

HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 1211-1229. © 2017 The Japan Institute of Heterocyclic Chemistry  
Received, 9th September, 2016, Accepted, 14th November, 2016, Published online, 6th February, 2017  
DOI: 10.3987/COM-16-S(S)72

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

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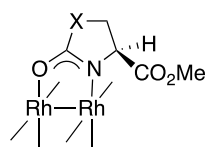
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**Abstract** – The first diastereo- and enantioselective construction of bridged bicyclic ring systems by an intramolecular C–H insertion reaction is described. With dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh<sub>2</sub>(*S*-PTTL)<sub>4</sub>, the C–H insertion of  $\alpha$ -alkyl- $\alpha$ -diazoesters containing an ethylene ketal moiety at the  $\gamma$ -position provided methyl 6,7-dioxabicyclo[2.2.1]heptane-3-carboxylate derivatives with up to 95% ee and perfect diastereoselectivity.

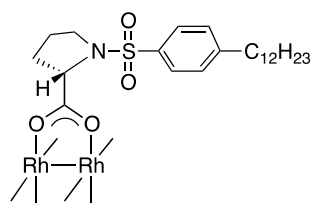
The development of catalytic asymmetric C–C bond forming reactions has been a subject of intensive investigation in the field of synthetic organic chemistry.<sup>1</sup> Among a wide variety of transition metal complexes used to catalyze a diverse array of transformations of  $\alpha$ -diazocarbonyl 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.<sup>2,3</sup> 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.<sup>4</sup> 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<sub>2</sub>(5*S*-MEPY)<sub>4</sub> (**1a**), Rh<sub>2</sub>(4*S*-MEOX)<sub>4</sub> (**1b**), and Rh<sub>2</sub>(4*S*-MPPIM)<sub>4</sub> (**1c**) is characteristic of enantioselective intramolecular

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

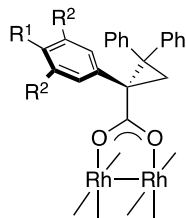
C–H insertion reactions of diazoacetates and diazoacetamides,<sup>5</sup> while Davies's dirhodium(II) carboxylate catalysts such as  $\text{Rh}_2(\text{S-DOSP})_4$  (**2**),  $\text{Rh}_2(\text{R-BPCP})_4$  (**3a**), and  $\text{Rh}_2[\text{R-3,5-di}(p\text{-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$  (**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  $\alpha$  to oxygen, as well as unactivated C–H bonds.<sup>6,7</sup> Our dirhodium(II) carboxylate catalysts that incorporate *N*-phthaloyl-(*S*)-amino acids as bridging ligands, such as  $\text{Rh}_2(\text{S-PTTL})_4$  (**4a**),  $\text{Rh}_2(\text{S-PTPA})_4$  (**4b**),  $\text{Rh}_2(\text{S-PTA})_4$  (**4c**), and  $\text{Rh}_2(\text{S-PTV})_4$  (**4d**), are especially well suited for intramolecular C–H insertion reactions of  $\alpha$ -diazo- $\beta$ -ketoesters,<sup>8</sup>  $\alpha$ -methoxycarbonyl- $\alpha$ -diazoacetamides,<sup>9</sup> aryldiazoacetates,<sup>10</sup> and diaryldiazomethanes.<sup>11</sup> Of these catalysts, dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate],  $\text{Rh}_2(\text{S-PTTL})_4$  (**4a**), with a bulky *tert*-butyl group has proven to be the most generally effective catalyst for a range of diazo substrates.<sup>12–14</sup>



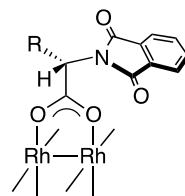
X = CH<sub>2</sub>:  $\text{Rh}_2(\text{5S-MEPY})_4$  (**1a**)  
 X = O:  $\text{Rh}_2(\text{4S-MEOX})_4$  (**1b**)  
 X = PhCH<sub>2</sub>CH<sub>2</sub>CON:  $\text{Rh}_2(\text{4S-MPPIM})_4$  (**1c**)



$\text{Rh}_2(\text{S-DOSP})_4$  (**2**)



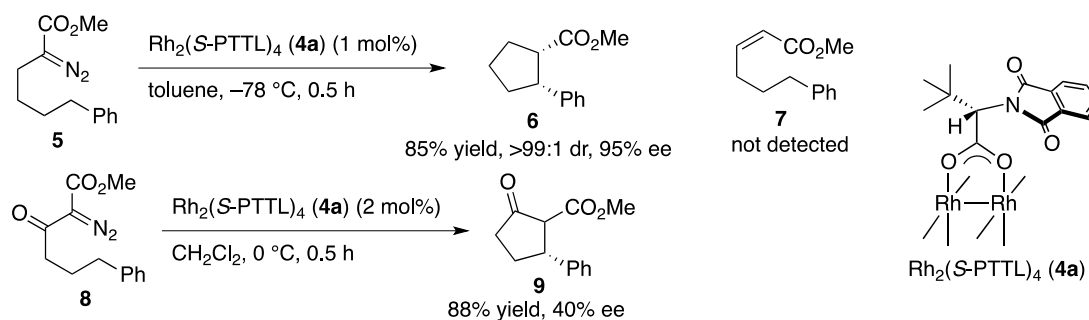
R<sup>1</sup> = Ph, R<sup>2</sup> = H:  $\text{Rh}_2(\text{R-BPCP})_4$  (**3a**)  
 R<sup>1</sup> = H, R<sup>2</sup> = 4-<sup>t</sup>BuC<sub>6</sub>H<sub>4</sub>:  
 $\text{Rh}_2[\text{R-3,5-di}(p\text{-}^t\text{BuC}_6\text{H}_4)\text{TPCP}]_4$  (**3b**)



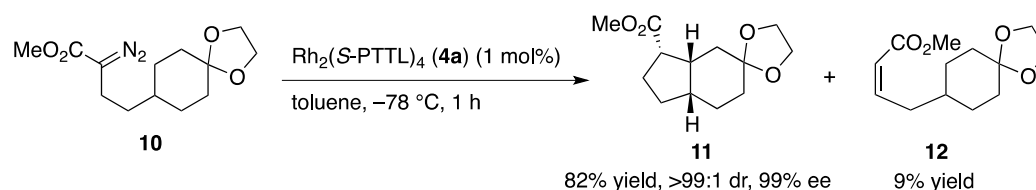
R = <sup>t</sup>Bu:  $\text{Rh}_2(\text{S-PTTL})_4$  (**4a**)  
 R = Bn:  $\text{Rh}_2(\text{S-PTPA})_4$  (**4b**)  
 R = Me:  $\text{Rh}_2(\text{S-PTA})_4$  (**4c**)  
 R = <sup>i</sup>Pr:  $\text{Rh}_2(\text{S-PTV})_4$  (**4d**)

Recently, we have demonstrated the first asymmetric intramolecular C–H insertion reaction of  $\alpha$ -alkyl- $\alpha$ -diazoesters<sup>15</sup> using  $\text{Rh}_2(\text{S-PTTL})_4$  (**4a**) at  $-78$  °C, in which even higher enantioselectivity (up to 95% ee) than that observed with the corresponding  $\alpha$ -diazo- $\beta$ -ketoesters<sup>8a</sup> as well as perfect *cis* diastereoselectivity was achieved with no evidence of the formation of  $\alpha,\beta$ -unsaturated esters via a 1,2-hydride shift of dirhodium(II) carbene intermediates (Scheme 1a).<sup>4p,16,17</sup> This protocol has enabled the first diastereo- and enantioselective construction of fused bicyclic ring systems with three contiguous stereogenic centers via desymmetrization of  $\sigma$ -symmetric  $\alpha$ -alkyl- $\alpha$ -diazoesters (Scheme 1b).<sup>18</sup> In continuation of our studies on dirhodium(II)-catalyzed asymmetric reactions with  $\alpha$ -alkyl- $\alpha$ -diazoesters,<sup>19–21</sup> we investigated the intramolecular C–H insertion of  $\alpha$ -alkyl- $\alpha$ -diazoester (**13**) containing a ketal moiety at the  $\gamma$ -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).

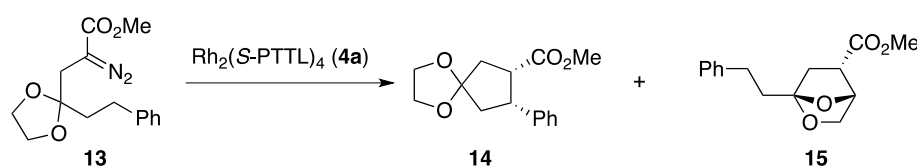
a) Enantioselective intramolecular C–H insertion reaction of  $\alpha$ -alkyl- $\alpha$ -diazooesters<sup>15</sup> and  $\alpha$ -dialzo- $\beta$ -ketoesters<sup>8a</sup>



b) Enantio- and diastereoselective desymmetrization<sup>18</sup>

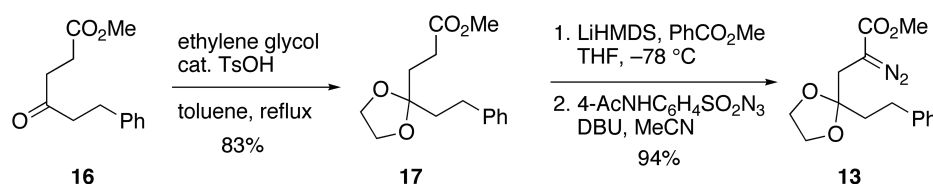


c) This work



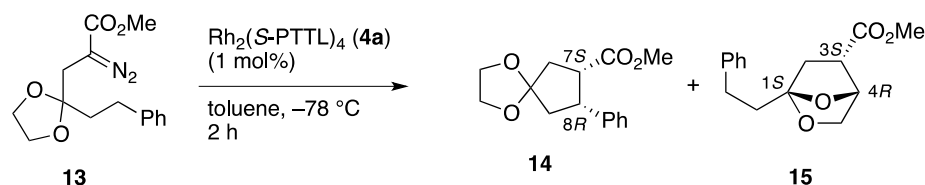
Scheme 1

The requisite  $\alpha$ -alkyl- $\alpha$ -diazooester (**13**) was prepared from the known  $\gamma$ -ketoester (**16**)<sup>22</sup> 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.<sup>23</sup> Thus, addition of ester (**17**) to a mixture of LiHMDS and methyl benzoate in THF at  $-78$  °C afforded an  $\alpha$ -benzoylated ester, which, upon diazo transfer with *p*-acetamidobenzenesulfonyl azide and DBU, gave  $\alpha$ -diazooester (**13**) in 94% yield over two steps.



Scheme 2

On the basis of our original work,<sup>15</sup> we initially explored the intramolecular C–H insertion of **13** in toluene at  $-78$  °C using 1 mol% of  $\text{Rh}_2(\text{S-PTTL})_4$  (**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  $\alpha,\beta$ -unsaturated ester (**19**) was detected

**Table 1.** Enantioselective Intramolecular C–H Insertion Reaction of  $\alpha$ -Alkyl- $\alpha$ -diazoester **13** Catalyzed by Dirhodium(II) Carboxylates<sup>a</sup>

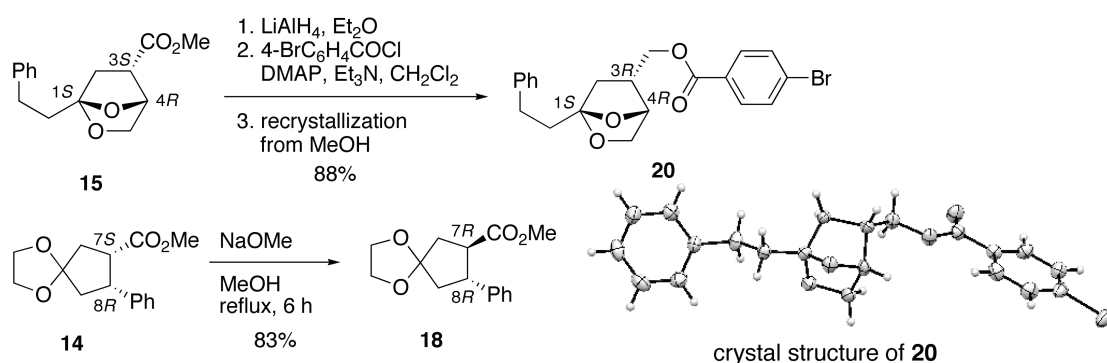
entry	solvent	temp, °C	time h	14		15		
				14 : 15 <sup>b</sup>	% yield <sup>c</sup>	% ee <sup>d</sup>	% yield <sup>c</sup>	% ee <sup>d</sup>
1	toluene	-78	2	22 : 78	19	97	76	95
2	toluene	-40	0.25	25 : 75	15	94	65	86
3	toluene	0	0.1	23 : 77	20	88	73	73
4	CH <sub>2</sub> Cl <sub>2</sub>	-78	2	8 : 92	6	80	81	81
5	Et <sub>2</sub> O	-78	2	17 : 83	15	89	78	83

<sup>a</sup>Typical procedure for C–H insertion reaction (entry 1): Rh<sub>2</sub>(S-PTTL)<sub>4</sub>·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. <sup>b</sup>Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup>Isolated yield. <sup>d</sup>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<sup>6c,24</sup> with little deactivating effect of a  $\beta$ -alkoxy group,<sup>25</sup> 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  $\sigma$ -symmetric  $\alpha$ -diazocarbonyl compounds.<sup>26,27</sup> 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  $\gamma$ -alkoxy groups in the ketal moiety that make the  $\beta$ -C–H bond less electron-rich.<sup>17f,28</sup> 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**),

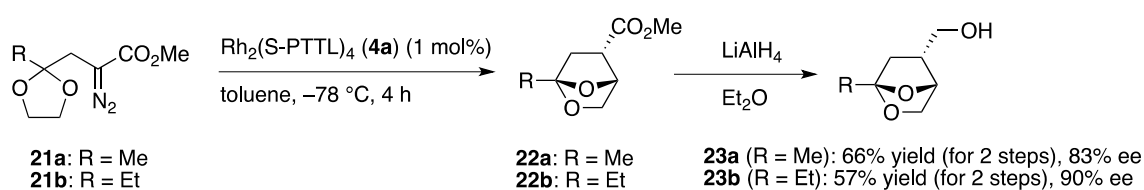
a sharp drop in enantioselectivity was observed. Ether had little impact on the site-selectivity but markedly reduced enantioselectivity.

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).<sup>29</sup> The absolute stereochemistry of **14** was established as 7*S*,8*R* by its conversion to the known *trans*-2-phenylcyclopentane-1-carboxylate (**18**), [ $\alpha$ ]<sub>D</sub><sup>23</sup> -52.7 (*c* 1.33, CHCl<sub>3</sub>) [lit.,<sup>30</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> +38.2 (*c* 2.2, CHCl<sub>3</sub>) for the (7*S*,8*S*)-enantiomer], by epimerization using sodium methoxide in MeOH.



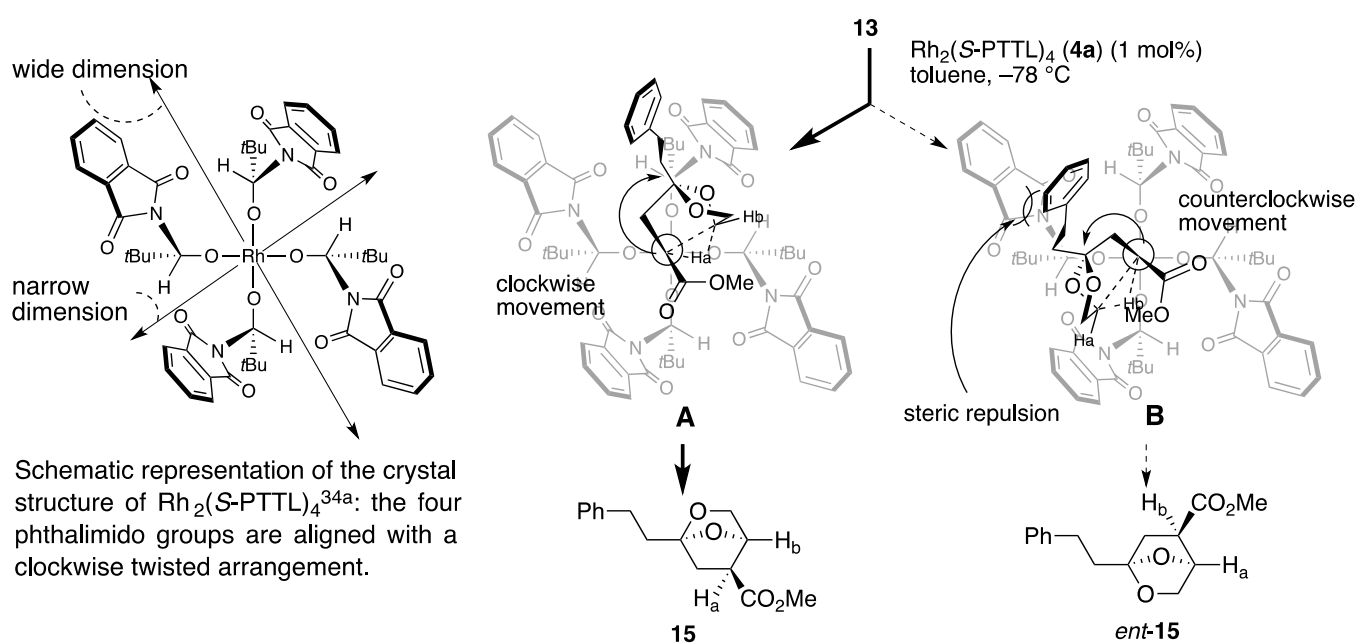
**Scheme 3**

Since both site-control and enantiocontrol in Rh<sub>2</sub>(*S*-PTTL)<sub>4</sub>-catalyzed reaction of  $\alpha$ -diazoester (**13**) proved to be a formidable challenge,<sup>31,32</sup> we next investigated the reaction of  $\alpha$ -alkyl- $\alpha$ -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<sub>2</sub>(*S*-PTTL)<sub>4</sub>-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  $\alpha,\beta$ -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<sub>4</sub>. 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  $\alpha$ -diazoester (**21a**), high enantioselectivity (90% ee) was achieved with ethyl-substituted  $\alpha$ -diazoester (**21b**).



**Scheme 4**

Although the site-selectivity remains to be elucidated,<sup>31</sup> the stereochemical outcome of the C–H insertion of  $\alpha$ -diazooester (**13**) can be explained on the basis of the crystal structure of  $\text{Rh}_2(\text{S-PTTL})_4$ , which was determined by Fox et al.,<sup>34a</sup> coupled with Doyle–Taber's mechanistic hypothesis (Scheme 5).<sup>35</sup>  $\text{Rh}_2(\text{S-PTTL})_4$  was shown to adopt a  $C_2$ -symmetric “chiral crown” conformation,<sup>4p,34,36</sup> in which the four phthalimido groups are protruded with a clockwise twisted arrangement<sup>37</sup> 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,<sup>34,37,38</sup> 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<sub>a</sub> 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



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  $\text{CH}_2\text{Cl}_2$ , 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**)<sup>22</sup> (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  $\text{NaHCO}_3$  ( $2 \times 50$  mL), water ( $2 \times 50$  mL) and brine ( $2 \times 30$  mL), and dried over  $\text{Na}_2\text{SO}_4$ . 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.89–1.94 (m, 2H,  $\text{PhCH}_2\text{CH}_2^-$ ), 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,  $\text{PhCH}_2\text{CH}_2^-$ ), 3.68 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 3.98 (s, 4H,  $\text{OCH}_2\text{CH}_2\text{O}$ ), 7.17–7.19 (m, 3H, Ar*H*), 7.28–7.29 (m, 2H, Ar*H*);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.6 ( $\text{CH}_2$ ), 29.9 ( $\text{CH}_2$ ), 32.1 ( $\text{CH}_2$ ), 39.2 ( $\text{CH}_2$ ), 51.5 ( $\text{CH}_3$ ), 65.1 ( $\text{CH}_2$ ), 110.3 (C), 125.7 (CH), 128.1 (CH), 128.3 (CH), 141.8 (C), 173.9 (C=O); ESI-HRMS  $m/z$  calcd for  $\text{C}_{15}\text{H}_{20}\text{O}_4\text{Na}$  ( $\text{M}+\text{Na}^+$ ) 287.1254, found 287.1251.

**Typical procedure for the preparation of  $\alpha$ -alkyl- $\alpha$ -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  $\text{NH}_4\text{Cl}$  (5 mL) and the whole was extracted with EtOAc ( $2 \times 10$  mL). The combined organic layers were washed with water (10 mL) and brine ( $2 \times 10$  mL), and dried over  $\text{Na}_2\text{SO}_4$ . Filtration and evaporation gave crude  $\beta$ -ketoester, which was used without further purification.

DBU (414 mg, 2.72 mmol) was added dropwise to a solution of crude  $\beta$ -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  $\text{Et}_2\text{O}$  ( $2 \times 25$  mL). The combined organic layers were washed with 10% aqueous NaOH ( $2 \times 10$  mL), water (10 mL) and brine ( $2 \times 10$  mL), and dried over  $\text{Na}_2\text{SO}_4$ . 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  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.96–2.01 (m, 2H,  $\text{PhCH}_2\text{CH}_2^-$ ), 2.64 (s, 2H, C3-*H*), 2.07–2.74 (m, 2H,  $\text{PhCH}_2\text{CH}_2^-$ ), 3.77 (s, 3H,  $\text{CO}_2\text{CH}_3$ ), 4.02 (s, 4H,  $-\text{OCH}_2\text{CH}_2\text{O}-$ ), 7.16–7.20 (m, 3H, Ar*H*), 7.28–7.30 (m, 2H, Ar*H*);  $^{13}\text{C}$  NMR (100

MHz, CDCl<sub>3</sub>)  $\delta$  29.5 (CH<sub>2</sub>), 30.4 (CH<sub>2</sub>), 38.6 (CH<sub>2</sub>), 51.7 (CH<sub>3</sub>), 52.5 (C=N<sub>2</sub>), 65.1 (CH<sub>2</sub>), 110.8 (C), 125.5 (CH), 128.0 (CH), 128.1 (CH), 141.5 (C), 167.5 (C=O); ESI-HRMS  $m/z$  calcd for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>Na (M+Na<sup>+</sup>) 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-phenylethyl)-6,7-dioxabicyclo[2.2.1]heptane-3-carboxylate (15).** Rh<sub>2</sub>(*S*-PTTL)<sub>4</sub>·2EtOAc (**4a**) (4.2 mg, 0.003 mmol, 1 mol%) was added to a solution of  $\alpha$ -alkyl- $\alpha$ -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<sub>3</sub>); IR (film) 2960, 2882, 1730, 1021 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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<sub>2</sub>CH<sub>3</sub>), 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*); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  38.9 (CH<sub>2</sub>), 40.9 (CH<sub>2</sub>), 45.9 (CH), 47.5 (CH), 60.6 (CH<sub>3</sub>), 64.0 (CH<sub>2</sub>), 64.8 (CH<sub>2</sub>), 116.7 (C), 128.23 (CH), 128.26 (CH), 128.33 (CH), 141.1 (C), 173.5 (C=O); ESI-HRMS  $m/z$  calcd for C<sub>15</sub>H<sub>18</sub>O<sub>4</sub>Na (M+Na<sup>+</sup>) 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<sub>6</sub>H<sub>6</sub>); IR (film) 2953, 1739, 1202, 702 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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<sub>2</sub>CH<sub>3</sub>), 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*); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  30.6 (CH<sub>2</sub>), 34.7 (CH<sub>2</sub>), 38.3 (CH<sub>2</sub>), 46.4 (CH), 51.3 (CH<sub>3</sub>), 67.6 (CH<sub>2</sub>), 77.5 (CH), 111.1 (C), 126.1 (CH), 128.6 (CH), 128.7 (CH), 142.2 (C), 171.4 (C=O); ESI-HRMS  $m/z$  calcd for C<sub>15</sub>H<sub>18</sub>O<sub>4</sub>Na (M+Na<sup>+</sup>) 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<sub>4</sub> (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  $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$ , 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,  $\text{Et}_2\text{O}/\text{hexane}/\text{Et}_3\text{N} = 66:33:1 \rightarrow 83:16:1$ ) 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<sub>2</sub>O);  $[\alpha]_D^{23} +41.4$  (*c* 1.09, C<sub>6</sub>H<sub>6</sub>); IR (film) 3734, 2892, 1455, 979  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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<sub>2</sub>OH), 3.30 (dd, *J* = 10.3, 6.3 Hz, 1H, CH<sub>2</sub>OH), 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*); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  30.8 (CH<sub>2</sub>), 35.1 (CH<sub>2</sub>), 39.2 (CH), 42.7 (CH<sub>2</sub>), 62.9 (CH<sub>2</sub>), 65.7 (CH<sub>2</sub>), 78.7 (CH), 110.4 (C), 126.1 (CH), 128.6 (CH), 128.7 (CH), 142.4 (C); ESI-HRMS *m/z* calcd for C<sub>14</sub>H<sub>18</sub>O<sub>3</sub>Na (M+Na<sup>+</sup>) 257.1148, found 257.1149.

4-Bromobenzoyl chloride (35.4 mg, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub> (5 mL). The organic layer was washed with water (5 mL) and brine (2 × 5 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation gave the crude product, which was purified by column chromatography (silica gel, hexane/EtOAc/Et<sub>3</sub>N = 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<sub>2</sub>O);  $[\alpha]_D^{25} +14.1$  (*c* 1.26, C<sub>6</sub>H<sub>6</sub>); IR (KBr) 3022, 2925, 1712, 1267  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (500 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  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<sub>2</sub>O<sub>2</sub>CAr), 4.13 (dd, *J* = 11.5, 6.3 Hz, 1H, CH<sub>2</sub>O<sub>2</sub>CAr), 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*); <sup>13</sup>C NMR (125 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  30.7 (CH<sub>2</sub>), 34.9 (CH<sub>2</sub>), 39.1 (CH<sub>2</sub>), 39.7 (CH), 64.9 (CH<sub>2</sub>), 65.7 (CH<sub>2</sub>), 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* calcd for C<sub>21</sub>H<sub>21</sub>BrO<sub>4</sub>Na (M+Na<sup>+</sup>) 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.<sup>29</sup>

**Methyl (7*R*,8*R*)-trans-8-phenyl-1,4-dioxaspiro[4.4]nonane-7-carboxylate (18).**<sup>30</sup> 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<sub>2</sub>O (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<sub>2</sub>SO<sub>4</sub>. Filtration and evaporation gave the crude product, which was purified by column chromatography (silica gel, toluene/EtOAc = 40:1) to provide **18**<sup>30</sup> (26.7 mg, 83%) as a colorless oil; TLC *R<sub>f</sub>* = 0.43 (3:1 hexane/EtOAc); [ $\alpha$ ]<sub>D</sub><sup>23</sup> -52.7 (*c* 1.33, CHCl<sub>3</sub>) lit.,<sup>30</sup> [ $\alpha$ ]<sub>D</sub><sup>23</sup> +38.2 (*c* 2.2, CHCl<sub>3</sub>) for the (7*S*,8*S*)-enantiomer; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  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<sub>2</sub>CH<sub>3</sub>), 3.90–4.01 (m, 4H, C2-*H*, C3-*H*), 7.20–7.33 (m, 5H, Ar*H*); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  40.8 (CH<sub>2</sub>), 44.3 (CH<sub>2</sub>), 46.4 (CH), 49.9 (CH), 51.7 (CH<sub>3</sub>), 64.4 (CH<sub>2</sub>), 64.5 (CH<sub>2</sub>), 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<sub>R</sub>* = 7.06 min for (7*R*,8*R*)-enantiomer; *t<sub>R</sub>* = 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  $\alpha$ -alkyl- $\alpha$ -diazoester, **21a** was prepared from methyl 3-(2-methyl-1,3-dioxolan-2-yl)propanoate<sup>39</sup> (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<sub>f</sub>* = 0.30 (3:1 hexane/EtOAc); IR (film) 2955, 2888, 2089, 1696, 1147, 1043 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.38 (s, 3H, *J* = 8.5, 4.8 Hz, CH<sub>3</sub>), 2.61 (s, 2H, C3-*H*), 3.77 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.93–3.99 (m, 4H, -OCH<sub>2</sub>CH<sub>2</sub>O-); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  23.2 (CH<sub>3</sub>), 31.9 (CH<sub>2</sub>), 51.6 (CH<sub>3</sub>), 52.5 (C=N<sub>2</sub>), 64.6 (CH<sub>2</sub>), 109.5 (C), 167.5 (C=O); ESI-HRMS *m/z* calcd for C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>Na (M+Na<sup>+</sup>) 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<sup>40</sup> (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<sub>f</sub>* = 0.43 (3:1 hexane/EtOAc); IR (film) 2974, 2882, 1739 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  0.91 (t, *J* = 7.6 Hz, 3H,

CH<sub>3</sub>CH<sub>2</sub>), 1.62 (q,  $J = 7.6$  Hz, 2H, CH<sub>3</sub>CH<sub>2</sub>), 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<sub>2</sub>CH<sub>3</sub>), 3.94 (s, 4H, -OCH<sub>2</sub>CH<sub>2</sub>O-); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 7.32 (CH<sub>3</sub>), 27.9 (CH<sub>3</sub>), 29.4 (CH<sub>2</sub>), 31.0 (CH<sub>2</sub>), 50.7 (CH<sub>3</sub>), 64.4 (CH<sub>2</sub>), 110.3 (C), 173.2 (C=O); APCI-HRMS  $m/z$  calcd for C<sub>9</sub>H<sub>17</sub>O<sub>4</sub> (M+H<sup>+</sup>) 189.1121, found 189.1124.

According to the typical procedure for the preparation of  $\alpha$ -alkyl- $\alpha$ -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<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 0.94 (t,  $J = 7.5$  Hz, 3H, CH<sub>3</sub>CH<sub>2</sub>-), 1.69 (q,  $J = 7.5$  Hz, 2H, CH<sub>3</sub>CH<sub>2</sub>-), 2.58 (s, 2H, C3-*H*), 3.77 (s, 3H, CO<sub>2</sub>CH<sub>3</sub>), 3.97 (m, 4H, -OCH<sub>2</sub>CH<sub>2</sub>O-); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 7.43 (CH<sub>3</sub>), 29.5 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 51.6 (CH<sub>3</sub>), 52.5 (C=N<sub>2</sub>), 65.1 (CH<sub>2</sub>), 111.5 (C), 167.6 (C=O); ESI-HRMS  $m/z$  calcd for C<sub>9</sub>H<sub>14</sub>N<sub>2</sub>O<sub>4</sub>Na (M+Na<sup>+</sup>) 237.0846, found 237.0846.

**Enantioselective intramolecular C–H insertion reaction of  $\alpha$ -alkyl- $\alpha$ -diazoester (21a).** (**1S\***,**3S\***,**4R\***)-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<sub>2</sub>(*S*-PTTL)<sub>4</sub>·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); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 1.51 (s, 3H, C1-CH<sub>3</sub>), 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<sub>2</sub>CH<sub>3</sub>), 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<sub>4</sub> (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<sub>2</sub>O/hexane/Et<sub>3</sub>N = 66:33:1) provided [(**1S\***,**3R\***,**4R\***)-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<sub>2</sub>O); [ $\alpha$ ]<sub>D</sub><sup>25</sup> +38.1 (*c* 1.01, acetone); IR (film) 3267, 2934 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, acetone-*d*<sub>6</sub>) δ 1.31 (dd,  $J = 12.0, 5.5$  Hz, 1H, C2-*H*), 1.46 (s, 3H, C1-CH<sub>3</sub>), 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<sub>2</sub>OH), 3.73–3.77 (m, 2H, CH<sub>2</sub>OH), 3.91 (d,  $J = 7.1$  Hz, 1H, C5-*H*), 4.05 (dd,  $J = 4.0, 3.6$  Hz, 1H, C4-*H*); <sup>13</sup>C NMR (125 MHz, acetone-*d*<sub>6</sub>) δ 18.9 (CH<sub>3</sub>), 40.9 (CH<sub>2</sub>), 44.0 (CH), 62.9 (CH<sub>2</sub>), 65.9 (CH<sub>2</sub>), 79.6 (CH), 109.1 (C); APCI-HRMS  $m/z$  calcd for C<sub>7</sub>H<sub>13</sub>O<sub>3</sub> (M+H<sup>+</sup>) 145.0859, found 145.0860.

Benzoyl chloride (33.7 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>N = 83:16:1) provided [(1*S*\*,3*R*\*,4*R*\*)-1-methyl-6,7-dioxabicyclo[2.2.1]heptan-3-yl]methyl benzoate as a colorless oil; TLC *R*<sub>f</sub> = 0.18 (4:1 hexane/EtOAc); [α]<sub>D</sub><sup>23</sup> +23.0 (*c* 1.05, acetone); IR (film) 2951, 2894, 1716, 1271 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 1.52 (s, 3H, C1-CH<sub>3</sub>), 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<sub>2</sub>OBz), 4.55 (dd, *J* = 11.3, 6.5 Hz, 1H, CH<sub>2</sub>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*); <sup>13</sup>C NMR (125 MHz, acetone-*d*<sub>6</sub>) δ 18.8 (CH<sub>3</sub>), 40.7 (CH), 40.8 (CH<sub>2</sub>), 65.4 (CH<sub>2</sub>), 66.1 (CH<sub>2</sub>), 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* calcd for C<sub>14</sub>H<sub>16</sub>O<sub>4</sub>Na (M+Na<sup>+</sup>) 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*<sub>R</sub> = 15.54 min for minor enantiomer; *t*<sub>R</sub> = 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<sub>2</sub>(S-PTTL)<sub>4</sub>·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); <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>) δ 0.98 (t, *J* = 7.2 Hz, 3H, C1-CH<sub>2</sub>CH<sub>3</sub>), 1.84 (q, *J* = 7.2 Hz, 2H, C1-CH<sub>2</sub>CH<sub>3</sub>), 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<sub>2</sub>CH<sub>3</sub>), 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<sub>4</sub> (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<sub>2</sub>O/hexane/Et<sub>3</sub>N = 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*<sub>f</sub> = 0.15 (2:1 Et<sub>2</sub>O/hexane); [α]<sub>D</sub><sup>24</sup> +41.1 (*c* 1.32, acetone); IR (film) 3398, 2923 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, acetone-*d*<sub>6</sub>) δ 1.31 (dd, *J* = 12.0, 5.5 Hz, 1H, C2-*H*), 1.46 (s, 3H,

C1-CH<sub>3</sub>), 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<sub>2</sub>OH), 3.73–3.77 (m, 2H, CH<sub>2</sub>OH), 3.91 (d,  $J = 7.1$  Hz, 1H, C5-*H*), 4.05 (dd,  $J = 4.0, 3.6$  Hz, 1H, C4-*H*); <sup>13</sup>C NMR (100 MHz, acetone-*d*<sub>6</sub>)  $\delta$  8.66 (CH<sub>3</sub>), 26.4 (CH<sub>2</sub>), 38.9 (CH<sub>2</sub>), 43.6 (CH), 63.0 (CH<sub>2</sub>), 65.9 (CH<sub>2</sub>), 79.3 (CH), 111.4 (C); APCI-HRMS  $m/z$  calcd for C<sub>8</sub>H<sub>15</sub>O<sub>3</sub> (M+H<sup>+</sup>) 151.1016, found 151.1017.

Benzoyl chloride (33.7 mg, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (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<sub>2</sub>Cl<sub>2</sub> (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<sub>3</sub>N = 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<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, acetone-*d*<sub>6</sub>)  $\delta$  1.52 (s, 3H, C1-CH<sub>3</sub>), 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<sub>2</sub>OBz), 4.55 (dd,  $J = 11.3, 6.5$  Hz, 1H, CH<sub>2</sub>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*); <sup>13</sup>C NMR (125 MHz, acetone-*d*<sub>6</sub>)  $\delta$  18.8 (CH<sub>3</sub>), 40.7 (CH), 40.8 (CH<sub>2</sub>), 65.4 (CH<sub>2</sub>), 66.1 (CH<sub>2</sub>), 79.2 (CH), 109.3 (C), 129.3 (CH), 130.2 (CH), 131.0 (C), 133.9 (CH), 166.5 (C=O); ESI-HRMS  $m/z$  calcd for C<sub>14</sub>H<sub>16</sub>O<sub>4</sub>Na (M+Na<sup>+</sup>) 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.

## ACKNOWLEDGEMENTS

This research was supported in part by a Grant-in-Aid from the Ministry of Education, Science, Sports and Culture, Japan, JSPS KAKENHI Grant Number JP15H05802 in Precisely Designed Catalysts with Customized Scaffolding (for S.M.), the Akiyama Life Science Foundation (for M.A.), and Takeda Science Foundation (for M.A.). We thank S. Oka, M. Kiuchi and T. Hirose of the Instrumental Analysis Division, Global Facility Center at Hokkaido University for MS measurements.

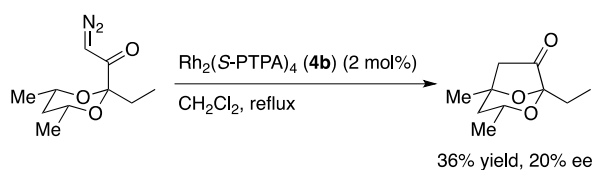
## REFERENCES AND NOTES

1. For recent books and reviews, see: (a) '*Comprehensive Asymmetric Catalysis*,' ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer, Berlin, 1999; (b) M. Shibasaki, M. Kanai, S. Matsunaga, and N. Kumagai, *Acc. Chem. Res.*, 2009, **42**, 1117; (c) '*Catalytic Asymmetric Synthesis*,' ed. by I. Ojima, John Wiley & Sons, Hoboken, 2010; (d) E. J. Corey and L. Kürti, 'Enantioselective Chemical

- Synthesis,' Direct Book Publishing, Dallas, 2010; (e) N. Kumagai, M. Kanai, and H. Sasai, [ACS Catal.](#), 2016, **6**, 4699.
- For the theoretical study of an exceptional reactivity of a dirhodium carbene complex generated from a diazo compound with a dirhodium(II) tetracarboxylate complex, see: (a) S. M. Sheehan, A. Padwa, and J. P. Snyder, [Tetrahedron Lett.](#), 1998, **39**, 949; (b) E. Nakamura, N. Yoshikai, and M. Yamanaka, [J. Am. Chem. Soc.](#), 2002, **124**, 7181; (c) J. F. Berry, [Dalton Trans.](#), 2012, **41**, 700.
  - For characterization of a reactive dirhodium carbene complex, see: (a) K. P. Kornecki, J. F. Briones, V. Boyarskikh, F. Fullilove, J. Autschbach, K. E. Schrote, K. M. Lancaster, H. M. L. Davies, and J. F. Berry, [Science](#), 2013, **342**, 351; (b) C. Werlé, R. Goddard, and A. Fürstner, [Angew. Chem. Int. Ed.](#), 2015, **54**, 15452; (c) C. Werlé, R. Goddard, P. Philipps, C. Farés, and A. Fürstner, [J. Am. Chem. Soc.](#), 2016, **138**, 3797.
  - For books and reviews, see: (a) M. P. Doyle, M. A. McKervey, and T. Ye, 'Modern Catalytic Methods for Organic Synthesis with Diazo Compounds,' Wiley-Interscience, New York, 1998; (b) M. P. Doyle and D. C. Forbes, [Chem. Rev.](#), 1998, **98**, 911; (c) H. M. L. Davies and R. E. J. Beckwith, [Chem. Rev.](#), 2003, **103**, 2861; (d) P. M. P. Gois and C. A. M. Afonso, [Eur. J. Org. Chem.](#), 2004, 3773; (e) H. M. L. Davies and J. R. Manning, [Nature](#), 2008, **451**, 417; (f) Z. Zhang and J. Wang, [Tetrahedron](#), 2008, **64**, 6577; (g) H. M. L. Davies and J. R. Denton, [Chem. Soc. Rev.](#), 2009, **38**, 3061; (h) H. M. L. Davies and J. Hansen, 'Catalytic Asymmetric Synthesis,' ed. by I. Ojima, John Wiley & Sons, Hoboken, 2010, Chapter 4; (i) C. N. Slattery, A. Ford, and A. R. Maguire, [Tetrahedron](#), 2010, **66**, 6681; (j) M. P. Doyle, R. Duffy, M. Ratnikov, and L. Zhou, [Chem. Rev.](#), 2010, **110**, 704; (k) M. P. Doyle, M. Ratnikov, and Y. Liu, [Org. Biomol. Chem.](#), 2011, **9**, 4007; (l) H. M. L. Davies and D. Morton, [Chem. Soc. Rev.](#), 2011, **40**, 1857; (m) M. P. Doyle, Y. Liu, and M. Ratnikov, [Org. React.](#), 2013, **80**, 1; (n) C. Zheng and S.-L. You, [RSC Adv.](#), 2014, **4**, 6173; (o) A. Ford, H. Miel, A. Ring, C. N. Slattery, A. R. Maguire, and M. A. McKervey, [Chem. Rev.](#), 2015, **115**, 9981; (p) A. DeAngelis, R. Panish, and J. M. Fox, [Acc. Chem. Res.](#), 2016, **49**, 115.
  - (a) M. P. Doyle, A. van Oeveren, L. J. Westrum, M. N. Protopopova, and T. W. Clayton, Jr., [J. Am. Chem. Soc.](#), 1991, **113**, 8982; (b) M. P. Doyle, A. B. Dyatkin, G. H. P. Roos, F. Cañas, D. A. Pierson, A. van Basten, P. Müller, and P. Polleux, [J. Am. Chem. Soc.](#), 1994, **116**, 4507; (c) M. P. Doyle, W. Hu, and M. V. Valenzuela, [J. Org. Chem.](#), 2002, **67**, 2954; (d) M. P. Doyle, [J. Org. Chem.](#), 2006, **71**, 9253 and references cited therein.
  - H. M. L. Davies and T. Hansen, [J. Am. Chem. Soc.](#), 1997, **119**, 9075; (b) H. M. L. Davies, Q. Jin, P. Ren, and A. Y. Kovalevsky, [J. Org. Chem.](#), 2002, **67**, 4165; (c) H. M. L. Davies, R. E. J. Beckwith, E. G. Antoulinakis, and Q. Jin, [J. Org. Chem.](#), 2003, **68**, 6126; (d) K. M. Chepiga, Y. Feng, N. A. Brunelli, C. W. Jones, and H. M. L. Davies, [Org. Lett.](#), 2013, **15**, 6136 and references cited therein.

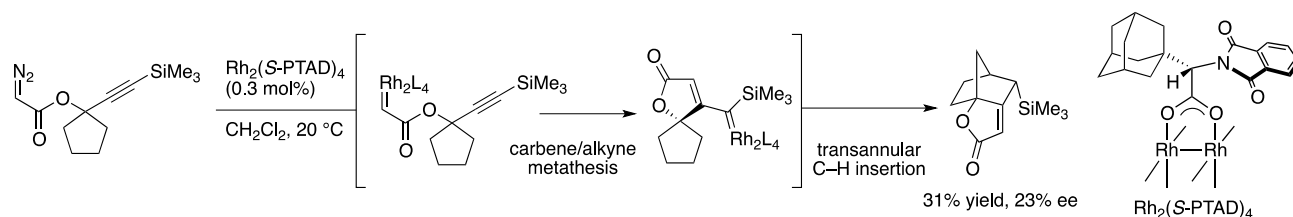
7. (a) C. Qin, V. Boyarskikh, J. H. Hansen, K. I. Hardcastle, D. G. Musaev, and H. M. L. Davies, *J. Am. Chem. Soc.*, 2011, **133**, 19198; (b) C. Qin and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 9792; (c) D. M. Guptill and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 17718; (d) K. Liao, S. Negretti, D. G. Musaev, J. Basca, and H. M. L. Davies, *Nature*, 2016, **533**, 230.
8. (a) S. Hashimoto, N. Watanabe, T. Sato, M. Shiro, and S. Ikegami, *Tetrahedron Lett.*, 1993, **34**, 5109; (b) T. Takahashi, H. Tsutsui, M. Tamura, S. Kitagaki, M. Nakajima, and S. Hashimoto, *Chem. Commun.*, 2001, 1604.
9. (a) M. Anada and S. Hashimoto, *Tetrahedron Lett.*, 1998, **39**, 79; (b) M. Anada, N. Watanabe, and S. Hashimoto, *Chem. Commun.*, 1998, 1517.
10. (a) H. Saito, H. Oishi, S. Kitagaki, S. Nakamura, M. Anada, and S. Hashimoto, *Org. Lett.*, 2002, **4**, 3887; (b) Y. Natori, H. Tsutsui, N. Sato, S. Nakamura, H. Nambu, M. Shiro, and S. Hashimoto, *J. Org. Chem.*, 2009, **74**, 4418; (c) M. Ito, R. Namie, J. Krishnamurthi, H. Miyamae, K. Takeda, H. Nambu, and S. Hashimoto, *Synlett*, 2014, **25**, 288.
11. Y. Natori, M. Ito, M. Anada, H. Nambu, and S. Hashimoto, *Tetrahedron Lett.*, 2015, **56**, 4324.
12. For a practical synthesis of  $\text{Rh}_2(\text{S-PTTL})_4$ , see: H. Tsutsui, T. Abe, S. Nakamura, M. Anada, and S. Hashimoto, *Chem. Pharm. Bull.*, 2005, **53**, 1366.
13. For the effective use of an immobilized catalyst based on  $\text{Rh}_2(\text{S-PTTL})_4$ , see: K. Takeda, T. Oohara, M. Anada, H. Nambu, and S. Hashimoto, *Angew. Chem. Int. Ed.*, 2010, **49**, 6979.
14. Davies et al. reported that dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-1-adamantylglycinate],  $\text{Rh}_2(\text{S-PTAD})_4$ , is a highly effective catalyst for intra- and intermolecular C–H insertion reactions: (a) R. P. Reddy, G. H. Lee, and H. M. L. Davies, *Org. Lett.*, 2006, **8**, 3437; (b) J. R. Denton and H. M. L. Davies, *Org. Lett.*, 2009, **11**, 787; (c) D. L. Ventura, Z. Li, M. G. Coleman, and H. M. L. Davies, *Tetrahedron*, 2009, **65**, 3052; (d) C. Soldi, K. N. Lamb, R. A. Aquitieri, M. González-López, M. J. Di Maso, and J. T. Shaw, *J. Am. Chem. Soc.*, 2014, **136**, 15142.
15. K. Minami, H. Saito, H. Tsutsui, H. Nambu, M. Anada, and S. Hashimoto, *Adv. Synth. Catal.*, 2005, **347**, 1483.
16. (a) N. Ikota, N. Takamura, S. D. Young, and B. Ganem, *Tetrahedron Lett.*, 1981, **22**, 4163; (b) D. F. Taber, M. J. Hennessy, and J. P. Louey, *J. Org. Chem.*, 1992, **57**, 436; (c) D. F. Taber, R. J. Herr, S. K. Pack, and J. M. Geremia, *J. Org. Chem.*, 1996, **61**, 2908; (d) C. F. Garcia, M. A. McKerverey, and T. Ye, *Chem. Commun.*, 1996, 1465; (e) D. F. Taber and P. V. Joshi, *J. Org. Chem.*, 2004, **69**, 4276; (f) W. Shi, F. Xiao, and J. Wang, *J. Org. Chem.*, 2005, **70**, 4318.
17. Fox et al. have demonstrated that a low reaction temperature (–78 °C) and the use of sterically demanding carboxylate ligands are key to the success of a number of intermolecular dirhodium(II)-catalyzed transformations of  $\alpha$ -alkyl- $\alpha$ -diazoesters and to the dramatic suppression of

- $\beta$ -hydride migration: (a) P. Panne and J. M. Fox, *J. Am. Chem. Soc.*, 2007, **129**, 22; (b) P. Panne, A. DeAngelis, and J. M. Fox, *Org. Lett.*, 2008, **10**, 2987; (c) A. DeAngelis, P. Panne, G. P. A. Yap, and J. M. Fox, *J. Org. Chem.*, 2008, **73**, 1435; (d) A. DeAngelis, V. W. Shurtleff, O. Dmitrenko, and J. M. Fox, *J. Am. Chem. Soc.*, 2011, **133**, 1650; (e) A. DeAngelis, O. Dmitrenko, and J. M. Fox, *J. Am. Chem. Soc.*, 2011, **135**, 9283; (f) A. DeAngelis, O. Dmitrenko, and J. M. Fox, *J. Am. Chem. Soc.*, 2012, **134**, 11035.
18. T. Miyazawa, K. Minami, M. Ito, M. Anada, S. Matsunaga, and S. Hashimoto, *Tetrahedron*, 2016, **72**, 3939.
19. For  $\text{Rh}_2(\text{S-PTTL})_4$ -catalyzed intramolecular 1,6-C–H insertion of 5-alkoxy-2-diazopentanoate, see: M. Ito, Y. Kondo, H. Nambu, M. Anada, K. Takeda, and S. Hashimoto, *Tetrahedron Lett.*, 2015, **56**, 1397.
20. For  $\text{Rh}_2(\text{S-PTTL})_4$ -catalyzed intermolecular C–H insertion with  $\alpha$ -alkyl- $\alpha$ -diazoesters, see: T. Goto, T. Onozuka, Y. Kosaka, M. Anada, K. Takeda, and S. Hashimoto, *Heterocycles*, 2012, **86**, 1647.
21. (a) T. Goto, K. Takeda, N. Shimada, H. Nambu, M. Anada, M. Shiro, K. Ando, and S. Hashimoto, *Angew. Chem. Int. Ed.*, 2011, **50**, 6803; (b) T. Goto, K. Takeda, M. Anada, K. Ando, and S. Hashimoto, *Tetrahedron Lett.*, 2011, **52**, 4200; (c) T. Goto, Y. Natori, K. Takeda, H. Nambu, and S. Hashimoto, *Tetrahedron: Asymmetry*, 2011, **22**, 907.
22. C. G. Overberger, J. Reichenthal, and J.-P. Anselme, *J. Org. Chem.*, 1970, **35**, 138.
23. (a) D. F. Taber, K. You, and Y. Song, *J. Org. Chem.*, 1995, **60**, 1093; (b) D. F. Taber, R. B. Sheth, and P. V. Joshi, *J. Org. Chem.*, 2005, **70**, 2851.
24. (a) J. Adams, M.-A. Poupart, L. Grenier, C. Schaller, N. Ouimet, and R. Frenette, *Tetrahedron Lett.*, 1989, **30**, 1749; (b) P. Wang and J. Adams, *J. Am. Chem. Soc.*, 1994, **116**, 3296.
25. H. M. L. Davies and J. Yang, *Adv. Synth. Catal.*, 2003, **345**, 1133.
26. Wardrop et al. have demonstrated the first enantioselective construction of a bridged bicyclic ring system via intramolecular C–H insertion of  $\sigma$ -symmetric  $\alpha$ -diazoketone derived from *meso*-2,3-pentanediol, in which up to 20% ee was observed with the use of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-phenylalaninate],  $\text{Rh}_2(\text{S-PTPA})_4$ : (a) D. J. Wardrop and R. E. Forslund, *Tetrahedron Lett.*, 2002, **43**, 737; (b) D. J. Wardrop, R. E. Forslund, C. L. Landrie, A. I. Velter, D. Wink, and B. Surve, *Tetrahedron: Asymmetry*, 2003, **14**, 929.

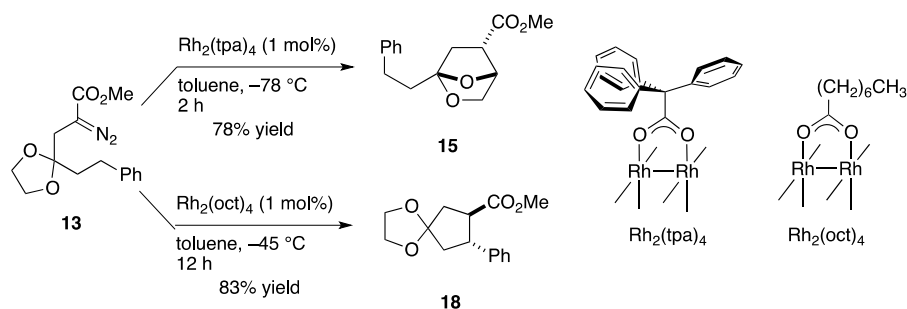


27. May et al. have developed an enantioselective carbene formation-alkyne methathesis-transannular C–H insertion cascade reaction from  $\sigma$ -symmetric alkynyl diazoacetate to give a bridged tricyclic

product, in which up to 23% ee was observed with the use of  $\text{Rh}_2(\text{S-PTAD})_4$ <sup>14</sup>: S. Jansone-Popova, P. Q. Le, and J. A. May, *Tetrahedron*, 2014, **70**, 4118.



28. D. F. Taber and Y. Song, *J. Org. Chem.*, 1996, **61**, 6706.
29. The crystal structure of **20** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 1495451 has been allocated.
30. W. Zhang, A. S. Matla, and D. Romo, *Org. Lett.*, 2007, **9**, 2111.
31. The results for the C–H insertion of **13** catalyzed by other dirhodium(II) carboxylates (1 mol%) in toluene at  $-78\text{ }^\circ\text{C}$  are follows:  $\text{Rh}_2(\text{S-PTA})_4$  (**4c**): 6 h, 95% combined yield of **14**, **18**, and **15**, **14:18:15** = 29 (96% ee): 10 (15% ee): 61 (89% ee);  $\text{Rh}_2(\text{S-PTV})_4$  (**4d**): 4 h, 94% combined yield of **14**, **18**, and **15**, **14:18:15** = 26 (94% ee): 21 (19% ee): 53 (90% ee).
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),  $\text{Rh}_2(\text{tpa})_4$ ,<sup>33</sup> with an exceptionally bulky ligand in toluene at  $-78\text{ }^\circ\text{C}$  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,  $\text{Rh}_2(\text{oct})_4$ , under the same conditions gave exclusively a *trans*-cyclopentane product (**18**) in 83% yield.



33. (a) S. Hashimoto, N. Watanabe, and S. Ikegami, *Tetrahedron Lett.*, 1992, **33**, 2709; (b) S. Hashimoto, N. Watanabe, and S. Ikegami, *J. Chem. Soc., Chem. Commun.*, 1992, 1508.
34. (a) A. DeAngelis, O. Dmitrenko, G. P. A. Yap, and J. M. Fox, *J. Am. Chem. Soc.*, 2009, **131**, 7230; (b) A. DeAngelis, D. T. Boruta, J.-B. Lubin, J. N. Plampin, III, G. P. A. Yap, and J. M. Fox, *Chem. Commun.*, 2010, **46**, 4541; (c) D. T. Boruta, O. Dmitrenko, G. P. A. Yap, and J. M. Fox, *Chem. Sci.*, 2012, **3**, 1589; (d) Ref. 17e; (e) R. A. Panish, S. R. Chintala, and J. M. Fox, *Angew. Chem. Int. Ed.*, 2016, **55**, 4983.
35. (a) M. P. Doyle, L. J. Westrum, W. N. E. Wolthuis, M. M. See, W. P. Boone, V. Bagheri, and M. M.

- Pearson, *J. Am. Chem. Soc.*, 1993, **115**, 958; (b) D. F. Taber, K. K. You, and A. L. Rheingold, *J. Am. Chem. Soc.*, 1996, **118**, 547; For a mechanism of dirhodium(II) carboxylate-catalyzed C–H insertion reaction based on DFT calculations: (c) Ref. 2b; (d) N. Yoshikai and E. Nakamura, *Adv. Synth. Catal.*, 2003, **345**, 1159; (e) J. Hansen, J. Autschbach, and H. M. L. Davies, *J. Org. Chem.*, 2009, **74**, 6555.
36. (a) V. N. G. Lindsay, W. Lin, and A. B. Charette, *J. Am. Chem. Soc.*, 2009, **131**, 16383; (b) V. N. G. Lindsay and A. B. Charette, *ACS Catal.*, 2012, **2**, 1221.
37. (a) A. Ghanem, M. G. Gardiner, R. M. Williamson, and P. Müller, *Chem. Eur. J.*, 2010, **16**, 3291; (b) F. G. Adly, M. G. Gardiner, and A. Ghanem, *Chem. Eur. J.*, 2016, **22**, 3447.
38. C. Werlé, R. Goddard, P. Phillips, C. Farés, and A. Fürstner, *Angew. Chem. Int. Ed.*, 2016, **55**, 10760.
39. A. Hernández, M. Marcos, and H. Rapoport, *J. Org. Chem.*, 1995, **60**, 2683.
40. A. J. Yu and A. R. Day, *J. Org. Chem.*, 1958, **23**, 1004.