 4.0 Hz, 1H, C4-*H*), 7.05–7.07 (m, 1H, Ar*H*), 7.10–7.14 (m, 4H, Ar*H*), 7.19–7.21 (m, 2H, Ar*H*), 7.71–7.73 (m, 2H, Ar*H*); ^{13}C NMR (125 MHz, C_6D_6) δ 30.7 (CH_2), 34.9 (CH_2), 39.1 (CH_2), 39.7 (CH), 64.9 (CH_2), 65.7 (CH_2), 78.3 (CH), 110.4 (C), 126.2 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 129.3 (C), 131.3 (CH), 132.0 (CH), 142.2 (C), 165.2 (C=O); ESI-HRMS *m/z* ca1cd for $C_{21}H_{21}BrO_4Na$ ($M+Na^+$) 439.0515, found 439.0517.

The absolute configuration of **20** was established to be (1*S*,3*R*,4*R*) by a single-crystal X-ray analysis. Suitable crystals of **20** for X-ray crystallographic analysis were obtained by recrystallization from MeOH.[29]

Methyl (7*R*,8*R*)-*trans*-8-phenyl-1,4-dioxaspiro[4.4]nonane-7-carboxylate (18).[30] A solution of **14** (97% ee, 32 mg, 0.12 mmol) and sodium methoxide (10 mg, 0.19 mmol) in MeOH (1 mL) was refluxed for 6 h. The mixture was poured into two-layered mixture of pH 7.0 phosphate buffer (1 mL) and Et_2O (2 mL), and the whole was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with water (5 mL) and brine (2 × 5 mL) and dried over Na_2SO_4. Filtration and evaporation gave the crude pruduct, which was purified by column chromatography (silica gel, toluene/EtOAc = 40:1) to provide **18**[30] (26.7 mg, 83%) as a colorless oil; TLC R_f = 0.43 (3:1 hexane/EtOAc); $[\alpha]_D^{23}$ –52.7 (*c* 1.33, $CHCl_3$) lit.,[30] $[\alpha]_D^{23}$ +38.2 (*c* 2.2, $CHCl_3$) for the (7*S*,8*S*)-enantiomer; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (ddd, *J* = 1.0, 1.0, 14.0 Hz, 1H, C9-*H*), 2.23 (ddd, *J* = 1.0, 10.5, 13.5 Hz, 1H, C6-*H*), 2.36 (dd, *J* = 8.5, 13.5 Hz, 1H, C6-*H*), 2.40 (dd, *J* = 8.5, 14.0 Hz, 1H, C9-*H*), 3.03 (dt, *J* = 8.5, 10.5 Hz, 1H, C7-*H*), 3.53 (dt, *J* = 8.5, 10.5 Hz, 1H, C8-*H*), 3.60 (s, 3H, CO_2CH_3), 3.90–4.01 (m, 4H, C2-*H*, C3-*H*), 7.20–7.33 (m, 5H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8 (CH_2), 44.3 (CH_2), 46.4 (CH), 49.9 (CH), 51.7 (CH_3), 64.4 (CH_2), 64.5 (CH_2), 115.7 (C), 126.7 (CH), 127.3 (CH), 128.5 (CH), 142.5 (C), 174.5 (C=O).
The enantiomeric excess of **18** was determined to be 97% by HPLC with a Daicel ChiralPak IB (hexane/2-propanol = 19:1, 1.0 mL/min): t_R = 7.06 min for (7*R*,8*R*)-enantiomer; t_R = 8.22 min for (7*S*,8*S*)-enantiomer.

Methyl 2-diazo-3-(2-methyl-1,3-dioxolan-2-yl)propanoate (21a). According to the typical procedure for the preparation of α-alkyl-α-diazoester, **21a** was prepared from methyl 3-(2-methyl-1,3-dioxolan-2-yl)propanoate[39] (237 mg, 1.36 mmol), LiHMDS (1.0 M solution in THF, 2.72 mL, 2.72 mmol), methyl benzoate (370 mg, 2.72 mmol), DBU (414 mg, 2.72 mmol) and *p*-acetamidobenzenesulfonyl azide (490 mg, 2.72 mmol). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3:1) to give **21a** (253 mg, 93%) as a yellow oil; TLC R_f = 0.30 (3:1 hexane/EtOAc); IR (film) 2955, 2888, 2089, 1696, 1147, 1043 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (s, 3H, *J* = 8.5, 4.8 Hz, C*H*$_3$), 2.61 (s, 2H, C3-*H*), 3.77 (s, 3H, CO_2CH_3), 3.93–3.99 (m, 4H, -OCH_2CH_2O-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (CH_3), 31.9 (CH_2), 51.6 (CH_3), 52.5 (C=N_2), 64.6 (CH_2), 109.5 (C), 167.5 (C=O); ESI-HRMS *m/z* ca1cd for $C_8H_{12}N_2O_4Na$ (M+Na^+) 223.0689, found 223.0689.

Methyl 2-diazo-3-(2-ethyl-1,3-dioxolan-2-yl)propanoate (21b). Following the procedure for the preparation of **17**, methyl 3-(2-ethyl-1,3-dioxolan-2-yl)propanoate was prepared from methyl 4-oxohexanoate[40] (3.59 g, 24.9 mmol), ethylene glycol (4.02 g, 64.7 mmol) and *p*-toluenesulfonic acid (474 mg, 2.49 mmol). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 5:1) to give the corresponding ketal (3.40 g, 75%) as a colorless oil; TLC R_f = 0.43 (3:1 hexane/EtOAc); IR (film) 2974, 2882, 1739 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.6 Hz, 3H,

CH3CH2), 1.62 (q, *J* = 7.6 Hz, 2H, CH3CH2), 2.00 (t, *J* = 7.7 Hz, 2H, C3-*H*), 2.38 (t, *J* = 7.7 Hz, 2H, C2-*H*), 3.67 (s, 3H, CO_2CH_3), 3.94 (s, 4H, -OCH_2CH_2O-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.32 (CH3), 27.9 (CH_3), 29.4 (CH_2), 31.0 (CH_2), 50.7 (CH_3), 64.4 (CH_2), 110.3 (C), 173.2 (C=O); APCI-HRMS m/*z* ca1cd for $C_9H_{17}O_4$ ($M+H^+$) 189.1121, found 189.1124.

According to the typical procedure for the preparation of α-alkyl-α-diazoester, **21b** was prepared from methyl 3-(2-ethyl-1,3-dioxolan-2-yl)propanoate (247 mg, 1.36 mmol), LiHMDS (1.0 M solution in THF, 2.72 mL, 2.72 mmol), methyl benzoate (370 mg, 2.72 mmol), DBU (414 mg, 2.72 mmol) and *p*-acetamidobenzenesulfonyl azide (490 mg, 2.72 mmol). The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 3:1) to give **21b** (253 mg, 93%) as a yellow oil; TLC R_f = 0.38 (2:1 hexane/EtOAc); IR (film) 2976, 2886, 2088, 1696, 1150, 1068 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, *J* = 7.5 Hz, 3H, CH_3CH_2-), 1.69 (q, *J* = 7.5 Hz, 2H, CH_3CH_2-), 2.58 (s, 2H, C3-*H*), 3.77 (s, 3H, CO_2CH_3), 3.97 (m, 4H, -OCH_2CH_2O-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.43 (CH_3), 29.5 (CH_2), 30.0 (CH_2), 51.6 (CH_3), 52.5 ($C=N_2$), 65.1 (CH_2), 111.5 (C), 167.6 (C=O); ESI-HRMS *m/z* ca1cd for $C_9H_{14}N_2O_4Na$ ($M+Na^+$) 237.0846, found 237.0846.

Enantioselective intramolecular C–H insertion reaction of α-alkyl-α-diazoester (21a). (1*S,3*S**,4*R**)-methyl 1-methyl-6,7-dioxabicyclo[2.2.1]heptane-3-carboxylate (22a).** According to the typical procedure for the enantioselective C–H insertion reaction, the reaction of **21a** (60 mg, 0.30 mmol) was conducted in the presence of Rh_2(*S*-PTTL)$_4$·2EtOAc (**4a**) (4.2 mg, 0.003 mmol, 1 mol%) in toluene (1.5 mL) at –78 °C for 4 h. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 15:1) to give a mixture of **22a** and an unidentified impurity (44 mg); ^{1}H NMR (400 MHz, acetone-d_6) δ 1.51 (s, 3H, C1-CH_3), 1.91 (dd, *J* = 12, 12 Hz, 1H, C2-*H*), 2.19 (dd, *J* = 5.6, 12 Hz, C2-*H*), 3.22 (dddd, *J* = 2.4, 4.8, 4.8, 11.2 Hz, 1H, C3-*H*), 3.51 (ddd, *J* = 2.4, 3.6, 7.2 Hz, 1H, C5-*H*), 3.66–3.68 (m, 1H, C5-*H*), 3.68 (s, 3H, CO_2CH_3), 4.84 (dd, *J* = 3.6, 5.2 Hz, 1H, C4-*H*).

A solution of the above mixture in THF (1 mL) was added dropwise to a solution of $LiAlH_4$ (15.5 mg, 0.41 mmol) in THF (2 mL) at 0 °C, and the whole was stirred at this temperature for 30 min. The standard workup as described above followed by column chromatography (silica gel, Et_2O/hexane/Et_3N = 66:33:1) provided [(1*S**,3*R**,4*R**)-1-methyl-6,7-dioxabicyclo[2.2.1]heptan-3-yl]methanol (**23a**) (28.5 mg, 66% from **21a**) as a colorless oil; TLC R_f = 0.12 (1:4 hexane/Et_2O); $[\alpha]_D^{25}$ +38.1 (*c* 1.01, acetone); IR (film) 3267, 2934 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 1.31 (dd, *J* = 12.0, 5.5 Hz, 1H, C2-*H*), 1.46 (s, 3H, C1-CH_3), 1.76 (dd, *J* = 12.0, 12.0 Hz, 2H, C2-*H*), 2.41–2.49 (m, 1H, C3-*H*), 3.43 (ddd, *J* = 7.1, 3.6, 2.0 Hz, 1H, C5-*H*), 3.54–3.60 (m, 2H, CH_2OH), 3.73–3.77 (m, 2H, CH_2OH), 3.91 (d, *J* = 7.1 Hz, 1H, C5-*H*), 4.05 (dd, *J* = 4.0, 3.6 Hz, 1H, C4-*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 18.9 (CH_3), 40.9 (CH_2), 44.0 (CH), 62.9 (CH_2), 65.9 (CH_2), 79.6 (CH), 109.1 (C); APCI-HRMS *m/z* ca1cd for $C_7H_{13}O_3$ ($M+H^+$) 145.0859, found 145.0860.

Benzoyl chloride (33.7 mg, 0.24 mmol) in CH_2Cl_2 (0.2 mL) was added to a solution of **23a** (25 mg, 0.17 mmol), 4-dimethylaminopyridine (1.5 mg, 0.012 mmol) and pyridine (28.5 mg, 0.36 mmol), in CH_2Cl_2 (1.5 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The standard workup as described above followed by column chromatography (silica gel, hexane/EtOAc/Et_3N = 83:16:1) provided [(1*S**,3*R**,4*R**)-1-methyl-6,7-dioxa-bicyclo[2.2.1]heptan-3-yl]methyl benzoate as a colorless oil; TLC R_f = 0.18 (4:1 hexane/EtOAc); $[\alpha]_D^{23}$ +23.0 (*c* 1.05, acetone); IR (film) 2951, 2894, 1716, 1271 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.52 (s, 3H, C1-CH_3), 1.57 (dd, *J* = 11.8, 5.8 Hz, 1H, C2-*H*), 1.95 (dd, *J* = 11.8, 11.8 Hz, 1H, C2-*H*), 2.70–2.80 (m, 1H, C3-*H*), 3.54 (ddd, *J* = 7.3, 3.7, 1.0 Hz, 1H, C5-*H*), 4.04 (d, *J* = 7.3 Hz, 1H, C5-*H*), 4.04 (d, *J* = 7.3 Hz, 1H, C5-*H*), 4.37 (dd, *J* = 11.3, 10.0 Hz, 1H, CH_2OBz), 4.55 (dd, *J* = 11.3, 6.5 Hz, 1H, CH_2OBz), 4.83 (dd, *J* = 4.0, 3.7 Hz, 1H, C4-*H*), 7.50–7.53 (m, 2H, Ar*H*), 7.62–7.66 (m, 1H, Ar*H*), 8.02–8.04 (m, 2H, Ar*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 18.8 (CH_3), 40.7 (CH), 40.8 (CH_2), 65.4 (CH_2), 66.1 (CH_2), 79.2 (CH), 109.3 (C), 129.3 (CH), 130.2 (CH), 131.0 (C), 133.9 (CH), 166.5 (C=O); ESI-HRMS *m/z* ca1cd for $C_{14}H_{16}O_4Na$ ($M+Na^+$) 271.0941, found 271.0938.

The enantiomeric excess of the benzoate of **23a** was determined to be 83% by HPLC with a Daicel ChiralPak IC (hexane/2-propanol = 49:1, 1.0 mL/min): t_R = 15.54 min for minor enantiomer; t_R = 23.73 min for major enantiomer.

Enantioselective intramolecular C–H insertion reaction of α-alkyl-α-diazoester (21b). (1*S,3*S**,4*R**)-methyl 1-ethyl-6,7-dioxabicyclo[2.2.1]heptane-3-carboxylate (22b).** According to the typical procedure for the enantioselective C–H insertion reaction, the reaction of **21b** (64.2 mg, 0.30 mmol) was conducted in the presence of Rh_2(*S*-PTTL)$_4$·2EtOAc (**4a**) (4.2 mg, 0.003 mmol, 1 mol%) in toluene (1.5 mL) at –78 °C for 4 h. The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 15:1) to give a mixture of **22b** and an unidentified impurity (48 mg); ^{1}H NMR (400 MHz, acetone-d_6) δ 0.98 (t, *J* = 7.2 Hz, 3H, C1-CH_2CH_3), 1.84 (q, *J* = 7.2 Hz, 2H, C1-C$H_2$$CH_3$), 1.90 (dd, *J* = 12.2, 11.6 Hz, 1H, C2-*H*), 2.14 (dd, *J* = 12.2, 5.2 Hz, 1H, C2-*H*), 3.18 (dddd, *J* = 2.3, 5.2, 5.2, 11.6 Hz, 1H, C3-*H*), 3.49 (ddd, *J* = 2.3, 3.6, 7.2 Hz, 1H, C5-*H*), 3.67 (s, 3H, CO_2CH_3), 3.68–3.70 (m, 1H, C5-*H*), 4.84 (dd, *J* = 3.6, 5.0 Hz, C4-*H*).

A solution of the above mixture in THF (1 mL) was added dropwise to a solution of $LiAlH_4$ (15.5 mg, 0.41 mmol) in THF (2 mL) at 0 °C, and the whole was stirred at this temperature for 30 min. The standard workup as described above followed by column chromatography (silica gel, Et_2O/hexane/Et_3N = 66:33:1) provided [(1*S**,3*R**,4*R**)-1-ethyl-6,7-dioxabicyclo[2.2.1]heptan-3-yl]methanol (**23b**) (31.8 mg, 57% from **21b**) as a colorless oil; TLC R_f = 0.15 (2:1 Et_2O/hexane); $[\alpha]_D^{24}$ +41.1 (*c* 1.32, acetone); IR (film) 3398, 2923 cm^{-1}; ^{1}H NMR (500 MHz, acetone-d_6) δ 1.31 (dd, *J* = 12.0, 5.5 Hz, 1H, C2-*H*), 1.46 (s, 3H,

C1-C*H*$_3$), 1.76 (dd, *J* = 12.0, 12.0 Hz, 2H, C2-*H*), 2.41–2.49 (m, 1H, C3-*H*), 3.43 (ddd, *J* = 7.1, 3.6, 2.0 Hz, 1H, C5-*H*), 3.54–3.60 (m, 2H, C*H*$_2$OH), 3.73–3.77 (m, 2H, C*H*$_2$OH), 3.91 (d, *J* = 7.1 Hz, 1H, C5-*H*), 4.05 (dd, *J* = 4.0, 3.6 Hz, 1H, C4-*H*); ^{13}C NMR (100 MHz, acetone-d_6) δ 8.66 (CH_3), 26.4 (CH_2), 38.9 (CH_2), 43.6 (CH), 63.0 (CH_2), 65.9 (CH_2), 79.3 (CH), 111.4 (C); APCI-HRMS *m/z* ca1cd for $C_8H_{15}O_3$ ($M+H^+$) 151.1016, found 151.1017.

Benzoyl chloride (33.7 mg, 0.24 mmol) in CH_2Cl_2 (0.2 mL) was added to a solution of **23b** (27 mg, 0.18 mmol), 4-dimethylaminopyridine (1.5 mg, 0.012 mmol) and pyridine (28.5 mg, 0.36 mmol), in CH_2Cl_2 (1.5 mL) at 0 °C, and the mixture was stirred at room temperature for 1 h. The standard workup as described above followed by column chromatography (silica gel, hexane/EtOAc/Et_3N = 83:16:1) to provide [(1*S**,3*R**,4*R**)-1-ethyl-6,7-dioxabicyclo[2.2.1]heptan-3-yl]methyl benzoate as a colorless oil; R_f = 0.20 (4:1 hexane/EtOAc); $[\alpha]_D^{24}$ +22.9 (*c* 1.02, acetone); IR (film) 2969, 2940, 1716, 1270 cm^{-1}; ^{1}H NMR (400 MHz, acetone-d_6) δ 1.52 (s, 3H, C1-C*H*$_3$), 1.57 (dd, *J* = 11.8, 5.8 Hz, 1H, C2-*H*), 1.95 (dd, *J* = 11.8, 11.8 Hz, 1H, C2-*H*), 2.70–2.80 (m, 1H, C3-*H*), 3.54 (ddd, *J* = 7.3, 3.7, 1.0 Hz, 1H, C5-*H*), 4.04 (d, *J* = 7.3 Hz, 1H, C5-*H*), 4.04 (d, *J* = 7.3 Hz, 1H, C5-*H*), 4.37 (dd, *J* = 11.3, 10.0 Hz, 1H, C*H*$_2$OBz), 4.55 (dd, *J* = 11.3, 6.5 Hz, 1H, C*H*$_2$OBz), 4.83 (dd, *J* = 4.0, 3.7 Hz, 1H, C4-*H*), 7.50–7.53 (m, 2H, Ar*H*), 7.62–7.66 (m, 1H, Ar*H*), 8.02–8.04 (m, 2H, Ar*H*); ^{13}C NMR (125 MHz, acetone-d_6) δ 18.8 (CH_3), 40.7 (CH), 40.8 (CH_2), 65.4 (CH_2), 66.1 (CH_2), 79.2 (CH), 109.3 (C), 129.3 (CH), 130.2 (CH), 131.0 (C), 133.9 (CH), 166.5 (C=O); ESI-HRMS *m/z* ca1cd for $C_{14}H_{16}O_4Na$ ($M+Na^+$) 271.0941, found 271.0938.

The enantiomeric excess of the benzoate of **23b** was determined to be 90% by HPLC with a Daicel ChiralPak ID (hexane/2-propanol = 49:1, 1.0 mL/min): t_R = 13.57 min for major enantiomer; t_R = 15.37 min for minor enantiomer.

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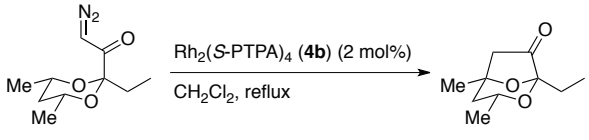

36% yield, 20% ee

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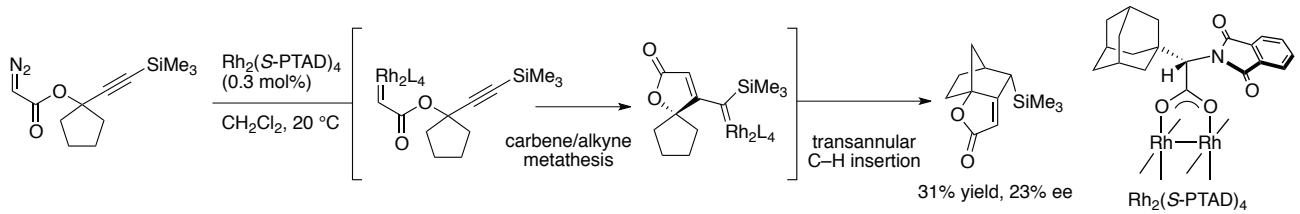

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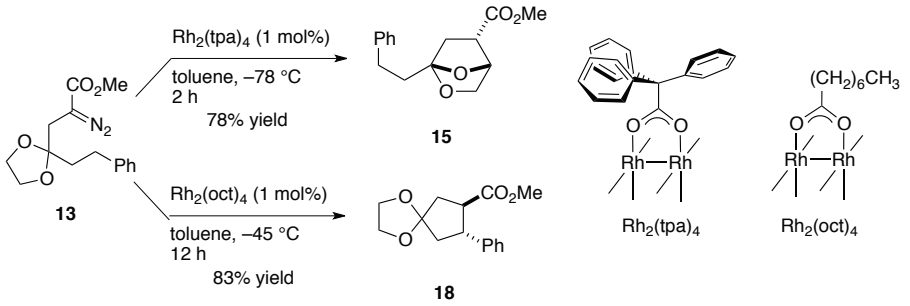
32. Perfect site-control in this system has been achieved by an appropriate choice of achiral catalysts. Intramolecular C–H insertion reaction of **13** in the presence of 1 mol% of dirhodium(II) tetrakis(triphenylacetate), Rh_2(tpa)$_4$,[33] with an exceptionally bulky ligand in toluene at –78 °C provided a dioxabicyclo[2.2.1]heptane product (**15**) as a sole product in 78% yield. On the other hand, the use of 1 mol% of dirhodium(II) tetraoctanate, Rh_2(oct)$_4$, under the same conditions gave exclusively a *trans*-cyclopentane product (**18**) in 83% yield.



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