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ENANTIOSELECTIVE SYNTHESIS OF 3-ARYLINDAN-1-ONES *VIA* INTRAMOLECULAR C–H INSERTION REACTIONS OF α-DIAZO-β-KETOESTERS CATALYZED BY CHIRAL DIRHODIUM(II) CARBOXYLATES†

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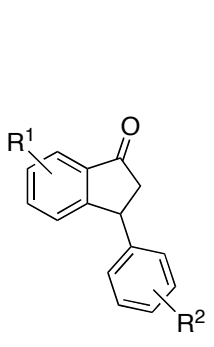
Abstract – A new, catalytic enantioselective route to 3-arylindan-1-ones, versatile intermediates for the synthesis of a number of bioactive and pharmaceutically interesting molecules, was developed by exploiting the chiral dirhodium(II) complex-catalyzed intramolecular C–H insertion reaction of α-diazo-β-ketoesters as a key step. Dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, proved to be the catalyst of choice for this process, providing enantioselectivities of up to 72% ee.

3-Arylindan-1-ones (**1**) are versatile intermediates in the synthesis of a number of important pharmaceuticals, such as the antidepressant indatraline,[1] the antipsychotic drug tefludazine,[2] the muscarinic receptor antagonist tolterodine,[3] and the endothelin receptor antagonists SB-209670 and



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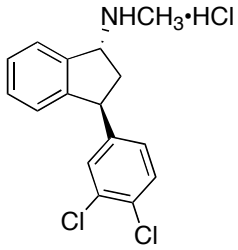
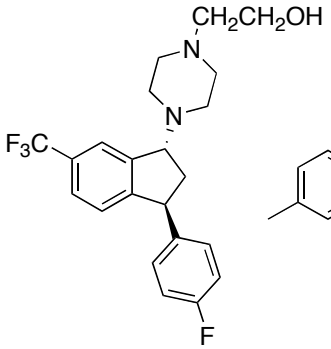
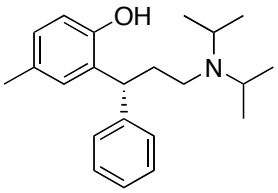


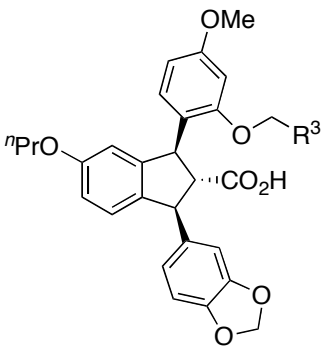
indatraline



tefludazine



tolterodine

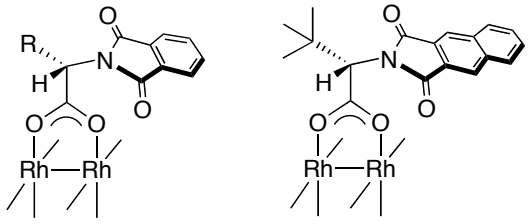


$R^3 = CO_2H$ **SB-209670**
$R^3 = CH_2OH$ **SB-217242**

† Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

SB-217242.[4] Because of their importance, several strategies have been developed to achieve the asymmetric synthesis of **1**, including a net stereospecific 1,3-hydrogen transfer of chiral 3-arylinden-1-ols, prepared by the methyloxazaborolidine (Me-CBS)-catalyzed enantioselective reduction of 3-arylinden-1-ones,[3,4a] Nazarov-type ring closure of alkylidene-1,3-carbonyl compounds carrying Evans' oxazolidinone as a chiral auxiliary,[4b] the enantioselective conjugate reduction of 3-arylinden-1-ones using baker's yeast,[5] the Friedel–Crafts cyclization of a chiral 3,3-diarylpropionic acid, prepared by an enantioselective intermolecular C–H insertion reaction with a chiral dirhodium(II) catalyst,[1d] and the enantioselective hydroacylation of 2-(1-arylvinyl)benzaldehydes catalyzed by a chiral cationic rhodium(I) complex.[6]

In recent years, we have been engaged in the enantioselective construction of five-membered carbocycles via a C–H insertion process,[7] catalyzed by chiral dirhodium(II) complexes, which incorporate *N*-phthaloyl- and *N*-benzene-fused-phthaloyl-(*S*)-amino acids as the bridging ligands.[8-11] These catalysts mediate intramolecular C–H insertion reactions of a structurally diverse array of α-diazocarbonyl compounds to give optically active cyclopentane,[8] cyclopentanone,[9] 2-indanone[10] and 1,1'-spirobi[indan-3,3'-dione][11] derivatives with a maximum of 95%, 80%, 98%, and 80% ee's, respectively. In a continuation of our work in this field, we wish to report a new method for the catalytic enantioselective synthesis of 3-arylindan-1-ones, based on an intramolecular C–H insertion process.



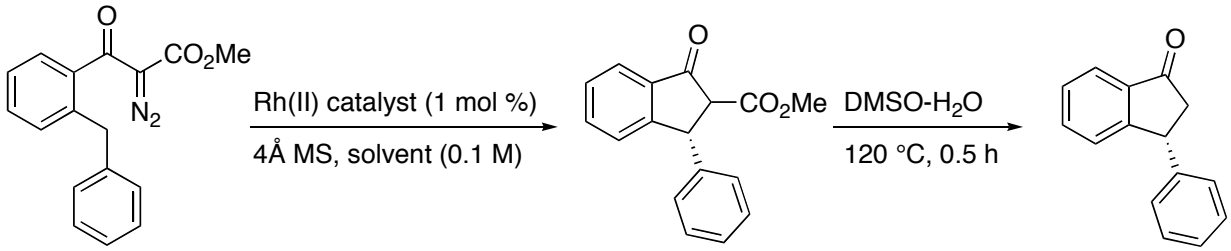
R = Bu^t: Rh_2(*S*-PTTL)$_4$ (**2a**)
R = Me: Rh_2(*S*-PTA)$_4$ (**2b**)
R = Bn: Rh_2(*S*-PTPA)$_4$ (**2c**)
R = Pr^i: Rh_2(*S*-PTV)$_4$ (**2d**)

Rh_2(*S*-BPTTL)$_4$ (**2e**)

In our initial studies, we explored the intramolecular C–H insertion reaction of methyl 3-(2-benzylphenyl)-2-diazo-3-oxopropanoate (**3a**) using 1 mol % of dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$ (**2a**),[12] in the presence of pulverized 4Å molecular sieves (MS).[13] The reaction in toluene at 0 °C proceeded smoothly to completion within 1 h, giving cyclic β-ketoester (**4a**) in 98% yield as an 85:15 equilibrium mixture of the keto and enol forms (Table 1, Entry 1). After the demethoxycarbonylation of **4a** to 3-phenylindan-1-one (**1a**), the magnitude of enantioselection at the insertion site (C-3) was determined to be 64% ee by HPLC (Daicel Chiralpak AS). The preferred absolute stereochemistry of **1a** [$[\alpha]_D^{23}$ –39.7° (*c* 1.26, $CHCl_3$) for 64% ee] was established as *R* by its transformation [*m*CPBA, cat. TsOH, CH_2Cl_2, reflux, 30 h][3] to the known

4-phenylchroman-2-one [$[\alpha]_D^{23}$ –26.5° (*c* 1.36, $CHCl_3$) for 64% ee; lit.,[14] $[\alpha]_D^{20}$ –45.1° (*c* 0.98, $CHCl_3$) for (*R*)-enantiomer (99.4% ee)]. A survey of solvents revealed that toluene was the optimal solvent for this transformation in terms of both product yield and enantioselectivity (Entries 1 vs 2 and 3). Using toluene as the solvent, we next evaluated the performance of some other chiral dirhodium(II) carboxylate catalysts, Rh_2(*S*-PTA)$_4$ (**2b**), Rh_2(*S*-PTPA)$_4$ (**2c**), and Rh_2(*S*-PTV)$_4$ (**2d**), derived from *N*-phthaloyl-(*S*)-alanine, -phenylalanine, and -valine, respectively. Although a uniform sense of asymmetric induction was observed in all cases, these catalysts resulted in much lower enantioselectivities than Rh_2(*S*-PTTL)$_4$ (Entries 4–6). Somewhat disappointingly, switching the catalyst to Rh_2(*S*-BPTTL)$_4$ (**2e**)[15] characterized by an extension of the phthalimido wall with one additional benzene ring had no beneficial effect in this system, and the same enantioselectivity as Rh_2(*S*-PTTL)$_4$ was found (64% ee, Entry 7). Thus we were gratified to find that enantioselectivity with Rh_2(*S*-PTTL)$_4$ was enhanced up to 70% ee by lowering the temperature of the reaction to –15 °C without significant loss

Table 1. Enantioselective Intramolecular C–H Insertion Reaction of α-Diazo-β-ketoester (**3a**) Catalyzed by Chiral Dirhodium(II) Carboxylates[a)]



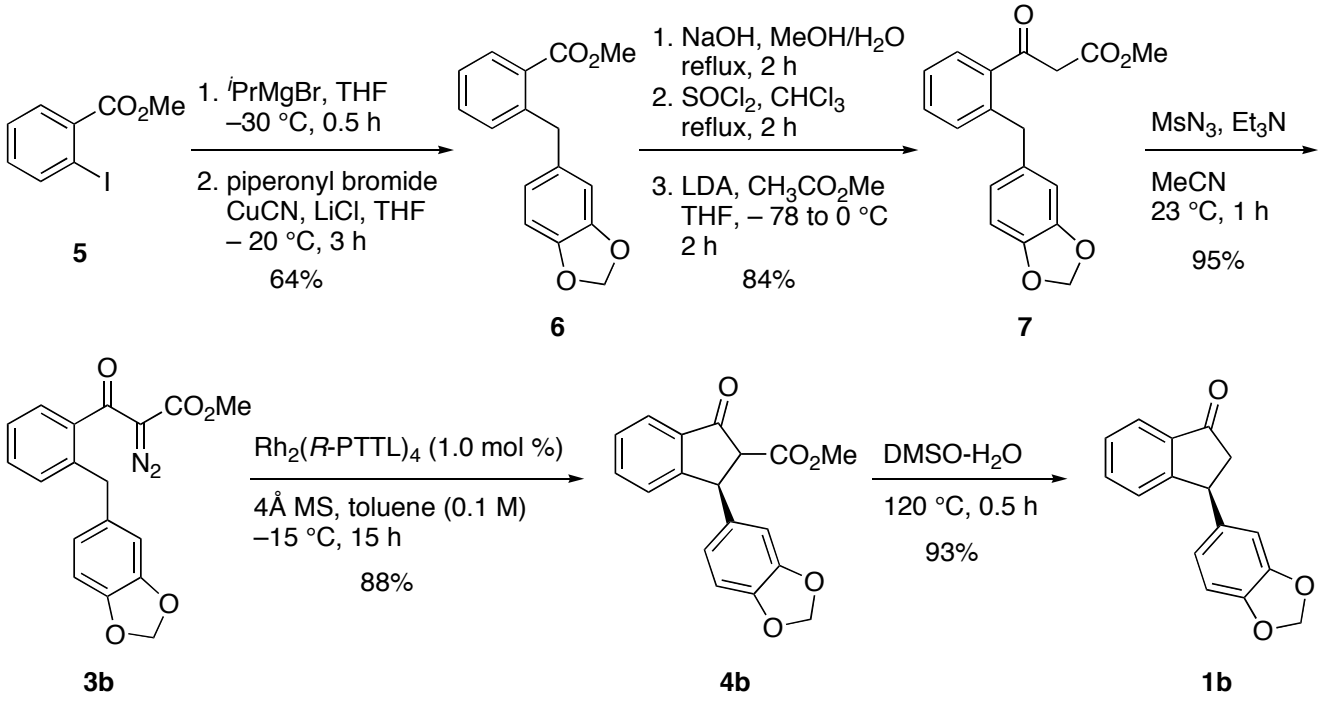
3a **4a** **1a**

					β-Ketoesters **4a**	3-Phenylindan-1-one **1a**	
Entry	Rh(II) catalyst	Solvent	*T* (°C)	Time (h)	Yield (%)[b)]	Yield (%)[b)]	Ee (%)[c)]
1	Rh_2(*S*-PTTL)$_4$ (**2a**)	toluene	0	1	98	93	64
2	Rh_2(*S*-PTTL)$_4$ (**2a**)	$CF_3C_6H_5$	0	1	89	95	60
3	Rh_2(*S*-PTTL)$_4$ (**2a**)	CH_2Cl_2	0	3	92	93	54
4	Rh_2(*S*-PTA)$_4$ (**2b**)	toluene	0	1.5	94	95	19
5	Rh_2(*S*-PTPA)$_4$ (**2c**)	toluene	0	1.5	96	96	4
6	Rh_2(*S*-PTV)$_4$ (**2d**)	toluene	0	1	94	94	32
7	Rh_2(*S*-BPTTL)$_4$ (**2e**)	toluene	0	1	91	93	64
8	Rh_2(*S*-PTTL)$_4$ (**2a**)	toluene	–15	3	91	93	70
9	Rh_2(*S*-BPTTL)$_4$ (**2e**)	toluene	–15	3	78	95	66
10	Rh_2(*S*-PTTL)$_4$ (**2a**)	toluene	–23	7	66	92	72

a) All reactions were performed on a 0.2 mmol scale. b) Isolated yield. c) Determined by HPLC (Daicel Chiralpak AS).

in product yield (Entry 8), whereas catalysis with Rh_2(*S*-BPTTL)$_4$ under the same condition resulted in 66% ee with a substantial decrease in product yield (Entry 9). Although a further enhancement of up to 72% ee was possible at a temperature –23 °C, –15 °C was found to be the temperature limit in terms of both reaction rate and product yield (Entry 10).[16]

Having identified the effectiveness of the combination of Rh_2(*S*-PTTL)$_4$ as the catalyst and toluene as the solvent, we then applied this protocol to the enantioselective synthesis of a key intermediate (**1b**) for serotonin and norepinephrine uptake inhibitors (Scheme 1).[17] The Cu(I)-catalyzed cross-coupling reaction of the arylmagnesium compound, prepared from **5** via an iodine-magnesium exchange, with piperonyl bromide in the presence of CuCN and LiCl afforded the benzhydryl derivative (**6**) in 64% yield.[18] Saponification of **6** and subsequent conversion to the acid chloride were followed by condensation with methyl lithioacetate to furnish the β-ketoester (**7**) in 84% overall yield, which, upon diazo transfer with methanesulfonyl azide, gave the α-diazo-β-ketoester (**3b**) in 95% yield.[19] The intramolecular C–H insertion reaction of **3b** using 1 mol % of Rh_2(*R*-PTTL)$_4$ at –15 °C proceeded uneventfully to afford the desired cyclic β-ketoester (**4b**) in 88% yield. Removal of the methoxycarbonyl group from **4b** gave (*S*)-3-(3,4-methylenedioxyphenyl)indan-1-one (**1b**) [$[\alpha]_D^{23}$ +28.6° (*c* 1.85, $CHCl_3$)] in 93% yield.[20] The enantiomeric purity of **1b** was determined to be 63% ee by HPLC (Daicel Chiralpak AS).



Scheme 1

In summary, the Rh_2(*S*-PTTL)$_4$-catalyzed intramolecular C–H insertion reaction of α-diazo-β-ketoesters shows considerable promise for the enantioselective synthesis of 3-arylindan-1-ones. Further evaluation of the scope of these intramolecular C–H insertion reactions is currently in progress.

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-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^1H NMR spectra were recorded on JEOL JNM-AL 400 (400 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane; δ_H 0.00). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant and integration. ^{13}C NMR spectra were recorded on JEOL JNM-AL 400 (100 MHz) spectrometer. Chemical shifts are reported relative to internal standard ($CDCl_3$; δ 77.0). Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). EI-MS spectra were obtained on a JEOL JMS-HX 110 spectrometer. Column chromatography was carried out on Kanto silica gel 60 N (63-210 mesh). Analytical thin layer chromatography (TLC) was carried out on Merck Kieselgel 60 F_{254} plates with visualization by ultraviolet, anisaldehyde stain solution or phosphomolybdic acid stain solution. Analytical high performance liquid chromatography (HPLC) was performed on JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575 intelligent UV/VIS detector. Detection was performed at 254 nm. Chiralpak AS and Chiralcel OD-H columns (0.46 cm × 25 cm) from Daicel were used. Retention times (t_R) and peak ratio were determined with Shimadzu C-R8A chromatopac integrator or JASCO-Borwin analysis system.

All non-aqueous reactions were carried out in flame-dried glassware under argon atmosphere. α-Phenyl-*o*-toluic acid was purchased from Aldrich, Inc. Reagents and solvents were purified by standard means. Dehydrated THF, CH_2Cl_2 and toluene were purchased from Kanto Chemical Co., Inc. Methanesulfonyl azide was prepared according to the procedure of Danheiser.[21] 4Å MS was used after pulverized and dried (150 °C, 1 mmHg, 12 h).

Methyl 3-(2-benzylphenyl)-2-diazo-3-oxopropanoate (3a). Thionyl chloride (2.8 mL, 37.7 mmol) was added to a solution of α-phenyl-*o*-toluic acid (4.0 g, 18.8 mmol) in $CHCl_3$ (60 mL). The mixture was refluxed for 4 h and evaporated in vacuo. The residue was dissolved in toluene (20 mL) and evaporated in vacuo. *n*-BuLi in *n*-hexane (1.59 M, 26.1 mL, 41.5 mmol) was added to a solution of $^iPr_2NH$ (6.4 mL, 45.6 mmol) in THF (42 mL) at –78 °C. After stirring at –78 °C for 30 min, methyl acetate (3.3 mL, 41.5 mmol) was added dropwise over 10 min. After stirring at –78 °C for 1 h, a solution of crude acid chloride in THF (19 mL) was added to the mixture via cannula. After stirring at –78 °C for 30 min, the mixture was allowed to warm to room temperature over 1 h. The reaction mixture was poured into 5% aqueous HCl (40 mL) at 0°C. The whole mixture was extracted with EtOAc (2 × 80 mL), and the combined organic layers were washed successively with water (50 mL) and brine (2 × 50 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (5.4 g), which was

purified by column chromatography (silica gel 150 g, 10:1 hexane/EtOAc) to afford methyl 3-(2-benzylphenyl)-3-oxopropanoate (4.70 g, 93%) as a white solid; R_f 0.46 (3:1 hexane/EtOAc); mp 35.5-36.0 °C (hexane/EtOAc); IR (KBr) ν 1739, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 76:24 mixture of keto/enol tautomers) keto tautomer: δ 3.69 (s, 3H, CO_2CH_3), 3.85 (s, 2H, $COCH_2CO_2CH_3$), 4.28 (s, 2H, $ArCH_2Ar$), 7.13-7.65 (m, 9H, Ar*H*); enol tautomer: δ 3.77 (s, 3H, CO_2CH_3), 4.19 (s, 2H, $ArCH_2Ar$), 5.25 (s, 1H, =C*H*–), 7.13-7.65 (m, 9H, Ar*H*), 12.4 (s, 1H, C=CO*H*); ^{13}C NMR (100 MHz, $CDCl_3$) keto tautomer: δ 39.1 (CH_2), 48.2 (CH_2), 52.4 (CH_3), 125.9 (CH), 126.2 (CH), 128.2 (CH), 128.8 (CH), 129.1 (CH), 131.9 (CH), 132.0 (CH), 136.5 (C), 140.5 (C), 141.5 (C), 167.7 (C), 195.7 (C); enol tautomer: δ 39.0 (CH_2), 51.4 (CH_3), 91.7 (CH), 125.9 (CH), 126.2 (CH), 128.2 (CH), 128.7 (CH), 128.9 (CH), 130.1 (CH), 130.8 (CH), 134.5 (C), 139.3 (C), 140.7 (C), 172.9 (C), 174.7 (C); LRMS (EI) m/z 268 (M^+), 250, 194, 165; HRMS (EI) calcd for $C_{17}H_{16}O_3$ (M^+) 268.1099, found 268.1105; Anal. Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 76.00; H, 6.05.

To a solution of methyl 3-(2-benzylphenyl)-3-oxopropanoate (2.0 g, 7.45 mmol) and triethylamine (2.1 mL, 14.9 mmol) in MeCN (25 mL) at 0 °C was added methanesulfonyl azide (994 mg, 8.21 mmol). After stirring at room temperature for 1 h, water (15 mL) was poured into the orange-colored reaction mixture. The whole mixture was extracted with EtOAc (2 × 30 mL), and the combined organic layers were washed successively with 5% aqueous NaOH (20 mL), water (20 mL) and brine (2 × 20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (2.5 g), which was purified by column chromatography (silica gel 50 g, 10:1 hexane/EtOAc) to afford **3a** (2.10 g, 96%) as a yellow solid; R_f 0.39 (3:1 hexane/EtOAc); mp 107-107.5 °C (hexane/EtOAc); IR (KBr) ν 2137, 1726, 1626 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.66 (s, 3H, CO_2CH_3), 4.06 (s, 2H, $ArCH_2Ar$), 7.10-7.29 (m, 8H, Ar*H*), 7.38 (dt, *J* = 2.0, 7.3 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.8 (CH_2), 52.1 (CH_3), 125.6 (CH), 126.0 (CH), 126.7 (CH), 128.1 (CH), 129.2 (CH), 130.3 (CH), 130.5 (CH), 137.8 (C), 138.3 (C), 140.0 (C), 160.4 (C), 188.4 (C); LRMS (EI) m/z 294 (M^+), 206, 178; HRMS (EI) calcd for $C_{17}H_{14}N_2O_3$ (M^+) 294.1004, found 294.1005; Anal. Calcd for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52. Found: C, 69.51; H, 4.78; N, 9.65.

Representative procedure for the enantioselective intramolecular C–H insertion reaction (Table 1, Entry 8): (3*R*)-Methyl 3-phenylindan-1-one-2-carboxylate (4a). Rh_2(*S*-PTTL)$_4$ (2.85 mg, 0.0020 mmol) was added to a solution of **3a** (58.9 mg, 0.2 mmol) and pulverized 4Å MS (58.9 mg) in toluene (2.0 mL) at –15 °C. After stirring at –15 °C for 3 h, the whole mixture was filtrated through a Celite pad. The filter cake was rinsed with EtOAc (10 mL) and the combined filtrates were evaporated in vacuo. The crude product (61.0 mg) was purified by column chromatography (silica gel 8 g, 15:1 hexane/EtOAc) to

afford **4a** (48.5 mg, 91%) as a white solid; R_f 0.48 (3:1 hexane/EtOAc); mp 120-122 °C; IR (KBr) ν 3277, 1719, 1658 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 85:15 mixture of keto/enol tautomers) keto tautomer: δ 3.71 (d, J = 4.6 Hz, 1H, COC*H*CO_2CH_3), 3.82 (s, 3H, CO_2CH_3), 5.02 (d, J = 4.6 Hz, 1H, ArC*H*Ar), 7.08-7.38 (m, 6H, Ar*H*), 7.46 (dt, J = 1.3, 7.6 Hz, 1H, Ar*H*), 7.62 (dt, J = 1.3, 7.6 Hz, 1H, Ar*H*), 7.83 (dd, J = 1.3, 7.6 Hz, 1H, Ar*H*); enol tautomer: δ 3.68 (s, 3H, CO_2CH_3), 4.75 (s, 1H, ArC*H*Ar), 7.08-7.85 (m, 9H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) keto tautomer: δ 48.6 (CH), 52.8 (CH_3), 63.4 (CH), 124.2 (CH), 126.6 (CH), 127.4 (CH), 127.8 (CH), 128.2 (CH), 128.9 (CH), 134.8 (C), 135.7 (CH), 141.6 (C), 156.1 (C), 168.7 (C), 198.3 (C); LRMS (EI) m/z 266 (M^+), 206, 178; HRMS (EI) calcd for $C_{17}H_{14}O_3$ (M^+) 266.0943, found 266.0941.

Representative procedure for demethoxycarbonylation (Table 1, Entry 8): (*R*)-3-phenylindan-1-one (1a).[22] **4a** (48.5 mg, 0.132 mmol) was treated with 95 % aqueous DMSO (1.5 mL) at 120 °C for 30 min. After cooling, the reaction was quenched with water (5 mL). The whole mixture was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with brine (4 mL), and dried over Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (49.1 mg), which was purified by column chromatography (silica gel 7 g, 15:1 hexane/EtOAc) to afford **1a** (35.3 mg, 93%) as a white solid; R_f 0.46 (3:1 hexane/EtOAc); mp 46.0-47.0 °C for 70% ee [lit.,[22] mp 77-78.5 °C for racemic **1a**]; $[\alpha]_D^{23}$ –43.0° (*c* 1.66, $CHCl_3$) for 70% ee; IR (KBr) ν 1703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.70 (dd, J = 3.6, 19.1 Hz, 1H, COCH_2), 3.24 (dd, J = 7.9, 19.1 Hz, 1H, COCH_2), 4.51 (dd, J = 3.6, 7.9 Hz, 1H, ArC*H*Ar), 7.12-7.35 (m, 6H, Ar*H*), 7.42 (dd, J = 7.3, 7.6 Hz, 1H, Ar*H*), 7.58 (t, J = 7.3 Hz, 1H, Ar*H*), 7.82 (d, J = 7.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.5 (CH), 46.9 (CH_2), 123.3 (CH), 126.8 (CH), 126.9 (CH), 127.6 (CH), 127.8 (CH), 128.8 (CH), 135.0 (CH), 136.6 (C), 143.6 (C), 157.8 (C), 205.9 (C); LRMS (EI) m/z 208 (M^+), 179, 165; HRMS (EI) calcd for $C_{15}H_{12}O$ (M^+) 208.0888, found 208.0898. The enantiomeric excess of **1a** was determined to be 70% by HPLC with a Chiralpak AS column (9:1 hexane/2-propanol, flow rate = 1.0 mL/min): t_R (minor) = 15.2 min for (*S*)-enantiomer; t_R (major) = 30.1 min for (*R*)-enantiomer. The absolute configuration of **1a** was determined to be *R* by chemical correlation (*vide infra*).

Determination of absolute configuration of 1a: (*R*)-4-phenylchroman-2-one from (*R*)-3-phenylindan-1-one (1a).[14] The chroman derivative was prepared according to the protocol reported by Andersson.[3] *m*CPBA (98%, 59.2 mg, 0.336 mmol) and *p*-TsOH·H_2O (3.2 mg, 0.0168 mmol) were added to a solution of **1a** (35.0 mg, 0.168 mmol, 64% ee) in CH_2Cl_2 (0.84 mL), and the mixture was refluxed for 30 h. After cooling, the reaction mixture was dissolved in CH_2Cl_2 (15 mL) and quenched with saturated aqueous $Na_2S_2O_3$ (5 mL). The layers were separated, and the organic layer was washed

successively with saturated aqueous $NaHCO_3$ (5 mL) and brine (2 × 5 mL), and dried over Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (48 mg), which was purified by column chromatography (silica gel 5 g, 30:1 toluene/EtOAc) to afford (*R*)-4-phenylchroman-2-one (28.2 mg, 75%) as a white solid; R_f 0.47 (20:1 toluene/EtOAc); mp 101-102 °C for 64% ee [lit.,[23] mp 110-112 °C for 95% ee]; $[\alpha]_D^{23}$ –26.5° (*c* 1.36, $CHCl_3$) for 64% ee [lit.,[14] $[\alpha]_D^{20}$ –45.1° (*c* 0.98, $CHCl_3$) for (*R*)-enantiomer (99.4% ee)]; IR (KBr) ν 1762 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.97-3.14 (m, 2H, OCOCH_2), 4.35 (t, *J* = 6.9 Hz, 1H, ArC*H*), 6.98 (d, *J* = 7.3 Hz, 1H, Ar*H*), 7.06-7.18 (m, 4H, Ar*H*), 7.27-7.39 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.0 (CH_2), 40.7 (CH), 117.0 (CH), 124.6 (CH), 125.7 (C), 127.5 (CH), 127.6 (CH), 128.2 (CH), 128.7 (CH), 129.0 (CH), 140.1 (C), 151.6 (C), 167.5 (C). The enantiomeric excess of 4-phenylchroman-2-one was determined to be 64% by HPLC with a Chiralcel OD-H column (19:1 hexane/2-propanol, flow rate = 1.0 mL/min): t_R (minor) = 14.6 min for (*S*)-enantiomer; t_R (major) = 16.8 min for (*R*)-enantiomer.

Methyl 2-piperonylbenzoate (6). The benzhydryl derivative (**6**) was prepared according to the protocol reported by Knochel.[18] A Grignard reagent was prepared from 2-bromopropane (2.2 mL, 22.9 mmol) and magnesium (557 mg, 22.9 mmol) in THF (16 mL). The solution of 2-propylmagnesium bromide was added to a solution of methyl 2-iodobenzoate (**5**) (5.0 g, 19.1 mmol) in THF (19 mL) at –30 °C. After stirring at –30 °C for 30 min, CuCN (342 mg, 3.82 mmol) and LiCl (323 mg, 7.63 mmol) were added to the mixture. After stirring at –20 °C for 30 min, a solution of piperonyl bromide (4.52 g, 21.0 mmol) in THF (10 mL) was added to the mixture at –20 °C via cannula. After stirring at –20 °C for 2.5 h, the reaction mixture was poured into saturated aqueous NH_4Cl (18 mL) and 25% aqueous NH_3 (2.0 mL) at 0 °C. The whole mixture was extracted with CH_2Cl_2 (2 × 70 mL), and the combined organic layers were washed successively with water (2 × 50 mL) and brine (2 × 50 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (4.50 g), which was purified by column chromatography (silica gel 100 g, toluene) to afford **6** (3.31 g, 64%) as a colorless oil; R_f 0.54 (3:1 hexane/EtOAc); IR (neat) 1720 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.85 (s, 3H, CO_2CH_3), 4.29 (s, 2H, ArCH_2Ar), 5.90 (s, 2H, OCH_2O), 6.60-6.63 (m, 2H, Ar*H*), 6.72 (d, *J* = 7.9 Hz, 1H, Ar*H*), 7.19-7.31 (m, 2H, Ar*H*), 7.43 (dt, *J* = 1.7, 7.6 Hz, 1H, Ar*H*), 7.89 (dd, *J* = 1.7, 7.6 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.2 (CH_2), 52.0 (CH_3), 100.7 (CH_2), 108.0 (CH), 109.4 (CH), 121.7 (CH), 126.2 (CH), 129.7 (C), 130.6 (CH), 131.3 (CH), 131.9 (CH), 134.6 (C), 142.2 (C), 145.6 (C), 147.5 (C), 167.9 (C); LRMS (EI) m/z 270 (M^+), 238, 180, 152; HRMS (EI) calcd for $C_{16}H_{14}O_4$ (M^+) 270.0892, found 270.0895.

Methyl 3-(2-piperonylphenyl)-3-oxopropanoate (7). A solution of NaOH (884 mg, 22.1 mmol) in water (15 mL) was added to a solution of **6** (2.98 g, 11.0 mmol) in MeOH (15 mL). The mixture was refluxed

for 2 h and the MeOH was evaporated in vacuo. The aqueous layer was washed with Et_2O (2 × 5 mL), acidified to pH 3 with 10% aqueous HCl, and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (2 × 20 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo. The crude methyl 2-piperonylbenzoate (2.69 g) thus obtained was used without further purification.

According to the procedure for preparation of methyl 3-(2-benzylphenyl)-3-oxopropanoate, **7** was prepared from crude methyl 2-piperonylbenzoate (2.69 g) and methyl acetate (1.84 mL, 23.1 mmol). The crude product (3.61 g) was purified by column chromatography (silica gel 130 g, 6:1 hexane/EtOAc) to afford **7** (2.89 g, 84% for 2 steps) as a white solid; R_f 0.36 (3:1 hexane/EtOAc); mp 77.0-77.5 °C (hexane/EtOAc); IR (KBr) ν 1729, 1687 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, almost keto form) δ 3.72 (s, 3H, $COCH_2CO_2CH_3$), 3.88 (s, 2H, $COCH_2CO_2CH_3$), 4.19 (s, 2H, $ArCH_2Ar$), 5.90 (s, 2H, OCH_2O), 6.59-6.63 (m, 2H, Ar*H*), 6.72 (d, 1H, *J* = 7.6 Hz, Ar*H*), 7.22-7.25 (m, 1H, Ar*H*), 7.31 (dt, 1H, *J* = 1.3, 7.6 Hz, Ar*H*), 7.43 (dt, 1H, *J* = 1.3, 7.6 Hz, Ar*H*), 7.64 (dd, 1H, *J* = 1.3, 7.6 Hz, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.7 (CH_2), 48.2 (CH_2), 52.4 (CH_3), 100.7 (CH_2), 108.0 (CH), 109.6 (CH), 121.9 (CH), 126.2 (CH), 128.8 (CH), 131.7 (CH), 132.0 (CH), 134.3 (C), 136.4 (C), 141.6 (C), 145.6 (C), 147.4 (C), 167.6 (C), 195.7 (C); LRMS (EI) m/z 312 (M^+), 294, 238, 152; HRMS (EI) calcd for $C_{18}H_{16}O_5$ (M^+) 312.0997, found 312.0988; Anal. Calcd for $C_{18}H_6O_5$: C, 69.22; H, 5.16. Found: C, 69.09; H, 5.12.

Methyl 3-(2-piperonylphenyl)-2-diazo-3-oxopropanoate (3b). According to the procedure for preparation of **3a** from methyl 3-(2-benzylphenyl)-3-oxopropanoate, **3b** was prepared from **7** (1.18 g, 3.78 mmol). The crude product (1.42 g) was purified by column chromatography (silica gel 40 g, 15:1 hexane/EtOAc) to afford **3b** (1.21 g, 95%) as a yellow solid; R_f 0.27 (3:1 hexane/EtOAc); mp 150 °C (decomp) (hexane/toluene); IR (KBr) ν 2146, 1724, 1625 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 3.69 (s, 3H, CO_2CH_3), 3.96 (s, 2H, $ArCH_2Ar$), 5.89 (s, 2H, OCH_2O), 6.57-6.60 (m, 2H, Ar*H*), 6.69 (d, *J* = 8.6 Hz, 1H, Ar*H*), 7.21-7.29 (m, 3H, Ar*H*), 7.38 (dt, *J* = 2.0, 7.3 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.4 (CH_2), 52.2 (CH_3), 100.7 (CH_2), 107.8 (CH), 109.7 (CH), 122.2 (CH), 125.6 (CH), 126.7 (CH), 130.3 (CH), 130.3 (CH), 133.8 (C), 137.7 (C), 138.4 (C), 145.7 (C), 147.4 (C), 160.5 (C), 188.4 (C); LRMS (EI) m/z 338 (M^+), 278, 250, 220, 193, 165, 152; HRMS (EI) calcd for $C_{18}H_{14}N_2O_5$ (M^+) 338.0902, found 338.0904; Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28. Found: C, 63.95; H, 4.14; N, 8.39.

Enantioselective intramolecular C–H insertion reaction: (*S*)-Methyl 3-(3,4-methylenedioxyphenyl)indan-1-one-2-carboxylate (4b). According to the procedure for C–H insertion reaction, **4b** was prepared from **3b** (67.7 mg, 0.20 mmol) and Rh_2(*R*-PTTL)$_4$ (2.85 mg, 0.0020 mmol) at –15 °C for 15 h.

The crude product (68.1 mg) was purified by column chromatography (silica gel 10 g, 7:1 hexane/EtOAc) to afford **4b** (54.7 mg, 88%) as a white solid; R_f 0.34 (3:1 hexane/EtOAc); mp 80-82 °C; IR (KBr) ν 3265, 1717, 1662 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, 84:16 mixture of keto/enol tautomers) keto tautomer: δ 3.64 (d, J = 4.9 Hz, 1H, COC*H*CO_2CH_3), 3.82 (s, 3H, CO_2CH_3), 4.94 (d, J = 4.9 Hz, 1H, ArC*H*Ar), 5.95 (s, 2H, OCH_2O), 6.56 (d, J = 1.7 Hz, 1H, Ar*H*), 6.68 (dd, J = 1.7, 7.9 Hz, 1H, Ar*H*), 6.77 (d, J = 7.9 Hz, 1H, Ar*H*), 7.31 (dd, J = 0.7, 7.6 Hz, 1H, Ar*H*), 7.45 (dt, J = 0.7, 7.6 Hz, 1H, Ar*H*), 7.63 (dt, J = 1.3, 7.6 Hz, 1H, Ar*H*), 7.82 (dd, J = 1.3, 7.6 Hz, 1H, Ar*H*); enol tautomer: δ 3.71 (s, 3H, CO_2CH_3), 4.67 (s, 1H, ArC*H*Ar), 5.90-5.95 (m, 2H, OCH_2O), 6.45-6.78 (m, 3H, Ar*H*), 7.29-7.83 (m, 4H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) keto tautomer: δ 48.3 (CH), 52.9 (CH_3), 63.6 (CH), 101.1 (CH_2), 107.9 (CH), 108.5 (CH), 121.3 (CH), 124.2 (CH), 126.6 (CH), 128.3 (CH), 134.8 (C), 135.4 (C), 135.7 (CH), 146.9 (C), 148.1 (C), 156.0 (C), 168.7 (C), 198.2 (C); LRMS (EI) m/z 310 (M^+), 278, 250, 220, 165; HRMS (EI) calcd for $C_{18}H_{14}O_5$ (M^+) 310.0841, found 310.0840.

(*S*)-3-(3,4-methylenedioxyphenyl)indan-1-one (1b).[20] According to the procedure for demethoxycarbonylation, **1b** was prepared from **4b** (54.7 mg, 0.176 mmol). The crude product (56 mg) was purified by column chromatography (silica gel 8 g, 8:1 hexane/EtOAc) to afford **1b** (41.2 mg, 93%) as a white solid; R_f 0.36 (3:1 hexane/EtOAc); mp 89.0-91.0 °C for 63 % ee; $[\alpha]_D^{23}$ +28.6° (*c* 1.85, $CHCl_3$) for 63% ee; IR (KBr) ν 1703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 2.63 (dd, J = 3.6, 19.1 Hz, 1H, COC*H*$_2$), 3.21 (dd, J = 7.9, 19.1 Hz, 1H, COC*H*$_2$), 4.51 (dd, J = 3.6, 7.9 Hz, 1H, ArC*H*), 5.93 (s, 2H, OCH_2O), 6.51 (d, J = 1.3 Hz, 1H, Ar*H*), 6.65 (dd, J = 1.3, 7.9 Hz, 1H, Ar*H*), 6.75 (d, J = 7.9 Hz, 1H, Ar*H*) 7.28 (d, J = 7.3 Hz, 1H, Ar*H*), 7.42 (dd, J = 7.3, 7.6 Hz, 1H, Ar*H*), 7.58 (t, J = 7.3 Hz, 1H, Ar*H*), 7.82 (d, J = 7.6 Hz, 1H, Ar*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.2 (CH), 46.9 (CH_2), 101.0 (CH_2), 107.7 (CH), 108.3 (CH), 120.8 (CH), 123.3 (CH), 126.7 (CH), 127.8 (CH), 135.0 (CH), 136.6 (C), 137.4 (C), 146.4 (C), 148.0 (C), 157.8 (C), 205.7 (C); LRMS (EI) m/z 252 (M^+), 194, 165; HRMS (EI) calcd for $C_{16}H_{12}O_3$ (M^+) 252.0786, found 252.0784. The enantiomeric excess of **1b** was determined to be 63% by HPLC with a Chiralpak AS column (19:1 hexane/2-propanol, flow rate = 1.0 mL/min): t_R = 40.6 min for minor enantiomer; t_R = 56.7 min for major enantiomer. A sample for combustion analysis was obtained by recrystallizations from hexane/EtOAc as colorless needles (56% ee); mp 102-103 °C; Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 76.11; H, 4.69.

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