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Dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate]: an exceptionally effective Rh(II) catalyst for enantiotopically selective aromatic C–H insertions of diazo ketoesters

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Abstract—Dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate], Rh_2[(*S*)-TFPTTL]$_4$, in which the phthalimido hydrogen atoms of the parent dirhodium(II) complex are substituted by fluorine atoms, dramatically enhances the reactivity and enantioselectivity (up to 97% ee) in intramolecular aromatic C–H insertion reactions of methyl 4-alkyl-2-diazo-4,4-diphenyl-3-oxopropionates. Catalysis with the use of 0.001 mol% of Rh_2[(*S*)-TFPTTL]$_4$ has achieved the highest turnover number (up to 98,000 with the methyl substituent) ever recorded for chiral dirhodium(II) complex-catalyzed carbene transformations, without compromising the yield or enantioselectivity of the process.

Transition metal complexes are known to catalyze a broad spectrum of diazo carbonyl compound transformations and the advantages of using dirhodium(II) carboxylate catalysts are well documented: The diazo decomposition occurs under much milder conditions and produces higher yields for many processes based on metal carbene species than are possible with other catalysts.[1] Therefore, it is not surprising that a great deal of effort continues to be devoted to the design, synthesis, and evaluation of chiral dirhodium(II) carboxylate catalysts, which allows highly enantioselective carbocyclic and heterocyclic systems to be constructed.[2] Doyle pioneered chiral dirhodium(II) carboxamidate catalysts with a rigid framework, which include Rh_2[(5*S*)-MEPY]$_4$ **1a**, Rh_2[(4*S*)-MEOX]$_4$ **1b**, and Rh_2[(4*S*)-MPPIM]$_4$ **1c**. These catalysts can place a chiral center in close proximity to the rhodium(II) carbene center,[3] but chiral dirhodium(II) carboxylate catalysts seem ineffective at creating an asymmetric environment around the rhodium(II) carbene center because of the conformational flexibility of the carboxylate ligand. The McKervey[4] and Davies[5] groups recently developed Rh_2[(*S*)-BSP]$_4$ **2a** and Rh_2[(*S*)-DOSP]$_4$ **2b**, chiral dirhodium(II) carboxylate catalysts that incorporate *N*-benzenesulfonyl derivatives of (*S*)-proline as bridging ligands, respectively. McKervey's Rh_2[(*S*)-BSP]$_4$ exhibits high levels of enantioselectivity with limited substrates,[4] but Davies' Rh_2[(*S*)-DOSP]$_4$ is an exceptionally effective catalyst for a wide variety of enantioselective intermolecular C–H insertions[6] and cyclopropanations,[7] a major breakthrough in this field. Our efforts led to the development of dirhodium(II) carboxylate catalysts such as Rh_2[(*S*)-PTA]$_4$ **3a** and Rh_2[(*S*)-PTTL]$_4$ **3d**, which incorporate *N*-phthaloyl-(*S*)-amino acids as bridging ligands.[8–12] These catalysts mediate intramolecular C–H insertions of a structurally diverse array of diazo carbonyl compounds,[8] intermolecular Si–H insertions,[9] intermolecular 1,3-dipolar cycloadditions via the generation of an ester–carbonyl ylide,[10] and [2,3]-sigmatropic rearrangements via the intramolecular formation of allylic or propargylic oxonium ylides[11] with a maximum of 98, 74, 93 and 79% ee, respectively. These catalysts contain two phthalimido groups in a pair of adjoining ligands, which are oriented to an axial coordination site of each octahedral rhodium centre. Although the effects of the amino acid alkyl substituents on the enantioselectivity have yet to be established, it is believed that the two phthalimido groups play a pivotal role as enantiocontrollers. In this respect, by devising dirhodium(II) carboxylate catalysts such as Rh_2[(*S*)-BPTV]$_4$ **4a** and Rh_2[(*S*)-BPTTL]$_4$ **4b** we have remarkably enhanced the enantioselectivity (typically 59 to 90% ee) in tandem formation and intermolecular 1,3-dipolar cycloaddition of keto-carbonyl

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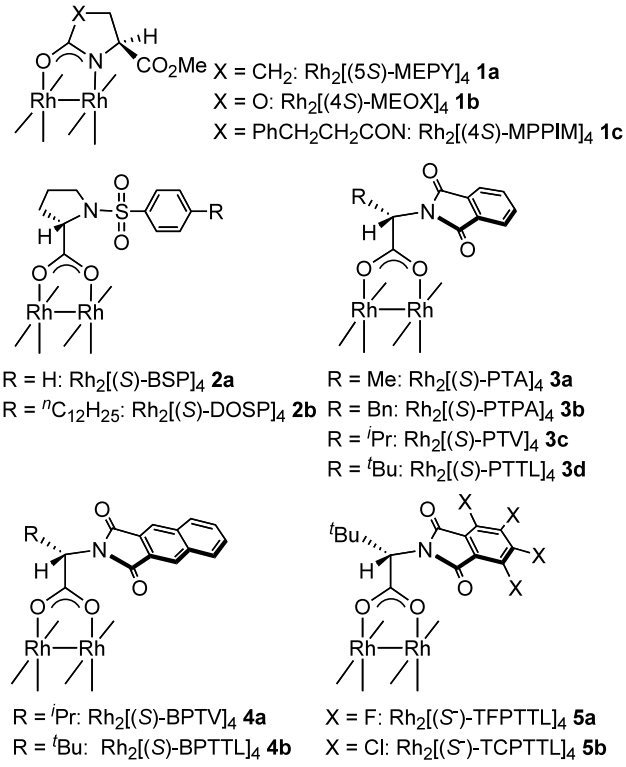
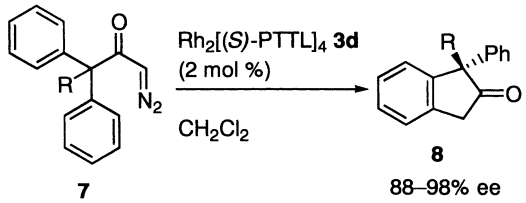
ylides. Rh_2[(*S*)-BPTV]$_4$ and Rh_2[(*S*)-BPTTL]$_4$ are characterized by an extension of the phthalimido group with an additional benzene ring.[12] Continuing our work on improving the catalytic performance by modifying the sterics and electronics of the phthalimido wall, we found that using *N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate as the bridging ligands greatly enhances the catalyst turnover number (up to 98,000) and enantioselectivity (up to 97% ee) in intramolecular aromatic C–H insertion reactions of methyl 4-alkyl-2-diazo-4,4-diphenyl-3-oxopropionates **6**.



It was recently demonstrated that modifying ligands with electron-donating[13] or electron-withdrawing[14] substituents at certain positions could greatly impact the rate and enantioselectivity of catalytic asymmetric reactions. Based on the general finding that dirhodium(II) catalysts with strongly electron-withdrawing carboxylate ligands show remarkably high reactivity towards diazo carbonyl compounds,[15] we envisaged that developing dirhodium(II) carboxylates that substitute halogen atoms for the phthalimido hydrogen atoms could facilitate the formation and ensuing transformation of the intermediate rhodium(II) carbene.[16] The enhanced reactivity should lower the reaction temperature, thereby leading to higher enantioselectivity. To test the feasibility of this approach, a new class of dirhodium (II) carboxylates, Rh_2[(*S*)-TFPTTL]$_4$ **5a** and Rh_2[(*S*)-TCPTTL]$_4$ **5b**[17] were prepared from $Rh_2(OAc)_4$ by ligand exchange reaction[18] with *N*-tetrafluorophthaloyl- and *N*-tetrachlorophthaloyl-(*S*)-*tert*-leucines, respectively. Their utility was examined through intramolecular aromatic C–H insertion reactions of methyl 4-alkyl-2-diazo-4,4-diphenyl-3-oxopropionates **6**.[19] Aromatic C–H insertion reactions of diazo carbonyl compounds are thought to proceed via an electrophilic attack of the rhodium(II) carbene carbon on the aromatic ring followed by a 1,2-hydride shift with a concurrent dissociation of the rhodium(II) catalyst and subsequent aromatization rather than via a direct C–H insertion mechanism.[8b,15,20] Therefore, the electrophilicity of a rhodium(II) carbene carbon is the principal influence on this process. We previously reported that Rh_2[(*S*)-PTTL]$_4$ **3d** mediates aromatic C–H insertion of 3-alkyl-1-diazo-3,3-diphenyl-2-propanones **7** to yield (*S*)-1-alkyl-1-phenyl-2-indanones **8** containing a chiral quaternary carbon atom in up to 98% ee (Eq. (1)).[8c] The use of the substituents such as methyl, propyl, and allyl groups resulted in high enantioselectivities (88–90% ee), but an exceedingly high order of differentiation of enantiotopic benzene rings was observed with **7b**, which bears an ethyl substituent at C-3. These results provide a strong incentive to enhance the enantioselectivity in a general sense.

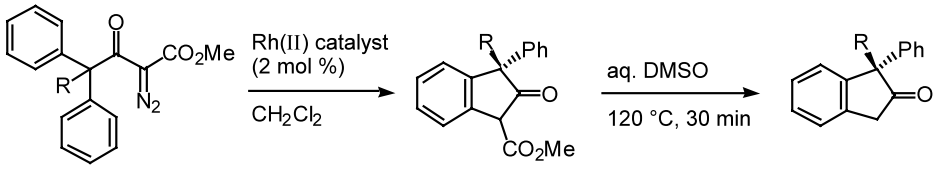


(1)

a: R = Me, **b**: R = Et, **c**: R = allyl, **d**: R = ^{n}Pr

At the onset, the aromatic C–H insertion reactions of diazo ketoester **6a** in dichloromethane at 0°C in the presence of 2 mol% of Rh_2[(*S*)-PTTL]$_4$ **3d**, Rh_2[(*S*)-TFPTTL]$_4$ **5a** and Rh_2[(*S*)-TCPTTL]$_4$ **5b** was explored (Table 1).[21] The reactions with the halogenated catalysts **5a** and **5b** proceeded to completion within 5 min, which was much faster than expected and resulted in a high yield of the cyclic ketoester **9a**. In contrast, the parent catalyst **3d** required longer reaction times (1 h). The sense and extent of differentiation between enantiotopic benzene rings were determined by demethoxycarbonylation of **9a** to the known (*S*)-(−)-1-methyl-1-phenyl-2-indanone **8a**.[8b] While a uniform sense of the enantiotopic selection was observed in all cases, the fluorinated catalyst **5a** exhibited the highest enantioselectivity of 97% ee (entry 2). Catalysts **3d** and **5b** showed little variation in enantioselectivity (92% ee versus 91% ee, entry 1 versus 3). These results strongly suggest that both catalysts **5a** and **5b** can create an asymmetric environment similar to **3d**. Lowering the reaction temperature to −10°C had little impact on the enantioselectivity, but produced a marked decrease in product yield (entries 4 and 5). Catalysis with **5a** was faster than using **5b**. These results also suggest that the minimal steric influence of the fluorine substituent coupled with its powerful electron-withdrawing effect is crucial for enhancement of the reactivity and enantioselectivity of this aromatic C–H insertion process. The utility of Rh_2[(*S*)-TFPTTL]$_4$ was extended to diazo ketoesters **6b** and **c**, which have ethyl and allyl substituents at C-3, respectively. Here again, a shorter reaction time and higher enantioselectivities were observed in each series (entries 6 versus 7 and 8 versus 9).

Table 1. Enantiotopically selective intramolecular aromatic C–H insertion reaction of diazo ketoester **6** catalyzed by chiral Rh(II) complexes[a]



6a-c **9a-c** **8a-c**

Entry	Substrate		Rh(II) complex	Temp. (°C)	Time	Ketoester **9**	(*S*)-2-Indanone **8**		
	R					Yield (%)[b]	Yield (%)[b]	$[\alpha]_D$ (*c*, $CHCl_3$)	Ee (%)
1	**6a**	Me	Rh_2[(*S*)-PTTL]$_4$ **3d**	0	1 h	89	96	−52.8 (1.12)	92[c]
2	**6a**	Me	Rh_2[(*S*)-TFPTTL]$_4$ **5a**	0	2 min	90	96	−56.3 (1.26)	97[c]
3	**6a**	Me	Rh_2[(*S*)-TCPTTL]$_4$ **5b**	0	5 min	87	97	−53.8 (1.27)	91[c]
4	**6a**	Me	Rh_2[(*S*)-TFPTTL]$_4$ **5a**	−10	20 min	70	97	−57.5 (1.24)	98[c]
5	**6a**	Me	Rh_2[(*S*)-TCPTTL]$_4$ **5b**	−10	1 h	64	94	−54.8 (1.30)	93[c]
6	**6b**	Et	Rh_2[(*S*)-PTTL]$_4$ **3d**	0	2 h	98	94	−90.2 (1.07)	96[d]
7	**6b**	Et	Rh_2[(*S*)-TFPTTL]$_4$ **5a**	0	10 min	94	98	−92.1 (1.07)	97[d]
8	**6c**	Allyl	Rh_2[(*S*)-PTTL]$_4$ **3d**	0	3 days	76	97	−69.6 (1.25)	93[e]
9	**6c**	Allyl	Rh_2[(*S*)-TFPTTL]$_4$ **5a**	0	9 h	69	94	−74.1 (1.31)	97[e]

[a] The following is a representative procedure (entry 2): Rh_2[(*S*)-TFPTTL]$_4$·2EtOAc (10.2 mg, 0.006 mmol, 2 mol%) was added in one portion to a solution of diazo ketoester **6a** (92.5 mg, 0.3 mmol) in CH_2Cl_2 (1.5 mL) at 0°C. The mixture was concentrated in vacuo and chromatographed on silica gel to afford **9a** (75.4 mg, 90%). A solution of **9a** (70 mg, 0.25 mmol) in 90% aqueous DMSO (1.5 mL) was heated at 120°C for 30 min. Standard workup followed by chromatography provided **8a** (53.8 mg, 97%).

[b] Isolated yield.

[c] Determined by HPLC [column, Daicel Chiralcel OD-H; eluent, 200:1 hexane:^{i}PrOH; retention time, 9.4 min (*S*, major) and 10.8 min (*R*, minor)].

[d] Determined by HPLC [column, Daicel Chiralcel OJ-H; eluent, 9:1 hexane:^{i}PrOH; retention time, 11.3 min (*S*, major) and 13.0 min (*R*, minor)].

[e] Determined by HPLC [column, Daicel Chiralcel OD-H; eluent, 200:1 hexane:^{i}PrOH; retention time, 8.3 min (*S*, major) and 9.9 min (*R*, minor)].

Once the effectiveness of Rh_2[(*S*)-TFPTTL]$_4$ was evaluated as a catalyst for this process, the amount of catalyst required for the reaction of diazo ketoester **6a** was investigated. For optimal results, catalytic asymmetric reactions based on rhodium(II)–carbene species usually require between 1–5 mol% of the catalyst. A few examples effectively employed less than 0.1 mol% of chiral dirhodium(II) catalysts.[22] Therefore, we were surprised to find that the catalyst loading could be dramatically reduced in this reaction without compromising the yield or the enantioselectivity (Table 2). When the amount of Rh_2[(*S*)-PTTL]$_4$ was reduced from the standard 2 mol% to 0.1 mol%, the reaction required 5.5 h more to reach completion (entries 1 versus 2). When the amount of Rh_2[(*S*)-TFPTTL]$_4$ was decreased from 2 mol% to 0.01 mol%, the reaction was completed within 2 h to give, after removal of the ester group, 2-indanone **8a** in a quantitative yield with essentially the same enantioselectivity (entries 3 versus 4). It is interesting that in each series decreasing the amount of catalyst increased the yield. Finally, an exceptionally high order of productivity of Rh_2[(*S*)-TFPTTL]$_4$ was demonstrated when 0.001 mol% catalyzed the reaction with the same yield and enantioselectivity as 0.01 mol% of the catalyst (entry 5).[23] It is noteworthy that turnover numbers as high as 98,000 were achieved, which is the highest ever recorded for chiral dirhodium(II) complex-catalyzed carbene transformations.

In summary, we demonstrated that Rh_2[(*S*)-TFPTTL]$_4$, the fluorinated analogue of Rh_2[(*S*)-PTTL]$_4$, is an exceptionally effective catalyst for asymmetric intramolecular aromatic C–H insertion reactions of methyl 4-alkyl-2-diazo-4,4-diphenyl-3-oxopropionates. A maximum of 97% ee and turnover numbers as high as 98,000 were achieved. Further studies to explore the scope of Rh_2[(*S*)-TFPTTL]$_4$-catalyzed reactions are currently in progress.[24]

Table 2. Enantioselective intramolecular aromatic C–H insertion reaction of diazo ketoester **6a** catalyzed by chiral Rh(II) complexes[a]

Entry	Rh(II) complex (mol%)	Time	Yield (%)[b]	Ee (%)[c]
1	Rh_2[(*S*)-PTTL]$_4$ **3d** (2.0)	1 h	89	92
2	Rh_2[(*S*)-PTTL]$_4$ **3d** (0.1)	6.5 h	98	93
3	Rh_2[(*S*)-TFPTTL]$_4$ **5a** (2.0)	2 min	90	97
4[d]	Rh_2[(*S*)-TFPTTL]$_4$ **5a** (0.01)	2 h	98	97
5[d,e]	Rh_2[(*S*)-TFPTTL]$_4$ **5a** (0.001)	48 h	98	97

[a] Unless otherwise noted the reactions were conducted using **6a** (92.5 mg, 0.3 mmol) in CH_2Cl_2 (1.5 mL) at 0°C.

[b] Isolated yield of **9a**.

[c] Determined by HPLC (Daicel Chiralcel OD-H) after demethoxycarbonylation.

[d] Rh_2[(*S*)-TFPTTL]$_4$ (3.0×10^{-4} M in CH_2Cl_2) was used.

[e] The reaction was conducted using **6a** (925 mg, 3.0 mmol) in CH_2Cl_2 (15 mL).

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17. Representative procedure for preparation of new chiral Rh(II) complexes: **Preparation of dirhodium(II) tetrakis[*N*-tetrafluorophthaloyl-(*S*)-*tert*-leucinate] 5a**: The following procedure is similar to that reported by Callot.[18] A mixture of $Rh_2(OAc)_4$·2MeOH (253 mg, 0.50 mmol) and *N*-tetrafluorophthaloyl-(*S*)-*tert*-leucine (920 mg, 2.51 mmol) in chlorobenzene (40 mL) was heated at reflux with vigorous stirring, while the solvent was distilled off at a rate such that 5 mL of the solvent was removed per hour. After completion of the reaction (3 h) was confirmed by TLC analysis, the dark green mixture was cooled to rt and diluted with EtOAc (40 mL). The whole was successively washed with saturated aq. $NaHCO_3$ (3×10 mL), water (10 mL) and brine (2×10 mL), and dried over Na_2SO_4. Filtration and evaporation in vacuo gave crude product (1.1 g of green semisolid) which was chromatographed on silica gel (2:1 hexane/EtOAc) followed by recrystallization (6:1 hexane/EtOAc, 20 mL) to provide bis(ethyl acetate) adduct of **5a** as green needles (770 mg, 83%): TLC R_f 0.69 (2:1 hexane/EtOAc); mp >280°C (hexane/EtOAc); $[\alpha]_D^{22}$ +291.6 (0.049, C_6H_6); IR (KBr) 3503, 2971, 1788, 1730, 1612, 1514, 1406 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 1.08 (36H, s), 1.26 (6H, t, $J=7.3$ Hz), 2.05 (6H, s), 4.13 (4H, q, $J=7.3$ Hz), 4.69 (4H, s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.2, 21.1, 27.7, 35.8, 60.8, 61.7, 113.5 ($^2J=7$ Hz), 143.2 (dmulti, $J\approx270$ Hz), 144.9 (dmulti, $J\approx264$ Hz), 161.9, 163.6, 172.2, 186.4; LRMS (FAB) m/z 1535 (M^++H). Anal. calcd for $C_{56}H_{40}F_{16}N_4O_{16}Rh_2$·2EtOAc·$H_2O$: C, 44.46; H, 3.38; N, 3.24; F, 17.58. Found: C, 44.25; H, 3.52; N, 3.29; F, 17.77%. **Dirhodium(II) tetrakis[*N*-tetrachlorophthaloyl-(*S*)-*tert*-leucinate], 5b**: Prepared starting from $Rh_2(OAc)_4$·2MeOH (506 mg, 1.0 mmol) and *N*-tetrachlorophthaloyl-(*S*)-*tert*-leucine (2.0 g, 5.0 mmol) by the same procedure as above. Column chromatography (silica gel, 15:1 benzene/Et_2O) followed by recrystallization (1:1 hexane/EtOAc, 40 mL) provided bis(ethyl acetate) adduct of **5b** as green prisms (1.36 g, 69%): TLC R_f 0.36 (5:1 hexane/EtOAc); mp >280°C (hexane/EtOAc); $[\alpha]_D^{22}$ +328.6 (0.054, C_6H_6); IR (KBr) 3650, 3495, 2965, 1784, 1728, 1613, 1385, 1372 cm^{-1}; ^1H NMR (270 MHz, C_6D_6, 60°C) δ 0.72 (6H, t, $J=7.0$ Hz), 1.43 (36H, s), 1.62 (6H, s), 3.65, (4H, q, $J=7.0$ Hz), 5.24 (4H, s); ^{13}C NMR (67.8 MHz, C_6D_6) δ 13.7, 20.4, 28.3, 36.9, 60.8, 61.7, 127.3, 127.8, 129.2, 129.9, 139.4, 139.8, 163.0, 163.6, 171.9, 186.8; LRMS (FAB) m/z 1798 (M^++H). Anal. calcd for $C_{56}H_{40}Cl_{16}N_4O_{16}Rh_2$·2EtOAc: C, 38.94; H, 2.86; N, 2.84; Cl, 28.73, found: C, 38.71; H, 2.66; N, 2.96; Cl, 28.93%.

18. Callot, H. J.; Metz, F. *Tetrahedron* **1985**, *41*, 4495.

19. Methyl 4-alkyl-2-diazo-4,4-diphenyl-3-oxopropionates **6** were prepared from diphenylacetic acid by the following sequence: (1) BuLi, THF, 0°C, then RX (MeI, EtI and CH_2=$CHCH_2Br$ for **6a**,**b** and **c**, respectively), 0°C; (2) cat. DMF, $SOCl_2$, toluene, reflux; (3) $LiCH_2CO_2Me$, THF, −78°C; (4) MsN_3, Et_3N, MeCN.

20. (a) Doyle, M. P.; Shanklin, M. S.; Pho, H. Q.; Mahapatro, S. N. *J. Org. Chem.* **1988**, *53*, 1017; (b) Cox, G. G.; Moody, C. J.; Austin, D. J.; Padwa, A. *Tetrahedron* **1993**, *49*, 5109.

21. We reported that in the presence of 2 mol% of Rh_2[(*S*)-PTTL]$_4$ aromatic C–H insertion of diazo ketoester **6a** resulted in a similar product yield and asymmetric induction as diazo ketone **7a**.[8c] Diazo ketoester **6** was chosen as the substrate for this study due to its stability and ease of handling.

22. (a) Doyle, M. P.; Kalinin, A. V. *J. Org. Chem.* **1996**, *61*, 2179; (b) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897; (c) Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q.-L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763.

23. A representative procedure (Table 2, entry 5): Rh_2[(*S*)-TFPTTL]$_4$·2EtOAc (3.0×10^{-4} M in CH_2Cl_2, 0.1 mL, 0.001 mol%) was added to a solution of diazo ketoester **6a** (925 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) at 0°C. After stirring for 48 h at 0°C, the mixture was concentrated in vacuo and purified by column chromatography (silica gel, 15:1 hexane/EtOAc) to give **9a** (824 mg, 98%) as a pale blue oil. A solution of **9a** (810 mg, 2.89 mmol) in 90% aqueous DMSO (5 mL) was heated at 120°C for 30 min. After the mixture cooled to rt, it was partitioned between EtOAc (50 mL) and water (20 mL). Then the organic layer was washed with brine, and dried over Na_2SO_4. Filtration and evaporation, followed by column chromatography (silica gel, 15: 1 hexane/EtOAc) afforded **8a** (623 mg, 97%) as a pale orange oil; $[\alpha]_D^{25}$ −58.3 (*c*1.33, $CHCl_3$) [lit.,[8b] $[\alpha]_D^{25}$ −59.7 (*c*1.03, $CHCl_3$) for (*S*)-**8a**].

24. Very recently, we found that Rh_2[(*S*)-TCPTTL]$_4$ is an effective catalyst for enantioselective benzylic amidation, see: Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561.