Catalytic enantioselective C–H functionalization of indoles with α-diazopropionates using chiral dirhodium(II) carboxylates: asymmetric synthesis of the (+)-α-methyl-3-indolylacetic acid fragment of acremoauxin A

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ABSTRACT

An enantioselective C–H functionalization of *N*-methoxymethyl (MOM)-protected 2,3-unsubstituted indoles with α-diazopropionates has been effected under catalysis by dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-triethylalaninate], Rh_2(*S*-PTTEA)$_4$, providing α-methyl-3-indolylacetates in high yields and with enantioselectivities of up to 86% ee. The effectiveness of this protocol was demonstrated by the first catalytic asymmetric synthesis of the (+)-α-methyl-3-indolylacetic acid fragment of acremoauxin A, a potent plant-growth inhibitor. Furthermore, the Fujioka protocol using a combination of TMSOTf and 2,2'-bipyridyl was shown to be superior for removal of the *N*-MOM group.

1. Introduction

Functionalized indoles are prevalent structural motifs in a large number of biologically active alkaloids and pharmaceuticals.[1] It is therefore not surprising that an enormous amount of effort has recently been devoted to the development of efficient methods for direct catalytic functionalization of indoles.[2] The majority of these studies have been focused on the Friedel–Crafts reaction and its enantioselective variants using a range of electrophilic reagents.[3] In this context, C–H functionalization of indoles with metal carbenes generated from α-diazocarbonyl compounds under catalysis by metal complexes is a potentially powerful means for installing functionalized alkyl groups on the pyrrole portion of the indole ring system.[4,5] Since publication of the seminal work of Davies and Lian on catalysis by Rh_2(*S*-DOSP)$_4$ **4**[6] (Figure 1),[7] the development of an enantioselective version of this catalytic process has been a challenging objective. Very recently, Fox and co-workers made a major breakthrough in this field when they demonstrated that enantioselective C–H functionalization of indoles with ethyl α-alkyl-α-diazoacetates under catalysis by Rh_2(*S*-NTTL)$_4$ **3**[8–10] provides α-alkyl-substituted 3-indolylacetates in high yields and enantioselectivities (82–96% yields, 79–99% ee, Scheme 1).[11,12] While the scope of the reaction was found to accommodate a wide array of substrates, an exceptionally high performance was achieved with diazoesters bearing longer-chained alkyl groups than α-methyl substituent when *N*-aryl or *N*-alkyl indole

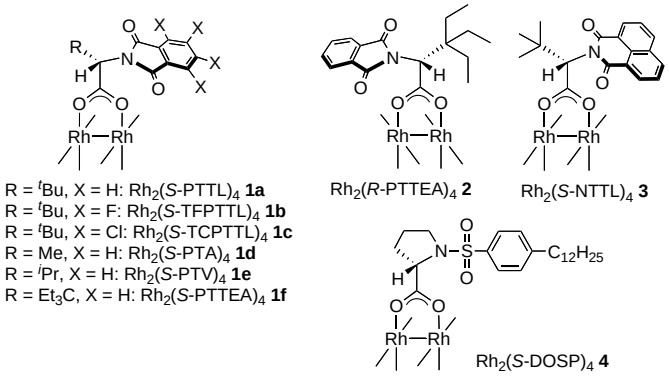
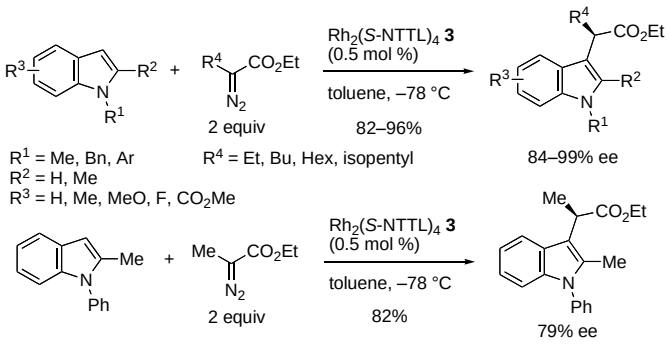


Figure 1. Chiral dirhodium(II) catalysts.



Scheme 1. The enantioselective C–H functionalization of indoles with ethyl α-alkyl-α-diazoacetates under catalysis by Rh_2(*S*-NTTL)$_4$ **3** reported by Fox.[11]

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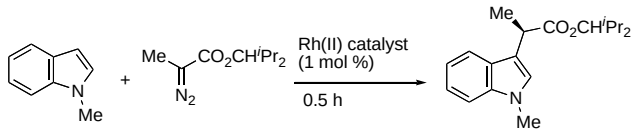
derivatives with small 2-substituents (R^2 = H, Me) were used. We have recently been engaged in the enantioselective C–H functionalization of indoles with α-diazopropionates catalyzed by chiral dirhodium(II) carboxylates. Although Fox and co-workers described the catalytic enantioselective reaction of 2-methyl-1-phenylindole with ethyl α-diazopropionate (79% ee, Scheme 1),[11] no examples of the reaction of 2,3-unsubstituted indoles with α-diazopropionates have been reported. Herein, we report the first example of a catalytic enantioselective C–H functionalization of 2,3-unsubstituted indoles with α-diazopropionates.

2. Results and discussion

At the outset, we explored the reaction of 2,3-unsubstituted *N*-methylindole **5a** (1.2 equiv) with 2,4-dimethyl-3-pentyl α-diazopropionate **6a** using 1 mol % of Rh_2(*S*-PTTL)$_4$ **1a**[13–15] (Table 1, entry 1). The reaction in dichloromethane at room temperature proceeded smoothly to give α-methyl-3-indolylacetate **7a** in 82% yield with no signs of α,β-unsaturated ester formation via a 1,2-hydride shift.[16] The enantiomeric excess of **7a** was determined to be 52% by HPLC using a Daicel Chiralcel OD-H column. To further enhance the enantioselectivity, we evaluated the performance of other chiral dirhodium(II) carboxylate catalysts. Although Rh_2(*S*-TFPTTL)$_4$ **1b**[17] and Rh_2(*S*-TCPTTL)$_4$ **1c**,[18–20] fluorinated and chlorinated analogues of **1a**, provided **7a** in high yields, poor enantioselectivities were obtained (43% and 22% ee, respectively, entries 2 and 3). Catalysis with Rh_2(*S*-PTA)$_4$ **1d** and Rh_2(*S*-PTV)$_4$ **1e** resulted in lower product yields and enantioselectivities than those obtained with **1a** (21% and 32% ee, respectively, entries 4 and 5). We recently developed dirhodium(II) tetrakis[*N*-phthaloyl-(*S*)-triethylalaninate], Rh_2(*S*-PTTEA)$_4$ **1f**, characterized by an exceptionally bulky triethylmethyl group, for the enantioselective intramolecular C–H insertion of aryldiazoacetates.[21] Gratifyingly, the use of **1f** was found to increase the enantioselectivity to 67% ee (entry 6). A survey of solvents with **1f** revealed that dichloromethane was the optimal solvent for this transformation in terms of both product yield and enantioselectivity (entry 6 vs entries 7–10).

Table 1
Enantioselective C–H functionalization of *N*-methylindole **5a** with 2,4-dimethyl-3-pentyl α-diazopropionate **6a** catalyzed by chiral dirhodium(II) carboxylates[a]



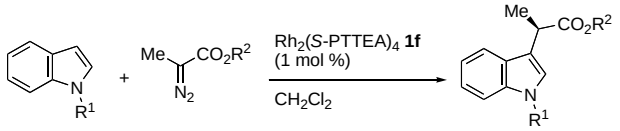
5a (1.2 equiv) **6a** **7a**

Entry	Rh(II) catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	Rh_2(*S*-PTTL)$_4$ **1a**	CH_2Cl_2	82	52
2	Rh_2(*S*-TFPTTL)$_4$ **1b**	CH_2Cl_2	84	43
3	Rh_2(*S*-TCPTTL)$_4$ **1c**	CH_2Cl_2	90	22
4	Rh_2(*S*-PTA)$_4$ **1d**	CH_2Cl_2	64	21
5	Rh_2(*S*-PTV)$_4$ **1e**	CH_2Cl_2	72	32
6	Rh_2(*S*-PTTEA)$_4$ **1f**	CH_2Cl_2	83	67
7	Rh_2(*S*-PTTEA)$_4$ **1f**	toluene	87	59
8	Rh_2(*S*-PTTEA)$_4$ **1f**	hexane	92	58
9	Rh_2(*S*-PTTEA)$_4$ **1f**	AcOEt	76	65
10	Rh_2(*S*-PTTEA)$_4$ **1f**	acetone	40	54

[a] All reactions were carried out as follows: Rh(II) catalyst (1 mol %) was added to a solution of **5a** (0.030 mL, 0.24 mmol, 1.2 equiv) and **6a** (39.7 mg, 0.20 mmol) in the indicated solvent (1 mL) at room temperature.
[b] Isolated yield.
[c] Determined by HPLC (Daicel Chiralcel OD-H).

Using Rh_2(*S*-PTTEA)$_4$ **1f** as a catalyst, we next examined the effects of the *N*-substitution of the indole ring (Table 2). As might be expected from precedents,[4,5g,5i,5l,11,22] the reaction of **6a** with indoles **5b** and **5c** carrying strongly electron-withdrawing Boc or Ts groups failed to give the corresponding indole products **7b** and **7c** (entries 2 and 3); instead, azine derived from **6a** was obtained as a major product. While the reaction of *N*-benzylindole **5d** proceeded smoothly to give **7d** in 89% yield with 74% ee (entry 4), *N*-methoxymethyl (MOM)-protected indole **5e** provided **7e** in 83% yield and with a greatly improved enantioselectivity of 82% ee (entry 5). An examination of the temperature profile demonstrated that lowering the reaction temperature to −40 or −60 °C had only a marginal effect on enantioselectivity (78% and 75% ee), although a sharp drop in product yield was observed (70% and 64%, respectively, entries 6 and 7). The effects of the ester moiety were also evaluated. Reactions of **5e** with *tert*-butyl and ethyl esters **6b** and **6c** resulted in lower enantioselectivities than that observed with **6a** (45% and 41% ee, respectively, entries 8 and 9). These results demonstrate that the use of the 2,4-dimethyl-3-pentyl ester moiety[23] is crucial for a high degree of enantioselection.

Table 2
Enantioselective C–H functionalization of indoles **5a**–**e** with α-diazopropionates **6a**–**c** catalyzed by Rh_2(*S*-PTTEA)$_4$ **1f**



5 (1.2 equiv) **6** **7**

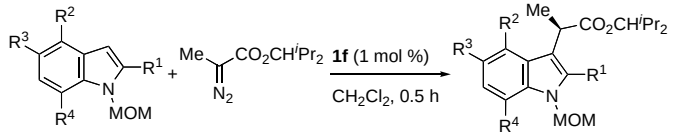
Entry	Indole **5**		Diazoester **6**		*T* (°C)	*t* (h)	Product **7**		
		R^1		R^2				Yield[a] (%)	ee[b] (%)
1	**5a**	Me	**6a**	^{i}Pr$_2$CH	23	0.5	**7a**	83	67
2	**5b**	Boc	**6a**	^{i}Pr$_2$CH	23	0.5	**7b**	ND[c]	–
3	**5c**	Ts	**6a**	^{i}Pr$_2$CH	23	0.5	**7c**	ND[c]	–
4	**5d**	Bn	**6a**	^{i}Pr$_2$CH	23	0.5	**7d**	89	74
5	**5e**	MOM	**6a**	^{i}Pr$_2$CH	23	0.5	**7e**	83	82
6	**5e**	MOM	**6a**	^{i}Pr$_2$CH	–40	2	**7e**	70	78
7	**5e**	MOM	**6a**	^{i}Pr$_2$CH	–60	15	**7e**	64	75
8	**5e**	MOM	**6b**	^{t}Bu	23	0.5	**7f**	72	45
9	**5e**	MOM	**6c**	Et	23	0.5	**7g**	69	32

[a] Isolated yield.
[b] Determined by HPLC.
[c] Not detected.

Under optimized reaction conditions, we then explored the scope of the reaction with respect to the indole component (Table 3). The reaction with 2-methylindole derivative **5f** resulted in only a trace amount of product **7h** (entry 1), which was markedly different from Fox's result with ethyl α-diazopropionate.[24] The reaction with 4-methylindole **5g** afforded **7i** in 72% yield and 69% ee (entry 2). The reaction was also tolerant of methoxy, bromo, and nitro groups at the 5-position of the *N*-MOM-protected indole nucleus (69–83% yields, 58–72% ee, entries 3–5). The highest enantioselectivity (86% ee) was obtained in the reaction with 7-methylindole **5k** (entry 6).

To determine the preferred absolute configuration of **7e**, we explored removal of the MOM protecting group (Scheme 2). Hydrolysis of **7e** with 2 M HCl in THF followed by treatment with 15% NaOH[25] provided indole **9** in 51% yield. Treatment with BBr_3,[26] aq. formic acid[27] or TMSI[28] gave a complex mixture of products. After considerable experimentation, the Fujioka protocol using a combination of TMSOTf and 2,2'-bipyridyl[29] proved to be the method of choice. Treatment of **7e** with TMSOTf (2 equiv) and 2,2'-bipyridyl (3 equiv) in CH_2Cl_2 at 0 °C led to the exclusive cleavage of the methyl ether linkage of

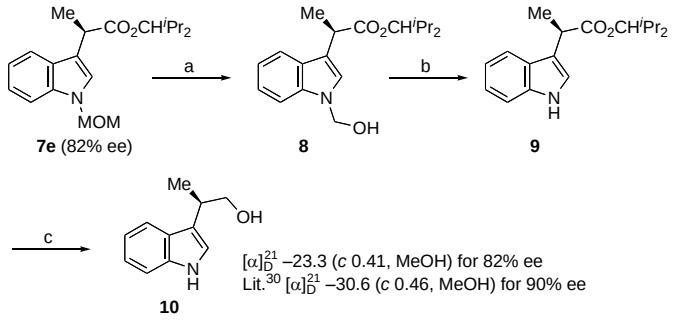
Table 3
Enantioselective C–H functionalization of indoles **5f**–**k** with 2,4-dimethyl-3-pentyl α-diazopropionate **6a** catalyzed by Rh_2(*S*-PTTEA)$_4$ **1f**



5 (1.2 equiv) **6a** **7**

Entry	Indole **5**					Product **7**		
		R^1	R^2	R^3	R^4		Yield[a] (%)	ee[b] (%)
1	**5f**	Me	H	H	H	**7h**	trace	–
2	**5g**	H	Me	H	H	**7i**	72	69
3	**5h**	H	H	MeO	H	**7j**	77	58
4	**5i**	H	H	Br	H	**7k**	83	64
5	**5j**	H	H	NO_2	H	**7l**	69	72
6	**5k**	H	H	H	Me	**7m**	83	86

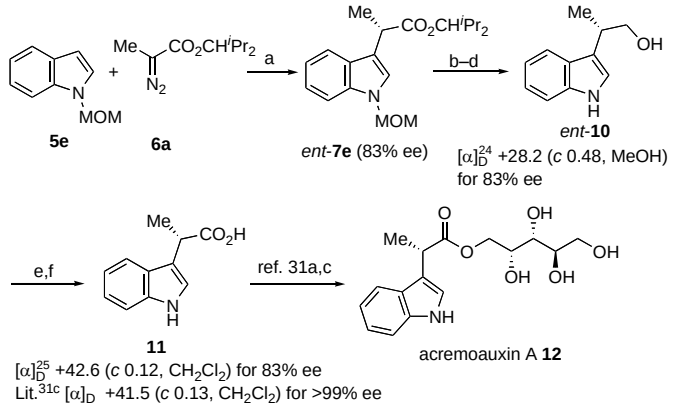
[a] Isolated yield.
[b] Determined by HPLC.



Scheme 2. Reagents and conditions: (a) TMSOTf, 2,2'-bipyridyl, CH_2Cl_2, 0 °C, 0.5 h; (b) NaOH, THF/H_2O (9:1), 24 h, 98% (two steps); (c) $LiAlH_4$, THF, 4 h, 87%.

the MOM protecting group to give **8**, which, upon exposure to NaOH in THF/H_2O (9:1), afforded **9** in 98% yield. Reduction of 2,4-dimethyl-3-pentyl ester **9** with $LiAlH_4$ provided the known alcohol **10** {$[\alpha]_D^{21}$ −23.3 (*c* 0.41, MeOH) for 82% ee; lit.,[30] $[\alpha]_D^{21}$ −30.6 (*c* 0.46, MeOH) for 90% ee of (*R*)-**10**} in 87% yield. Thus, the preferred absolute configuration of **7e** was established as *R*.

Using the present catalytic protocol, we conducted an asymmetric synthesis of (+)-α-methyl-3-indolylacetic acid **11**,[31] a phytohormone of the auxin class[32] and a constituent of a potent plant-growth inhibitor acremoauxin A **12** (Scheme 3).[33,34] Alcohol *ent*-**10** was prepared using Rh_2(*R*-PTTEA)$_4$ **2**. Fortunately, Overman and Govek reported the chemoselective oxidation of a primary alcohol tethered to an unmasked indole substituent to carboxylic acid in the total synthesis of (+)-asperazine.[35] Following this precedent, oxidation of alcohol *ent*-**10** under standard Parikh–Doering conditions[36] and subsequent Lindgren–Kraus oxidation[37] of the crude aldehyde provided carboxylic acid **11** in 61% yield. The spectroscopic data (^{1}H and ^{13}C NMR, and IR) of synthetic material **11** were identical to those reported by Baran and co-workers.[31c] The sign of optical rotation of synthetic product **11** {$[\alpha]_D^{25}$ +42.6 (*c* 0.12, CH_2Cl_2) for 83% ee} was the same as that reported in the literature {lit.[31c] $[\alpha]_D$ +41.5 (*c* 0.13, CH_2Cl_2) for >99% ee}.[38] This is the first catalytic asymmetric synthesis of the (+)-α-methyl-3-indolylacetic acid fragment of **12**.



Scheme 3. Reagents and conditions: (a) Rh_2(*R*-PTTEA)$_4$ **2** (1 mol %), CH_2Cl_2, 0.5 h, 83%; (b) TMSOTf, 2,2'-bipyridyl, CH_2Cl_2, 0 °C, 0.5 h; (c) NaOH, THF/H_2O (9:1), 24 h, 98% (two steps); (d) $LiAlH_4$, THF, 4 h, 97%; (e) SO_3·pyridine, Et_3N, DMSO; (f) $NaClO_2$, NaH_2PO_4·H_2O, 2-methyl-2-butene, THF/H_2O, 61% (two steps).

3. Conclusion

We have developed a catalytic enantioselective C–H functionalization protocol for *N*-methoxymethyl (MOM)-protected 2,3-unsubstituted indoles using 2,4-dimethyl-3-pentyl α-diazopropionates. In this process, Rh_2(*S*-PTTEA)$_4$, which is characterized by an exceptionally bulky triethylmethyl group, has emerged as the catalyst of choice for providing α-methyl-3-indolylacetates in high yields and with enantioselectivities of up to 86% ee. This represents the first example of a catalytic enantioselective C–H functionalization of 2,3-unsubstituted indoles with α-diazopropionates. Using this methodology, we achieved the first catalytic asymmetric synthesis of the (+)-α-methyl-3-indolylacetic acid fragment of acremoauxin A. In our approach, the use of a MOM group as a protecting group on the indole nitrogen was not only crucial for high levels of enantioselection but also synthetically advantageous since the removal of the *N*-MOM group could be conducted efficiently under the Fujioka conditions. Further applications of this methodology to catalytic asymmetric synthesis of indole alkaloids as well as stereochemical studies are currently in progress.

4. Experimental

4.1. General

Optical rotations were measured on a JASCO P-1030 digital polarimeter at the sodium D line (589 nm). IR spectra were recorded on a JASCO FT/IR-5300 spectrometer and absorbance bands are reported in wavenumber (cm^{-1}). ^{1}H NMR spectra were recorded on JEOL JNM-ECX 400P (400 MHz) spectrometer or JNM-ECA 500 (500 MHz) spectrometer. Chemical shifts are reported relative to internal standard (tetramethylsilane at δ_H 0.00 or $CDCl_3$ at δ_H 7.26). Data are presented as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants, integration and assignment. ^{13}C NMR spectra were recorded on JEOL JNM-ECX 400P (100 MHz) spectrometer or JEOL JNM-ECA 500 (125 MHz) spectrometer. The following internal references were used ($CDCl_3$ at δ 77.0). EI mass spectra were recorded on a JEOL JMS-FABmate spectrometer, operating with ionization energy of 70 eV. ESI mass spectra were recorded on a JEOL JMS-T100LCP 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. Visualization was accomplished with UV light, anisaldehyde stain solution or phosphomolybdic acid stain solution followed by heating. Analytical high performance liquid chromatography (HPLC) was performed on a JASCO PU-1580 intelligent HPLC pump with JASCO UV-1575

intelligent UV/VIS detector. Detection was performed at 254 nm. Chiralcel OD-H, Chiralpak AD-H, Chiralpak IC columns (0.46 cm × 25 cm) and Chiralpak IC-3 column (0.46 cm × 15 cm) from Daicel were used. Retention times (t_R) and peak ratios were determined with JASCO-Borwin analysis system.

All non-aqueous reactions were carried out in flame-dried glassware under Ar atmosphere unless otherwise noted. Reagents and solvents were purified by standard means. Dehydrated CH_2Cl_2, THF and DMF were purchased from Kanto Chemical Co., Inc. Chiral dirhodium(II) carboxylates **1a**–**f**[14a,17a,18a,21] and **2**,[21] 1-methoxymethylindole **5e**,[39] 1-methoxymethyl-5-nitroindole **5j**[40] and α-diazopropionates **6a**,[23c] **6b**[41] and **6c**[41] were prepared according to literature procedures.

4.2. Preparation of *N*-MOM-protected indoles

4.2.1. 1-Methoxymethyl-2-methylindole 5f

A solution of 2-methylindole (1.00 g, 6.16 mmol) in DMF (5 mL) was added to a solution of NaH (60% in oil, 0.34 g, 8.38 mmol) in DMF (10 mL) at 0 °C. After stirring for 0.5 h at room temperature, MOMCl (0.70 mL, 9.22 mmol) was added to the reaction mixture. After stirring for 1 h, the reaction was quenched by addition of water (30 mL). The mixture was extracted with EtOAc (2 × 20 mL) and the combined organic layers were washed with water (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (1.65 g), which was purified by column chromatography (silica gel, 20:1 hexane/EtOAc) to provide **5f** (1.20 g, 90%) as a colorless oil: TLC R_f = 0.38 (20:1 hexane/EtOAc); IR (neat) ν 2948, 2252, 1460, 1308 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H, CH_3Ar), 3.24 (s, 3H, CH_3OCH$_2$), 5.43 (s, 2H, CH$_3$OCH_2), 6.29 (s, 1H, *Ar*), 7.09 (ddd, *J* = 0.9, 7.7, 8.2 Hz, 1H, *Ar*), 7.16 (ddd, *J* = 1.4, 7.2, 8.2 Hz, 1H, *Ar*), 7.40 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.51 (d, *J* = 7.2 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4 (CH_3), 55.5 (CH_3), 73.6 (CH_2), 101.7 (CH), 109.0 (CH), 119.7 (CH), 120.0 (CH), 121.1 (CH), 128.2 (C), 136.7 (CH), 137.5 (C); HRMS (ESI) calcd for $C_{11}H_{14}NO$ $(M + H)^+$ 176.10699, found 176.10708.

4.2.2. 1-Methoxymethyl-4-methylindole 5g

According to the procedure for the preparation of **5f**, **5g** was prepared from 4-methylindole (0.500 g, 3.08 mmol). The crude product was purified by column chromatography (silica gel, 20:1 hexane/EtOAc) to provide the title compound (0.639 g, 96%) as a colorless oil: TLC R_f = 0.31 (20:1 hexane/EtOAc); IR (neat) ν 2928, 2251, 1519, 1493, 1303, 1236 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H, CH_3Ar), 3.23 (s, 3H, CH_3OCH$_2$), 5.45 (s, 2H, CH$_3$OCH_2), 6.56 (dd, *J* = 0.9, 3.2 Hz, 1H, *Ar*), 6.95 (ddd, *J* = 0.9, 0.9, 8.2 Hz, 1H, *Ar*), 7.15 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.17 (d, *J* = 3.2 Hz, 1H, *Ar*), 7.33 (d, *J* = 8.2 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7 (CH_3), 55.9 (CH_3), 77.5 (CH_2), 101.1 (CH), 107.5 (CH), 120.5 (CH), 122.3 (CH), 127.5 (CH), 129.0 (C), 130.5 (CH), 136.1 (C); HRMS (ESI) calcd for $C_{11}H_{14}NO$ $(M + H)^+$ 176.10699, found 176.10704.

4.2.3. 5-Methoxy-1-methoxymethylindole 5h

According to the procedure for the preparation of **5f**, **5h** was prepared from 5-methoxyindole (0.500 g, 3.40 mmol). The crude product was purified by column chromatography (silica gel, 10:1 hexane/EtOAc) to provide the title compound (0.583 g, 90%) as a colorless oil: TLC R_f = 0.29 (10:1 hexane/EtOAc); IR (neat) ν 2938, 1486, 1239, 1151, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.23 (s, 3H, CH_3OCH$_2$), 3.86 (s, 3H, CH_3OAr), 5.42 (s, 2H, CH$_3$OCH_2), 6.46 (d, *J* = 2.7 Hz, 1H, *Ar*), 6.90 (dd, *J* = 2.3, 9.1 Hz, 1H, *Ar*), 7.10 (d, *J* = 2.3 Hz, 1H, *Ar*), 7.15 (d, *J* = 3.2 Hz, 1H, *Ar*), 7.38 (d, *J* = 8.6 Hz, 1H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.7 (CH_3), 55.8 (CH_3), 77.6 (CH_2), 102.1 (CH), 102.6 (CH), 110.6 (CH), 112.3 (CH), 128.7 (CH), 129.6 (C), 131.5 (C), 154.5 (C); HRMS (ESI) calcd for $C_{11}H_{14}NO_2$ $(M + H)^+$ 192.10191, found 192.10193.

4.2.4. 5-Bromo-1-methoxymethylindole 5i

According to the procedure for the preparation of **5f**, **5i** was prepared from 5-bromoindole (0.500 g, 2.55 mmol). The crude product was purified by column chromatography (silica gel, 10:1 hexane/EtOAc) to provide the title compound (0.596 g, 97%) as a colorless oil: TLC R_f = 0.26 (10:1 hexane/EtOAc); IR (neat) ν 2936, 2360, 1452, 1328, 1183, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.22 (s, 3H, CH_3OCH$_2$), 5.43 (s, 2H, CH$_3$OCH_2), 6.48 (d, *J* = 3.2 Hz, 1H, *Ar*), 7.18 (d, *J* = 3.2 Hz, 1H, *Ar*), 7.32 (dd, *J* = 1.8, 8.6 Hz, 1H, *Ar*), 7.37 (d, *J* = 8.6 Hz, 1H, *Ar*), 7.76 (d, *J* = 1.8 Hz, 1H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.9 (CH_3), 77.5 (CH_2), 102.0 (CH), 111.4 (CH), 113.5 (C), 123.4 (CH), 125.0 (CH), 129.2 (CH), 130.8 (C), 134.9 (C); HRMS (ESI) calcd for $C_{10}H_{11}BrNO$ $(M + H)^+$ 240.00185, found 240.00228.

4.2.5. 1-Methoxymethyl-7-methylindole 5k

According to the procedure for the preparation of **5f**, **5k** was prepared from 7-methylindole (0.500 g, 3.08 mmol). The crude product was purified by column chromatography (silica gel, 20:1 hexane/EtOAc) to provide the title compound (0.658 g, 99%) as a colorless oil: TLC R_f = 0.25 (20:1 hexane/EtOAc); IR (neat) ν 2930, 1462, 1305 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.74 (s, 3H, CH_3Ar), 3.23 (s, 3H, CH_3OCH$_2$), 5.53 (s, 2H, CH$_3$OCH_2), 6.49 (d, *J* = 3.2 Hz, 1H, *Ar*), 6.98 (d, *J* = 7.2 Hz, 1H, *Ar*), 7.04 (dd, *J* = 7.2, 7.7 Hz, 1H, *Ar*), 7.10 (d, *J* = 3.2 Hz, 1H, *Ar*), 7.47 (d, *J* = 7.2 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2 (CH_3), 55.2 (CH_3), 79.3 (CH_2), 102.3 (CH), 118.9 (CH), 120.5 (CH), 121.9 (C), 124.9 (CH), 130.1 (CH), 130.4 (C); HRMS (ESI) calcd for $C_{11}H_{14}NO$ $(M + H)^+$ 176.10699, found 176.10714.

4.3. Enantioselective C–H functionalization of indoles with α-diazopropionates

4.3.1. Typical procedure for the C–H functionalization of indoles: (*R**)-2,4-Dimethyl-3-pentyl 2-[(1-methyl)-1*H*-indol-3-yl]propionate 7a (Table 1, entry 6)

Rh_2(*S*-PTTEA)$_4$·2EtOAc **1f** (3.18 mg, 0.002 mmol, 1 mol %) was added in one portion to a solution of 2,4-dimethyl-3-pentyl α-diazopropionate **6a** (39.7 mg, 0.200 mmol) and 1-methylindole **5a** (0.030 mL, 0.235 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. After stirring for 0.5 h at room temperature, the reaction mixture was concentrated in vacuo, and the residue was purified by column chromatography (silica gel, 20:1 hexane/EtOAc) to provide **7a** (50.2 mg, 83%) as a colorless oil: TLC R_f = 0.43 (10:1 hexane/EtOAc); $[\alpha]_D^{24}$ −24.0 (*c* 0.99, $CHCl_3$) for 67% ee; IR (neat) ν 2966, 1730, 1471, 1371, 1330, 1242, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.72 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.82 (d, *J* = 6.8 Hz, 3H, CH(CH_3)$_2$), 0.84 (d, *J* = 7.2 Hz, 3H, CH(CH_3)$_2$), 1.63 (d, *J* = 7.2 Hz, 3H, CH_3CHAr), 1.77–1.92 (m, 2H, CH(CH$_3$)$_2$), 3.76 (s, 3H, CH_3N), 4.06 (q, *J* = 7.2 Hz, 1H, CH$_3$CHAr), 4.58 (t, *J* = 6.3 Hz, 1H, CO$_2$CH), 7.03 (s, 1H, *Ar*), 7.10 (m, 1H, *Ar*), 7.21 (m, 1H, *Ar*), 7.28 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.68 (d, *J* = 8.2 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0 (CH_3), 17.2 (CH_3), 18.3 (CH_3), 19.4 (CH_3), 19.5 (CH_3), 29.4 (CH), 32.7 (CH_3), 37.2 (CH), 82.6 (CH), 109.1 (CH), 114.3 (C), 118.9 (CH), 119.4 (CH), 121.6 (CH), 126.3 (CH), 127.0 (C), 136.9 (C), 175.3 (CO); HRMS (EI^+) calcd for $C_{19}H_{27}NO_2$ $(M)^+$ 301.20418, found 301.20346. The enantiomeric excess of **7a** was determined to be 67% by HPLC with a Daicel Chiralpak OD-H

column (eluent: 100:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 8.5 min for minor enantiomer; t_R = 9.5 min for major enantiomer. The preferred absolute configuration of **7a** was not determined.

4.3.2. (*R**)-2,4-Dimethyl-3-pentyl 2-[(1-benzyl)-1*H*-indol-3-yl]propionate 7d (Table 2, entry 4)

According to the typical procedure for C–H functionalization of indole, **7d** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (39.7 mg, 0.200 mmol) and 1-benzylindole **5d** (49.7 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 30:1 hexane/EtOAc) to provide **7d** (67.4 mg, 89%) as a colorless oil: TLC R_f = 0.43 (10:1 hexane/EtOAc); $[\alpha]_D^{21}$ −16.4 (*c* 1.00, $CHCl_3$) for 74% ee; IR (neat) ν 2966, 1728, 1468, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.64 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.70 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.78 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.81 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 1.63 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CHAr), 1.76–1.87 (m, 2H, C*H*(CH$_3$)$_2$), 4.07 (q, *J* = 7.2 Hz, 1H, CH$_3$C*H*Ar), 4.57 (t, *J* = 6.3 Hz, 1H, CO$_2$C*H*), 5.27 (d, *J* = 16.3 Hz, 1H, ArCH*H*), 5.32 (d, *J* = 16.3 Hz, 1H, ArCH*H*), 7.06–7.17 (m, 5H, *Ar*), 7.22–7.29 (m, 4H, *Ar*), 7.72 (d, *J* = 7.7 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9 (CH$_3$), 17.2 (CH$_3$), 18.1 (CH$_3$), 19.4 (CH$_3$), 19.4 (CH$_3$), 29.4 (CH), 29.4 (CH), 37.2 (CH), 49.9 (CH$_2$), 82.5 (CH), 109.6 (CH), 115.0 (C), 119.1 (CH), 119.6 (CH), 121.8 (CH), 125.6 (CH), 126.6 (CH), 127.3 (C), 127.5 (CH), 128.6 (CH), 136.4 (C), 137.5 (C), 175.0 (CO); HRMS (ESI) calcd for $C_{25}H_{31}NO_2Na$ (M + Na)$^+$ 400.22470, found 400.22451. The enantiomeric excess of **7d** was determined to be 74% by HPLC with a Daicel Chiralpak OD-H column (eluent: 100:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 16.0 min for minor enantiomer; t_R = 17.7 min for major enantiomer. The preferred absolute configuration of **7d** was not determined.

4.3.3. (*R*)-2,4-Dimethyl-3-pentyl 2-[(1-methoxymethyl)-1*H*-indol-3-yl]propionate 7e (Table 2, entry 5)

According to the typical procedure for C–H functionalization of indole, **7e** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (79.3 mg, 0.400 mmol) and 1-methoxymethylindole **5e** (77.4 mg, 0.480 mmol). The crude product was purified by column chromatography (silica gel, 5:1 hexane/Et_2O) to provide **7e** (111 mg, 83%) as a colorless oil: TLC R_f = 0.30 (10:1 hexane/EtOAc); $[\alpha]_D^{20}$ −20.3 (*c* 1.04, $CHCl_3$) for 82% ee; IR (neat) ν 2966, 1730, 1466, 1181, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.65 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.71 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.80 (d, *J* = 6.3 Hz, 3H, CH(C*H*$_3$)$_2$), 0.82 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 1.64 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CHAr), 1.75–1.90 (m, 2H, C*H*(CH$_3$)$_2$), 3.19 (s, 3H, C*H*$_3$OCH$_2$), 4.05 (q, *J* = 7.2 Hz, 1H, CH$_3$C*H*Ar), 4.58 (t, *J* = 6.3 Hz, 1H, CO$_2$C*H*), 5.39 (d, *J* = 10.9 Hz, 1H, CH$_3$OCH*H*), 5.44 (d, *J* = 11.3 Hz, 1H, CH$_3$OCH*H*), 7.15 (m, 1H, *Ar*), 7.15 (s, 1H, *Ar*), 7.23 (m, 1H, *Ar*), 7.45 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.70 (d, *J* = 7.7 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9 (CH$_3$), 17.2 (CH$_3$), 18.0 (CH$_3$), 19.3 (CH$_3$), 19.5 (CH$_3$), 29.4 (CH), 37.1 (CH), 55.7 (CH$_3$), 77.3 (CH$_2$), 82.6 (CH), 109.8 (CH), 115.9 (C), 119.6 (CH), 119.9 (CH), 122.3 (CH), 125.4 (CH), 127.8 (C), 136.5 (C), 174.9 (CO); HRMS (ESI) calcd for $C_{20}H_{29}NO_3Na$ (M + Na)$^+$ 354.20451, found 354.20480. The enantiomeric excess of **7e** was determined to be 82% by HPLC analysis with a Daicel Chiralpak IC column (eluent: 100:1 hexane/2-propanol; flow: 1.0 mL/min): t_R (minor) = 9.8 min for (*S*)-**7e**; t_R (major) = 11.0 min for (*R*)-**7e**.

4.3.4. (*R**)-*tert*-Butyl 2-[(1-methoxymethyl)-1*H*-indol-3-yl]propionate 7f (Table 2, entry 8)

According to the typical procedure for C–H functionalization of indole, **7f** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), *tert*-butyl α-diazopropionate **6b** (31.2 mg, 0.200 mmol) and **5e** (38.7 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 10:1 hexane/EtOAc) to provide **7f** (41.6 mg, 72%) as a colorless oil: TLC R_f = 0.13 (10:1 hexane/EtOAc); $[\alpha]_D^{22}$ −24.4 (*c* 1.06, $CHCl_3$) for 45% ee; IR (neat) ν 2978, 1726, 1466, 1367, 1149, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H, (C*H*$_3$)$_3$C), 1.56 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CHAr), 3.23 (s, 3H, C*H*$_3$OCH$_2$), 3.90 (q, *J* = 7.2 Hz, 1H, CH$_3$C*H*Ar), 5.42 (s, 2H, CH$_3$OC*H*$_2$), 7.11 (s, 1H, *Ar*), 7.15 (dd, *J* = 7.2, 8.0 Hz, 1H, *Ar*), 7.24 (dd, *J* = 8.0, 8.0 Hz, 1H, *Ar*), 7.45 (d, *J* = 8.4 Hz, 1H, *Ar*), 7.69 (d, *J* = 7.6 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8 (CH$_3$), 28.0 (CH$_3$), 37.8 (CH), 55.8 (CH$_3$), 77.3 (CH$_2$), 80.4 (C), 109.8 (CH), 116.0 (C), 119.6 (CH), 119.8 (CH), 122.3 (CH), 125.3 (CH), 127.8 (C), 136.6 (C), 174.3 (CO); HRMS (ESI) calcd for $C_{17}H_{23}NO_3Na$ (M + Na)$^+$ 312.15701, found 312.15655. The enantiomeric excess of **7f** was determined to be 45% by HPLC with a Daicel Chiralpak OD-H column (eluent: 100:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 10.6 min for major enantiomer; t_R = 11.4 min for minor enantiomer. The preferred absolute configuration of **7f** was not determined.

4.3.5. (*R**)-Ethyl 2-[(1-methoxymethyl)-1*H*-indol-3-yl]propionate 7g (Table 2, entry 9)

According to the typical procedure for C–H functionalization of indole, **7g** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), ethyl α-diazopropionate **6c** (25.6 mg, 0.200 mmol) and **5e** (38.7 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 10:1→5:1 hexane/EtOAc) to provide **7g** (36.0 mg, 69%) as a colorless oil: TLC R_f = 0.10 (10:1 hexane/EtOAc); $[\alpha]_D^{22}$ −19.5 (*c* 1.00, $CHCl_3$) for 32% ee; IR (neat) ν 2980, 1731, 1466, 1330, 1181, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 6.8 Hz, 3H, C*H*$_3$CH$_2$O), 1.60 (d, *J* = 7.2 Hz, 3H, C*H*$_3$CHAr), 3.25 (s, 3H, C*H*$_3$OCH$_2$), 4.00 (q, *J* = 7.2 Hz, 1H, CH$_3$C*H*Ar), 4.07–4.20 (m, 2H, CH$_3$C*H*$_2$O), 5.42 (s, 2H, CH$_3$OC*H*$_2$), 7.13 (s, 1H, *Ar*), 7.16 (dd, *J* = 7.2, 7.7 Hz, 1H, *Ar*), 7.25 (d, *J* = 7.2, 8.2 Hz, 1H, *Ar*), 7.46 (d, *J* = 8.2 Hz, 1H, *Ar*), 7.69 (d, *J* = 7.7 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH$_3$), 17.9 (CH$_3$), 36.9 (CH), 55.9 (CH$_3$), 60.7 (CH$_2$), 77.4 (CH$_2$), 109.9 (CH), 115.7 (C), 119.5 (CH), 120.0 (CH), 122.4 (CH), 125.4 (CH), 127.7 (C), 136.7 (C), 175.0 (CO); HRMS (ESI) calcd for $C_{15}H_{19}NO_3Na$ (M + Na)$^+$ 284.12571, found 284.12538. The enantiomeric excess of **7g** was determined to be 32% by HPLC with a Daicel Chiralpak OD-H column (eluent: 9:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 8.0 min for major enantiomer; t_R = 10.7 min for minor enantiomer. The preferred absolute configuration of **7g** was not determined.

4.3.6. (*R**)-2,4-Dimethyl-3-pentyl 2-[(1-methoxymethyl-4-methyl)-1*H*-indol-3-yl]propionate 7i (Table 3, entry 2)

According to the typical procedure for C–H functionalization of indole, **7i** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (39.7 mg, 0.200 mmol) and 1-methoxymethyl-4-methylindole **5g** (42.1 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 5:1 hexane/Et_2O) to provide **7i** (49.5 mg, 72%) as a colorless oil: TLC R_f = 0.18 (5:1 hexane/Et_2O); $[\alpha]_D^{22}$ −28.1 (*c* 0.89, $CHCl_3$) for 69% ee; IR (neat) ν 2966, 1730, 1465, 1181, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.64 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.72 (d, *J* = 6.8 Hz, 3H, CH(C*H*$_3$)$_2$), 0.81 (d, *J* = 7.2 Hz, 3H, CH(C*H*$_3$)$_2$), 0.83 (d, *J* = 7.7 Hz, 3H, CH(C*H*$_3$)$_2$), 1.61 (d, *J* = 6.8 Hz, 3H, C*H*$_3$CHAr), 1.76–1.90 (m, 2H, C*H*(CH$_3$)$_2$), 2.76 (s, 3H, C*H*$_3$Ar), 3.18 (s, 3H, C*H*$_3$OCH$_2$), 4.40 (q, *J* = 6.8 Hz, 1H, CH$_3$C*H*Ar), 4.58 (t, *J* = 6.3 Hz, 1H, CO$_2$C*H*), 5.36 (d, *J* = 11.3 Hz, 1H, CH$_3$OCH*H*), 5.44 (d, *J* = 11.3 Hz, 1H, CH$_3$OCH*H*), 6.89 (d, *J* = 7.2 Hz, 1H, *Ar*), 7.11 (dd, *J* = 7.7, 7.7 Hz, 1H, *Ar*), 7.18 (s, 1H, *Ar*), 7.31 (d, *J* = 8.2 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9 (CH$_3$), 17.2 (CH$_3$),

19.4 (CH_3), 19.5 (CH_3), 19.8 (CH_3), 20.5 (CH_3), 29.4 (CH), 29.4 (CH), 37.5 (CH), 55.7 (CH_3), 77.4 (CH_2), 82.6 (CH), 107.9 (CH), 116.9 (C), 122.2 (CH), 125.8 (CH), 126.4 (C), 130.8 (C), 136.6 (C), 175.5 (CO); HRMS (ESI) calcd for $C_{21}H_{31}NO_3Na$ $(M + Na)^+$ 368.21962, found 368.21912. The enantiomeric excess of **7i** was determined to be 69% by HPLC with a Daicel Chiralpak OD-H column (eluent: 200:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 15.5 min for minor enantiomer; t_R = 17.9 min for major enantiomer. The preferred absolute configuration of **7i** was not determined.

4.3.7. (*R**)-2,4-Dimethyl-3-pentyl 2-[(5-methoxy-1-methoxymethyl)-1*H*-indol-3-yl]propionate 7j (Table 3, entry 3)

According to the typical procedure for C–H functionalization of indole, **7j** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (39.7 mg, 0.200 mmol) and 5-methoxy-1-methoxymethylindole **5h** (45.9 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 5:1 hexane/Et_2O) to provide **7j** (55.6 mg, 77%) as a colorless oil: TLC R_f = 0.13 (10:1 hexane/EtOAc); $[\alpha]_D^{22}$ −24.7 (*c* 1.12, $CHCl_3$) for 58% ee; IR (neat) ν 2966, 1730, 1488, 1222, 1172, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, *J* = 6.3 Hz, 3H, $CH(CH_3)_2$), 0.72 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.81 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.83 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 1.63 (d, *J* = 7.2 Hz, 3H, CH_3CHAr), 1.76–1.91 (m, 2H, $CH(CH_3)_2$), 3.18 (s, 3H, CH_3OCH_2), 3.86 (s, 3H, CH_3OAr), 4.00 (q, *J* = 7.2 Hz, 1H, CH_3CHAr), 4.58 (t, *J* = 6.3 Hz, 1H, CO_2CH), 5.35 (d, *J* = 11.3 Hz, 1H, CH_3OCHH), 5.40 (d, *J* = 11.3 Hz, 1H, CH_3OCHH), 6.89 (dd, *J* = 2.3, 8.6 Hz, 1H, *Ar*), 7.12 (s, 1H, *Ar*), 7.13 (d, *J* = 2.3 Hz, 1H, *Ar*), 7.34 (d, *J* = 8.6 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0 (CH_3), 17.2 (CH_3), 17.8 (CH_3), 19.4 (CH_3), 19.5 (CH_3), 29.4 (CH), 29.4 (CH), 37.1 (CH), 55.6 (CH_3), 55.8 (CH_3), 77.5 (CH_2), 82.6 (CH), 101.3 (CH), 110.7 (CH), 112.6 (CH), 115.4 (C), 126.0 (CH), 128.3 (C), 131.7 (C), 154.3 (C), 174.9 (CO); HRMS (ESI) calcd for $C_{21}H_{31}NO_4Na$ $(M + Na)^+$ 384.21453, found 384.21465. The enantiomeric excess of **7j** was determined to be 58% by HPLC with a Daicel Chiralpak AD-H column (eluent: 9:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 5.3 min for minor enantiomer; t_R = 6.2 min for major enantiomer. The preferred absolute configuration of **7j** was not determined.

4.3.8. (*R**)-2,4-Dimethyl-3-pentyl 2-[(5-bromo-1-methoxymethyl)-1*H*-indol-3-yl]propionate 7k (Table 3, entry 4)

According to the typical procedure for C–H functionalization of indole, **7k** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (39.7 mg, 0.200 mmol) and 5-bromo-1-methoxymethylindole **5i** (57.6 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 5:1 hexane/Et_2O) to provide **7k** (67.9 mg, 83%) as a colorless oil: TLC R_f = 0.11 (10:1 hexane/EtOAc); $[\alpha]_D^{22}$ −36.0 (*c* 1.12, $CHCl_3$) for 64% ee; IR (neat) ν 2966, 1731, 1469, 1353, 1177, 1097 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.66 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.71 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.82 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.84 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 1.62 (d, *J* = 7.2 Hz, 3H, CH_3CHAr), 1.78–1.90 (m, 2H, $CH(CH_3)_2$), 3.18 (s, 3H, CH_3OCH_2), 3.98 (q, *J* = 7.2 Hz, 1H, CH_3CHAr), 4.58 (t, *J* = 6.3 Hz, 1H, CO_2CH), 5.36 (d, *J* = 10.9 Hz, 1H, CH_3OCHH), 5.41 (d, *J* = 10.9 Hz, 1H, CH_3OCHH), 7.75 (s, 1H, *Ar*), 7.32 (d, *J* = 0.9 Hz, 1H, *Ar*), 7.32 (s, 1H, *Ar*), 7.85 (d, *J* = 0.9 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9 (CH_3), 17.2 (CH_3), 17.8 (CH_3), 19.3 (CH_3), 19.5 (CH_3), 29.4 (CH), 37.0 (CH), 55.8 (CH_3), 77.5 (CH_2), 82.9 (CH), 111.4 (CH), 113.4 (C), 115.5 (C), 122.4 (CH), 125.2 (CH), 126.5 (CH), 129.5 (C), 135.2 (C), 174.5 (CO); HRMS (ESI) calcd for $C_{20}H_{28}BrNO_3Na$ $(M + Na)^+$ 432.11448, found 432.11508. The enantiomeric excess of **7k** was determined to be 64% by HPLC with a Daicel Chiralpak AD-H column (eluent: 9:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 4.5 min for minor enantiomer; t_R = 5.8 min for major enantiomer. The preferred absolute configuration of **7k** was not determined.

4.3.9. (*R**)-2,4-Dimethyl-3-pentyl 2-[(1-methoxymethyl-5-nitro)-1*H*-indol-3-yl]propionate 7l (Table 3, entry 5)

According to the typical procedure for C–H functionalization of indole, **7l** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (39.7 mg, 0.200 mmol) and 1-methoxymethyl-5-nitroindole **5j** (45.9 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 3:1 hexane/EtOAc) to provide **7l** (52.1 mg, 69%) as a colorless oil: TLC R_f = 0.50 (5:1 hexane/EtOAc); $[\alpha]_D^{22}$ −71.0 (*c* 0.50, $CHCl_3$) for 72% ee; IR (neat) ν 2967, 1731, 1519, 1336, 1179, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.63 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.71 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.83 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.85 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 1.67 (d, *J* = 7.2 Hz, 3H, CH_3CHAr), 1.77–1.94 (m, 2H, $CH(CH_3)_2$), 3.23 (s, 3H, CH_3OCH_2), 4.09 (q, *J* = 7.2 Hz, 1H, CH_3CHAr), 4.59 (t, *J* = 6.3 Hz, 1H, CO_2CH), 5.43 (d, *J* = 10.9 Hz, 1H, CH_3OCHH), 5.47 (d, *J* = 10.9 Hz, 1H, CH_3OCHH), 7.31 (s, 1H, *Ar*), 7.50 (d, *J* = 9.1 Hz, 1H, *Ar*), 8.16 (d, *J* = 1.8, 9.1 Hz, 1H, *Ar*), 8.70 (d, *J* = 2.3 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.9 (CH_3), 17.1 (CH_3), 17.8 (CH_3), 19.3 (CH_3), 19.5 (CH_3), 29.3 (CH), 36.8 (CH), 56.1 (CH_3), 77.8 (CH_2), 83.3 (CH), 110.1 (CH), 117.1 (CH), 118.1 (C), 118.3 (CH), 127.3 (C), 128.4 (CH), 139.4 (C), 142.0 (C), 174.2 (CO); HRMS (ESI) calcd for $C_{20}H_{28}N_2O_5Na$ $(M + Na)^+$ 399.18904, found 399.18926. The enantiomeric excess of **7l** was determined to be 72% by HPLC with a Daicel Chiralpak AD-H column (eluent: 9:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 7.2 min for minor enantiomer; t_R = 11.6 min for major enantiomer. The preferred absolute configuration of **7l** was not determined.

4.3.10. (*R**)-2,4-Dimethyl-3-pentyl 2-[(1-methoxymethyl-7-methyl)-1*H*-indol-3-yl]propionate 7m (Table 3, entry 6)

According to the typical procedure for C–H functionalization of indole, **7m** was prepared from **1f** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (39.7 mg, 0.200 mmol) and 1-methoxymethyl-7-methylindole **5k** (42.1 mg, 0.24 mmol). The crude product was purified by column chromatography (silica gel, 5:1 hexane/Et_2O) to provide **7m** (57.3 mg, 83%) as a colorless oil: TLC R_f = 0.17 (5:1 hexane/Et_2O); $[\alpha]_D^{22}$ −9.7 (*c* 0.95, $CHCl_3$) for 86% ee; IR (neat) ν 2968, 1725, 1463, 1183, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.67 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.72 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.82 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 0.84 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 1.61 (d, *J* = 7.2 Hz, 3H, CH_3CHAr), 1.76–1.91 (m, 2H, $CH(CH_3)_2$), 2.72 (s, 3H, CH_3Ar), 3.19 (s, 3H, CH_3OCH_2), 4.03 (q, *J* = 7.2 Hz, 1H, CH_3CHAr), 4.58 (t, *J* = 6.3 Hz, 1H, CO_2CH), 5.46 (d, *J* = 10.9 Hz, 1H, CH_3OCHH), 5.54 (d, *J* = 11.3 Hz, 1H, CH_3OCHH), 6.98 (d, *J* = 7.2 Hz, 1H, *Ar*), 7.05 (dd, *J* = 7.2, 7.7 Hz, 1H, *Ar*), 7.09 (s, 1H, *Ar*), 7.52 (d, *J* = 7.7 Hz, 1H, *Ar*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0 (CH_3), 17.2 (CH_3), 18.3 (CH_3), 19.2 (CH_3), 19.4 (CH_3), 19.5 (CH_3), 29.4 (CH), 36.9 (CH), 55.1 (CH_3), 79.2 (CH_2), 82.6 (CH), 115.3 (C), 117.2 (CH), 120.2 (CH), 121.9 (C), 125.1 (CH), 127.5 (CH), 129.1 (C), 134.8 (C), 175.0 (CO); HRMS (ESI) calcd for $C_{21}H_{31}NO_3Na$ $(M + Na)^+$ 368.21962, found 368.21957. The enantiomeric excess of **7m** was determined to be 86% by HPLC with a Daicel Chiralpak IC column (eluent: 200:1 hexane/2-propanol; flow: 1.0 mL/min): t_R = 17.5 min for minor enantiomer; t_R = 18.9 min for major enantiomer. The preferred absolute configuration of **7m** was not determined.

4.4. Determination of absolute configuration of (*R*)-2,4-dimethyl-3-pentyl 2-[(1-methoxymethyl)-1*H*-indol-3-yl]propionate 7e (Scheme 2)

4.4.1. (*R*)-2,4-Dimethyl-3-pentyl 2-(1*H*-indol-3-yl)propionate 9

TMSOTf (0.061 mL, 0.33 mmol) was added to a solution of **7e** (55.0 mg, 0.166 mmol) and 2,2'-bipyridyl (77.8 mg, 0.498 mmol) in CH_2Cl_2 (1.0 mL) at 0 °C. After stirring for 0.5 h at 0 °C, the reaction was quenched by addition of water (3 mL). The mixture was extracted with EtOAc (2 × 5 mL), and the combined organic layers were washed with 1 M aq. HCl (2 × 3 mL), saturated aq. $NaHCO_3$ (3 mL) and brine (3 mL), and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished (*R*)-2,4-dimethyl-3-pentyl 2-[(1-hydroxymethyl)-1*H*-indol-3-yl]propionate **8** (60.5 mg), which was used without further purification. NaOH (66.4 mg, 1.66 mmol) was added to the solution of **8** (60.5 mg) in THF (3.6 mL) and water (0.4 mL). After stirring for 24 h at room temperature, the reaction was quenched with addition of saturated NH_4Cl (10 mL). The mixture was extracted with EtOAc (2 × 10 mL), and the combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (62.0 mg), which was purified by column chromatography (silica gel, 6:1 hexane/EtOAc) to provide **9** (47.3 mg, 99%) as a yellow oil: $[\alpha]_D^{22}$ −40.4 (*c* 0.71, $CHCl_3$) for 82% ee; IR (neat) ν 3412, 2968, 1716, 1459, 1186 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.66 (d, *J* = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 0.71 (d, *J* = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 0.80 (d, *J* = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 0.83 (d, *J* = 6.9 Hz, 3H, CH(C*H*$_3$)$_2$), 1.64 (d, *J* = 6.9 Hz, 3H, C*H*$_3$CHAr), 1.77–1.90 (m, 2H, C*H*(CH$_3$)$_2$), 4.07 (q, *J* = 6.8 Hz, 1H, CH$_3$C*H*Ar), 4.58 (t, *J* = 6.3 Hz, 1H, CO$_2$C*H*), 7.10–7.13 (m, 1H, *Ar*), 7.17 (s, 1H, *Ar*), 7.19 (m, 1H, *Ar*), 7.35 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.71 (d, *J* = 8.0 Hz, 1H, *Ar*), 8.03 (brs, 1H, N*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 16.9 (CH_3), 17.2 (CH_3), 18.0 (CH_3), 19.3 (CH_3), 19.5 (CH_3), 29.4 (CH), 29.4 (CH), 37.2 (CH), 77.2 (CH), 82.6 (CH), 111.1 (CH), 115.7 (C), 119.3 (CH), 121.5 (CH), 122.0 (CH), 126.5 (C), 136.1 (C), 175.2 (CO); HRMS (ESI) calcd for $C_{18}H_{25}NO_2Na$ $(M + Na)^+$ 310.17775, found 310.17797.

4.4.2. (*R*)-2-(1*H*-indol-3-yl)propane-1-ol 10[30]

$LiAlH_4$ (22.7 mg, 0.598 mmol) was added to a solution of **9** (43.0 mg, 0.150 mmol) in THF (1.0 mL) at 0 °C. After stirring for 4 h at room temperature, the reaction was quenched with addition of water (0.023 mL). 15% aq. NaOH (0.023 mL) and water (0.069 mL) were added to the reaction mixture. After stirring for 0.5 h at room temperature, filtration and evaporation in vacuo furnished the crude product (34.8 mg), which was purified by column chromatography (silica gel, 1:1 hexane/EtOAc) to provide **10** (22.7 mg, 87%) as a colorless oil: $[\alpha]_D^{24}$ −23.3 (*c* 0.41, MeOH) for 82% ee [lit.,[30] $[\alpha]_D^{25}$ +30.6 (*c* 0.46, MeOH) for (*S*)-**10** (90% ee)]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.41 (d, *J* = 7.3 Hz, 3H, C*H*$_3$CHAr), 3.30–3.34 (m, 1H CH$_3$C*H*Ar), 3.80–3.86 (m, 2H, C*H*$_2$OH), 7.07 (s, 1H, *Ar*), 7.10 (m, 1H, *Ar*), 7.22 (m, 1H, *Ar*), 7.38 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.67 (d, *J* = 8.0 Hz, 1H, *Ar*), 8.07 (brs, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2 (CH_3), 33.9 (CH), 67.8 (CH_2), 111.3 (CH), 117.9 (C), 119.2 (CH), 119.3 (CH), 121.2 (CH), 122.1 (CH), 126.7 (C), 136.5 (C).

4.5. Synthesis of (*S*)-(+)-α-methyl-3-indolylacetic acid 11, a constituent of acremoauxin A 12 (Scheme 3)

4.5.1. (*S*)-2,4-Dimethyl-3-pentyl 2-[(1-methoxymethyl)-1*H*-indol-3-yl]propionate *ent*-7e

According to the typical procedure for C–H functionalization of indole, *ent*-**7e** was prepared from Rh_2(*R*-PTTEA)$_4$·2EtOAc **2** (3.18 mg, 0.002 mmol, 1 mol %), **6a** (79.3 mg, 0.400 mmol) and **5e** (77.4 mg, 0.48 mmol). The crude product was purified by column chromatography (silica gel, 5:1 hexane/Et_2O) to provide *ent*-**7e** (110 mg, 83%) as a colorless oil: $[\alpha]_D^{25}$ +20.6 (*c* 1.26, $CHCl_3$) for 83% ee.

4.5.2. (*S*)-2,4-Dimethyl-3-pentyl 2-(1*H*-indol-3-yl)propionate *ent*-9

According to the procedure for the preparation of **9**, *ent*-**9** was prepared from *ent*-**7e** (185.4 mg, 0.559 mmol). The crude product was purified by column chromatography (silica gel, 6:1 hexane/EtOAc) to provide the title compound (156.0 mg, 97%) as a colorless oil: $[\alpha]_D^{25}$ +40.6 (*c* 0.98, $CHCl_3$) for 83% ee.

4.5.3. (*S*)-2-(1*H*-indol-3-yl)propane-1-ol *ent*-10[30]

According to the procedure for the preparation of **10**, *ent*-**10** was prepared from *ent*-**9** (153.5 mg, 0.534 mmol). The crude product was purified by column chromatography (silica gel, 1:1 hexane/EtOAc) to provide the title compound (90.5 mg, 97%) as a colorless oil: $[\alpha]_D^{24}$ +28.2 (*c* 0.48, MeOH) for 83% ee [lit.,[30] $[\alpha]_D^{25}$ +30.6 (*c* 0.46, MeOH) for 90% ee].

4.5.3. (*S*)-(+)-α-methyl-3-indolylacetic acid 11[31]

SO_3·pyridine complex (114 mg, 0.718 mmol) was added to a solution of *ent*-**10** (30.0 mg, 0.171 mmol) and Et_3N (0.11 mL, 0.789 mmol) in DMSO (1.0 mL) at room temperature. After stirring for 0.5 h at room temperature, the reaction mixture was poured into a mixture of saturated aq. NH_4Cl (5 mL) and saturated aq. $NaHCO_3$ (5 mL). The mixture was extracted with EtOAc (2 × 5 mL) and the combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo gave the crude aldehyde, which was used without further purification. NaH_2PO_4·H_2O (534 mg, 3.42 mmol) and $NaClO_2$ (70.0 mg, 0.619 mmol) were added to the solution of the crude aldehyde in THF (1.0 mL), ^{t}BuOH (0.3 mL), 2-methyl-2-butene (0.3 mL) and water (1.0 mL). After stirring for 0.5 h, the reaction mixture was poured into saturated aq. NH_4Cl (5 mL), and whole was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (109 mg), which was purified by column chromatography (silica gel, 1:1 hexane/EtOAc) to provide **11** (19.8 mg, 61%) as a dark yellow oil: $[\alpha]_D^{25}$ +42.6 (*c* 0.12, CH_2Cl_2) for 83% ee [lit.,[31c] $[\alpha]_D$ +41.5 (*c* 0.13, CH_2Cl_2) for >99% ee]; IR (neat) ν 3415, 2983, 1709, 1458, 1248 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 7.3 Hz, 3H, C*H*$_3$CHAr), 4.05 (q, *J* = 7.3 Hz, 1H, CH$_3$C*H*Ar), 7.13 (dd, *J* = 7.3, 8.0 Hz, 1H, *Ar*), 7.15 (s, 1H, *Ar*), 7.20 (dd, *J* = 7.3, 7.3 Hz, 1H, *Ar*), 7.36 (d, *J* = 8.0 Hz, 1H, *Ar*), 7.69 (d, *J* = 7.6 Hz, 1H, *Ar*), 8.07 (brs, 1H, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5 (CH_3), 36.7 (CH), 111.2 (CH), 114.9 (C), 119.3 (CH), 119.7 (CH), 121.7 (CH), 122.4 (CH), 126.3 (C), 136.2 (C), 180.0 (CO). The enantiomeric excess of **11** was determined to be 83% by HPLC analysis with a Daicel Chiralpak IC-3 column [eluent: 9:1 hexane/2-propanol (contained 0.1% AcOH); flow: 0.5 mL/min; 40 °C]: t_R (major) = 12.2 min for (*S*)-**11**; t_R (minor) = 18.2 min for (*R*)-**11**.

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References and notes

1. (a) Dewick, P. M. *Medicinal Natural Products: A Biosynthetic Approach*; John Wiley & Sons Inc.: Chichester, 2009; (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489–4497.
2. For reviews, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550–556; (b) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903–2915; (c) Bandini, M.; Eichholzer, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; (d) Bartoli, G.; Bencivenni, G.; Dalpozzo, R. *Chem. Soc. Rev.* **2010**, *39*, 4449–4465.
3. For recent examples, see: (a) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292–293; (b) Jia, Y.-X.; Zhong, J.; Zhu, S.-F.; Zhang, C.-M.; Zhou, Q.-L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5565–5567; (c) Evans, D. A.; Fandrick, K. R.; Song, H.-J.; Scheidt, K. A.; Xu, R. *J. Am. Chem. Soc.* **2007**, *129*, 10029–10041; (d) Blay, G.; Fernández, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601–2604; (e) Cheung, H. Y.; Yu, W.-Y.; Lam, F. L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chan, A. S. C. *Org. Lett.* **2007**, *9*, 4295–4298; (f) Matsuzawa, H.; Kanao, K.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2007**, *9*, 5561–5564; (g) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 4016–4018; (h) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815–1818; (i) Schätz, A.; Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Chem. Eur. J.* **2008**, *14*, 7259–7265; (j) Arai, T.; Yokoyama, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4989–4992; (k) Nakamura, S.; Hyodo, K.; Nakamura, Y.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2008**, *350*, 1443–1448; (l) Singh, P. K.; Singh, V. K.; *Org. Lett.* **2008**, *10*, 4121–4124; (m) Suyama, K.; Matsumoto, K.; Katsuki, T. *Heterocycles* **2009**, *77*, 817–824; (n) Adachi, S.; Tanaka, F.; Watanabe, K.; Harada, T. *Org. Lett.* **2009**, *11*, 5206–5209; (o) Liu, Y.; Shang, D.; Zhou, X.; Liu, X.; Feng, X. *Chem. Eur. J.* **2009**, *15*, 2055–2058.
4. For a review, see: Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109–1119.
5. (a) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.* **1977**, *42*, 3945–3949; (b) Wood, J. L.; Stoltz, B. M.; Dietrich, H.-J.; Pflum, D. A.; Petsch, D. T. *J. Am. Chem. Soc.* **1997**, *119*, 9641–9651; (c) Muthusamy, S.; Gunanathan, C.; Babu, S. A.; Suresh, E.; Dastidar, P. *Chem. Commun.* **2002**, 824–825; (d) Gibe, R.; Kerr, M. A. *J. Org. Chem.* **2002**, *67*, 6247–6249; (e) Yadav, J. S.; Reddy, B. V. S.; Satheesh, G. *Tetrahedron Lett.* **2003**, *44*, 8331–8334; (f) Muthusamy, S.; Gnanaprakasam, B. *Tetrahedron Lett.* **2008**, *49*, 475–480; (g) Zhang, X.-J.; Liu, S.-P.; Yan, M. *Chin. J. Chem.* **2008**, *26*, 716–720; (h) Antos, J. M.; McFarland, J. M.; Iavarone, A. T.; Francis, M. B. *J. Am. Chem. Soc.* **2009**, *131*, 6301–6308; (i) Chan, W.-W.; Yeung, S.-H.; Zhou, Z.; Chan, A. S. C.; Yu, W.-Y. *Org. Lett.* **2010**, *12*, 604–607; (j) Lian, Y.; Davies, H. M. L. *Org. Lett.* **2010**, *12*, 924–927; (k) Popp, B. V.; Ball, Z. T. *J. Am. Chem. Soc.* **2010**, *132*, 6660–6662; (l) Johansen, M. B.; Kerr, M. A. *Org. Lett.* **2010**, *12*, 4956–4959.
6. For reviews, see: (a) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459–2469; (b) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857–1869. For recent examples, see: (c) Briones, J. F.; Hansen, J.; Hardcastle, K. I.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 17211–17215; (d) Hansen, J.; Gregg, T. M.; Ovalles, S. R.; Lian, Y.; Autschbach, J.; Davies, H. M. L. *J. Am. Chem. Soc.* **2011**, *133*, 5076–5085.
7. Davies and Lian recently developed an enantioselective [3+2] annulation of indoles with styryldiazoacetates catalyzed by Rh_2(*S*-DOSP)$_4$ **4**. In this report, an enantioselective C–H functionalization of 1,2-dimethyl indole with phenyldiazoacetate using **4** was described where asymmetric induction (<5% ee) was observed. Lian, Y.; Davies, H. M. L. *J. Am. Chem. Soc.* **2010**, *132*, 440–441.
8. (a) Müller, P.; Allenbach, Y.; Robert, E. *Tetrahedron: Asymmetry* **2003**, *14*, 779–785; (b) Müller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Flack, H. D. *Org. Lett.* **2004**, *6*, 1725–1728; (c) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 4641–4644; (d) Ghanem, A.; Gardiner, M. G.; Williamson, R. M.; Müller, P. *Chem. Eur. J.* **2010**, *16*, 3291–3295.
9. (a) Marcoux, D.; Charette, A. B. *Angew. Chem. Int. Ed.* **2008**, *47*, 10155–10158; (b) Marcoux, D.; Goudreau, S. R.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 8939–8955.
10. DeAngelis, A.; Boruta, D. T.; Lubin, J.-B.; Plampin, J. N., III; Yap, G. P. A.; Fox, J. M. *Chem. Commun.* **2010**, *46*, 4541–4543.
11. DeAngelis, A.; Shurtleff, V. W.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 1650–1653.
12. Fox and co-workers also reported the mechanism of a Rh(II)-catalyzed enantioselective C–H functionalization of indoles with ethyl α-alkyl-α-diazoacetates based on DFT calculations. See Ref. 11.
13. (a) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85–86; (b) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887–3890; (c) Minami, K.; Saito, H.; Tsutsui, H.; Nambu, H.; Anada, M.; Hashimoto, S. *Adv. Synth. Catal.* **2005**, *347*, 1483–1487.
14. For a practical synthesis of Rh_2(*S*-PTTL)$_4$ **1a**, see: (a) Tsutsui, H.; Abe, T.; Nakamura, S.; Anada, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2005**, *53*, 1366–1368. For an immobilization of **1a**, see: (b) Takeda, K.; Oohara, T.; Anada, M.; Nambu, H.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2010**, *49*, 6979–6983.
15. DeAngelis, A.; Dmitrenko, O.; Yap, G. P. A.; Fox, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 7230–7231.
16. (a) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163–4166; (b) Doyle, M. P.; Zhou, Q.-L. *Tetrahedron: Asymmetry* **1995**, *6*, 2157–2160; (c) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908–2910.
17. (a) Tsutsui, H.; Yamaguchi, Y.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Tetrahedron*: *Asymmetry* **2003**, *14*, 817–821; (b) Anada, M.; Tanaka, M.; Washio, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 4559–4562; (c) Shimada, N.; Nakamura, S.; Anada, M.; Shiro, M.; Hashimoto, S. *Chem. Lett.* **2009**, *38*, 488–489.
18. (a) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561–9564; (b) Shimada, N.; Anada, M.; Nakamura, S.; Nambu, H.; Tsutsui, H,; Hashimoto, S. *Org. Lett.* **2008**, *10*, 3603–3606; (c) Nambu, H.; Hikime, M.; Krishnamurthi, J.; Kamiya, M.; Shimada, N.; Hashimoto, S. *Tetrahedron Lett.* **2009**, *50*, 3675–3678; (d) Shimada, N.; Hanari, T.; Kurosaki, Y.; Takeda, K.; Anada, M.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2010**, *75*, 6039–6042.
19. Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383–16385.
20. (a) Sato, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *J. Org. Chem.* **2009**, *74*, 7522–7524; (b) Sato, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Chem. Commun.* **2009**, 6264–6266.
21. Natori, Y.; Tsutsui, H.; Sato, N.; Nakamura, S.; Nambu, H.; Shiro, M.; Hashimoto, S. *J. Org. Chem.* **2009**, *74*, 4418–4421.
22. Hedley, S. J.; Ventura, D. L.; Dominiak, P. M.; Nygren, C. L.; Davies, H. M. L. *J. Org. Chem.* **2006**, *71*, 5349–5356.
23. (a) Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109–5112; (b) Kitagaki, S.; Matsuda, H.; Watanabe, N.; Hashimoto, S. *Synlett* **1997**, 1171–1174; (c) Goto, T.; Takeda, K.; Shimada, N.; Nambu, H.; Anada, M.; Shiro, M.; Ando, K.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2011**, 10.1002/anie.201101905.
24. Fox and co-workers reported that the reaction of 2-methylindole derivatives with ethyl α-alkyl-α-diazoacetates provided the corresponding products in high yields and enantioselectivities, but experiments with large substituents (Et, *n*-Bu, CF_3, Ph and I) at the indole 2-position were unsuccessful. See Ref. 11.
25. Meyers, A. I.; Miller, D. B.; White F. H. *J. Am. Chem. Soc.* **1988**, *110*, 4778–4787.
26. Nicolaou, K. C.; Huang, X.; Giuseppone, N.; Bheema Rao, P.; Bella, M.; Reddy, M. V.; Snyder, S. A. *Angew. Chem. Int. Ed.* **2001**, *40*, 4705–4709.
27. Nakatsuka, S.; Miyazaki, H.; Goto, T. *Tetrahedron Lett.* **1980**, *21*, 2817–2820.
28. Meyers, A. I.; Highsmith, T. K.; Buonora, P. T. *J. Org. Chem.* **1991**, *56*, 2960–2964.
29. Fujioka, H.; Kubo, O.; Senami, K.; Minamitsuji, Y.; Maegawa, T. *Chem. Commun.* **2009**, 4429–4431.
30. Akita, H.; Todoroki, R.; Endo, H.; Ikari, Y.; Oishi, T. *Synthesis* **1993**, 513–516.
31. For resolution of α-methyl-3-indolylacetic acid, see: (a) Yoshida, N.; Sassa, T. *Agric. Biol. Chem.* **1990**, *54*, 2681–2683; (b) Kato,

K.; Gong, Y.; Tanaka, S.; Katayama, M.; Kimoto, H. *Biotechnol. Lett.* **1999**, *21*, 457–461. For an asymmetric synthesis of (+)-α-methyl-3-indolylacetic acid via a highly diastereoselective coupling of indole with camphorsultam propionate, see: (c) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc*. **2007**, *129*, 12857–12869.

32. Bukovac, M. J.; Schlender, K. K.; Sell, H. M. *Nature* **1964**, *202*, 617–618.
33. For an isolation of acremoauxin A **12**, see: Sassa, T.; Yoshida, N.; Haruki, E. *Agric. Biol. Chem.* **1989**, *53*, 3105–3107.
34. For syntheses of acremoauxin A **12**, see: Ref. 31a and 31c.
35. Govek, S. P.; Overman, L. E. *Tetrahedron* **2007**, *63*, 8499–8513.
36. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc*. **1967**, *89*, 5505–5507.
37. (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888–890; (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175–1176; (c) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825–4830; (d) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091–2096; (e) Hayashida, J.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4373–4376.
38. The enantiomeric excess of **11** was determined to be 83% by HPLC analysis with a Daicel Chiralpak IC-3 column.
39. Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324–3330.
40. (a) Gasparotto, V.; Castagliuolo, I.; Ferlin, M. G. *J. Med. Chem.* **2007**, *50*, 5509–5513; (b) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. *J. Am. Chem. Soc.* **2010**, *132*, 14676–14681.
41. Bachmann, S.; Fielenbach, D.; Jørgensen, K. A. *Org. Biomol. Chem*. **2004**, *2*, 3044–3049.