Pergamon

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Tetrahedron: *Asymmetry* 14 (2003) 941–949

TETRAHEDRON: *ASYMMETRY*

Intermolecular C–H activation at benzylic positions: synthesis of (+)-imperanene and (−)-α-conidendrin

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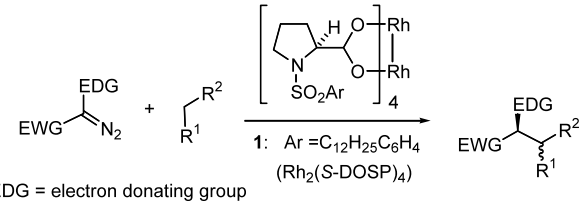
Received 12 December 2002; accepted 4 February 2003

Abstract—An efficient C–H activation of primary benzylic positions by means of rhodium carbenoid induced C–H insertions is described. This key step was used in concise syntheses of (+)-imperanene and (−)-α-conidendrin.

1. Introduction

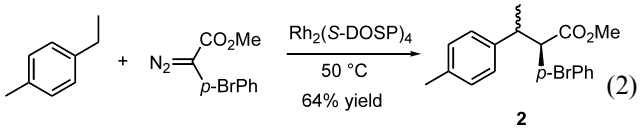
The development of practical methods for intermolecular C–H activation is of great interest because this would offer new disconnection strategies for the synthesis of complex natural products. Metal induced C–H activation processes are areas of intense current research.[1,2] One very practical approach for C–H activation is by means of metal carbenoid induced C–H insertion.[3] The intramolecular version of this reaction is well established and can be achieved with excellent asymmetric induction.[3] In contrast, the intermolecular version was not considered to be synthetically useful because it was compromised by problems of chemoselectivity and the propensity of the carbenoid to dimerize.[3,4] In the last few years, we have discovered that donor/acceptor substituted carbenoids are capable of undergoing highly regioselective intermolecular C–H insertions.[5,6] When the reactions are catalyzed by Rh_2(*S*-DOSP)$_4$ **1**, high levels of asymmetric induction are obtained (Eq. (1)). In our original studies on alkanes,[5e] C–H insertion occurred at either 2° or 3° centres, and the regioselectivity was controlled by a delicate balance of electronic and steric effects.



(1)

EDG = electron donating group
EWG = electron withdrawing group

Intermolecular metal carbenoid C–H activation is tolerant to many functional groups and is especially favored at benzylic and allylic sites and positions α to oxygen and nitrogen.[5,6] Even with these electronically activated sites for C–H insertion, 1° carbons display great reluctance to undergo C–H insertion. For example, tetraethoxysilane is an exceptional substrate for C–H activation while tetramethoxysilane is not.[5f] An impressive example of the difference between a 1° and a 2° site is the reaction of 4-ethyltoluene, which undergoes clean benzylic C–H insertion at the methylene group to form **2** (Eq. (2)).[5m]



(2)

2

2° vs 1° selectivity >95 : 5

A further demonstration of this chemoselectivity is the reaction with toluene (Eq. (3)).[5m] Even though ethylbenzene undergoes benzylic C–H activation cleanly, in the reaction with toluene a mixture of three products are obtained. The C–H activation product **3** is a minor component while the major component is a mixture of regioisomers **4a** and **4b** derived from double cyclopropanation of the aromatic ring.

As the exploration of the C–H activation chemistry of substituted donor/acceptor carbenoids has become more extensive, general reactivity principles and guidelines have been recognized.[5,6] One of these generalizations is that 1° sites are not favored for C–H activation.

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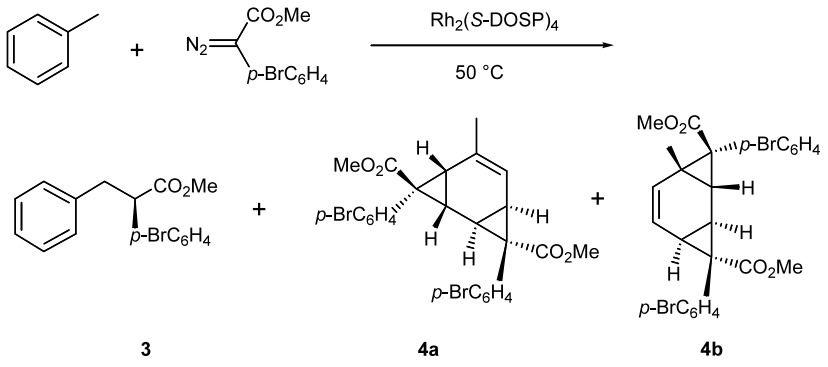
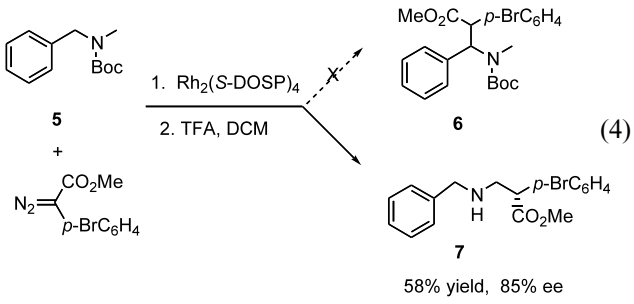
0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00154-X



(3)

Thus the *N*-Boc protected benzylmethylamine **5** was expected to be a good substrate for benzylic C–H activation to form **6**. In actual fact, however, this substrate underwent an unprecedented C–H activation at the methyl group to form **7**,[51] a process which allows access to some very interesting β-amino acid derivatives. With this unexpected discovery of a clean C–H activation at a 1° site, we have carried out a study to evaluate the generality of 1° site C–H activation and the results of these studies are described herein (Eq. (4)).

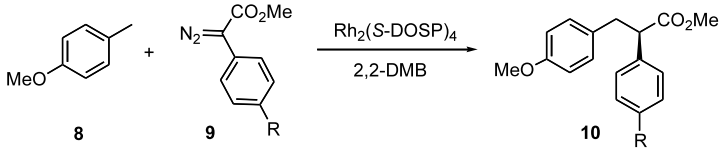


(4)

2. Results and discussion

We propose that the reason for the unreactivity of **5** at the electronically favored *N*-benzyl site is because the carbenoid is very sterically encumbered and unable to approach this site for reaction.[51] In order to design systems capable of clean reactions at 1° C–H sites, the site would need to be electronically activated while the rest of the molecule must have no activated sites or the sites would need to be sterically protected. One obvious system would be 4-methoxytoluene **8** as the methoxy group would activate the 1° benzylic site and sterically encumber the benzene ring. $Rh_2(S\text{-DOSP})_4$ catalyzed the decomposition of methyl bromophenyldiazoacetate **9a** at 50°C resulting in efficient C–H activation generating **10a** in 71% yield and 74% ee. No C–H activation of the methyl group next to oxygen occurred, presumably because the electron lone pairs of oxygen are delocalized into the benzene ring and are not sufficiently activating of the methyl group. In order to explore the scope of this reaction, the effect of temperature and the *p*-substituent on the diazo compound was examined and the results are summarized in Table 1. In the case of **9a**, which would generate the most electrophilic carbenoid, an efficient reaction was obtained at 23 and 0°C, and as expected,[5,6] the enantioselectivity steadily improved on lowering the temperature. In the case of methyl phenyldiazoacetate **9b**, good yields of **10b** were obtained at 50 and 25°C only, while in the case of methyl *p*-methoxyphenyldiazoacetate **9c**, a low yield of

Table 1. C–H insertion to *p*-methylanisole

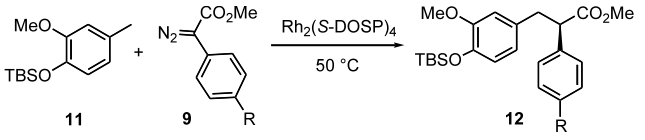


	R	Temp. (°C)	Yield (%)[a]	ee (%)
a	Br	50	71	74
		23	73	80
		0	69	83
b	H	50	67	71
		23	67	79
		0	[14]	ND
c	OMe	50	35	67

[a] The yield in parenthesis is the NMR yield with internal standard.

10c was obtained even at 50°C. The absolute stereochemistry of **10b** was determined to be (*R*) by hydrolysis of **10b** to the known (*R*) acid.[7] This asymmetric induction is in agreement with our published model[6] that predicts that the (*R*) enantiomer would be formed. The absolute configuration of the other products is assigned assuming a similar stereochemical effect.

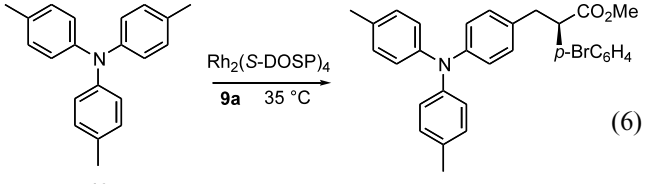
Very efficient reactions were also obtained with the even more electron-rich aromatic system **11**. The reaction of aryldiazoacetates **9a** and **9b** with **11** at 50°C resulted in very effective C–H insertion to form **12a** and **12b** in 80% yield and 75–77% ee (Eq. (5)). Once again, the methoxy derivative **9c** was less effective at the C–H activation: product **12c** was formed in only 30% yield. The demonstration that **11** with a very electron-rich aromatic ring is an appropriate substrate underlines how steric hindrance can protect the aromatic ring from reaction with the carbenoid.



11 9 12 (5)

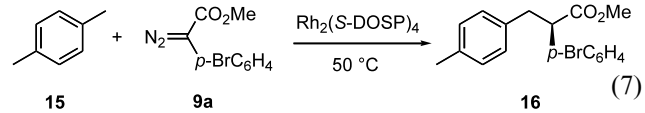
	R	yield, %	ee, %
a	Br	80	77
b	H	80	75
c	OMe	30	67

A very intriguing example of this chemistry is the reaction of **9a** with tritolylamine **13**. When the reaction was conducted with an excess of tritolylamine (5 equiv.), the C–H activation product was obtained in 53% yield and 81% ee (Eq. (6)).



13 (5 equiv.) 14 (53% yield, 81% ee) (6)

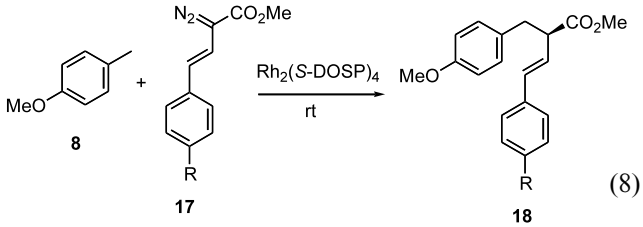
In order to determine if the C–H activation into a methyl site required the presence of a strong electron-donating group in the *para* position, the reaction was extended to *p*-xylene **15**. The presence of the *para* substituents block the ring from cyclopropanation reactions and the $Rh_2(S\text{-DOSP})_4$ catalyzed reaction of **9a** at 50°C generated the C–H activation product **16** in 70% yield and 74% ee (Eq. (7)). This result contrasts sharply with the outcome of the carbenoid reaction with toluene (Eq. (3)).[5m]



15 9a 16 (7)

70% yield, 74% ee

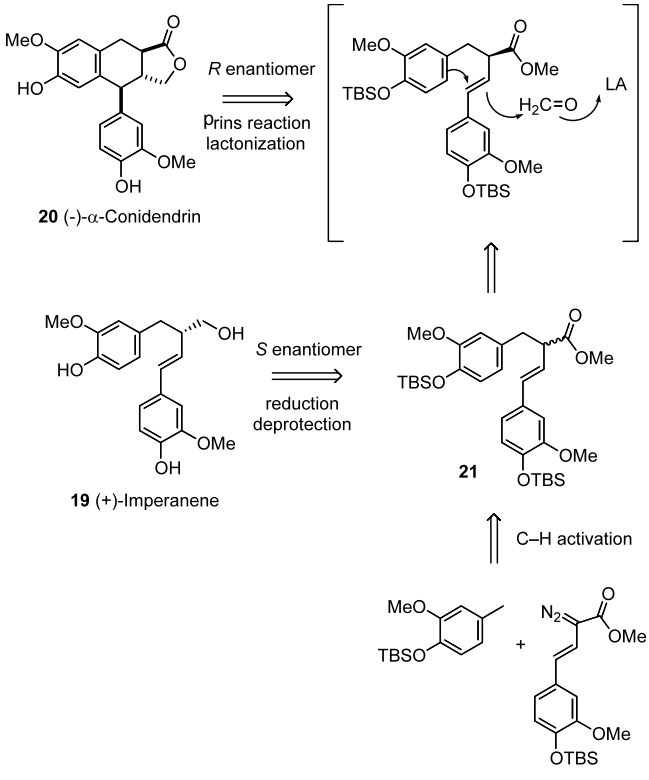
Carbenoids derived from vinyldiazoacetates also behave as donor/acceptor carbenoids,[6] and furthermore, are capable of inducing intermolecular C–H activation as illustrated in Eq. (8). The methyl *p*-bromophenylvinyldiazoactate **17a** gave the C–H activation product **18a** in 51% yield and 94% ee. Similar reactions were possible with the phenylvinyldiazoacetate **17b**.



8 17 18 (8)

	R	yield, %	ee, %
a	Br	51	94
b	H	53	92

The potential of these methods in total synthesis is illustrated in retrosynthetic analyses for (+)-imperanene **19**[8] and (−)-α-conidendrin **20**[9] (Scheme 1). (+)-Imperanene would be readily derived from the *S* enantiomer of the C–H activation product **21**, while (−)-α-conidendrin would be derived from the *R* enantiomer of **21** by means of a Lewis acid induced cascade involving Prins reaction, aromatic electrophilic substitution and lac-



Scheme 1.

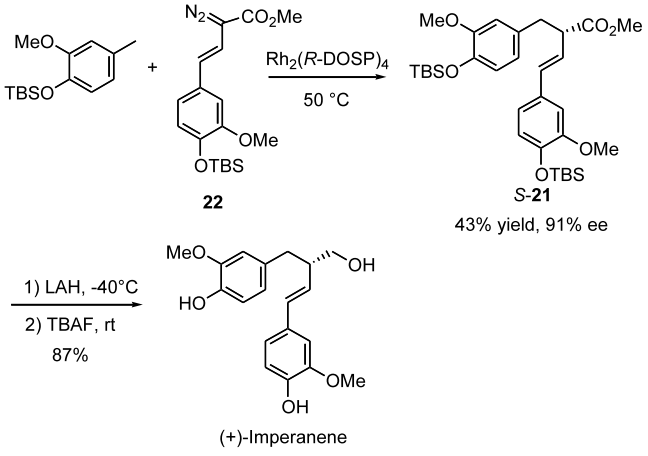
tonization. Thus, the absolute stereochemistry in (+)-imperanene and (−)-α-conidendrin would be established during the C–H activation step.

The total synthesis of (+)-imperanene **19** is summarized in Scheme 2. $Rh_2(R\text{-DOSP})_4$-catalyzed decomposition of **22** in the presence of **11** at 50°C generates the C–H activation product (*S*)-**21** in 43% yield and 91% ee. Lithium aluminum hydride reduction of (*S*)-**21** followed by silyl deprotection generates (+)-imperanene **19** in 87% yield. The specific rotation of **19** ($[\alpha]_D^{25}$ +115.2 (*c* 1.05, $CHCl_3$, 92% ee)) is in agreement with the literature value[8c] ($[\alpha]_D^{25}$ +103 (*c* 1.7, $CHCl_3$, 93% ee)) and demonstrates that $Rh_2(R\text{-DOSP})_4$ generates the *S* configured C–H insertion product. The sense of asymmetric induction observed in this case is in agreement with our predictive model.[6]

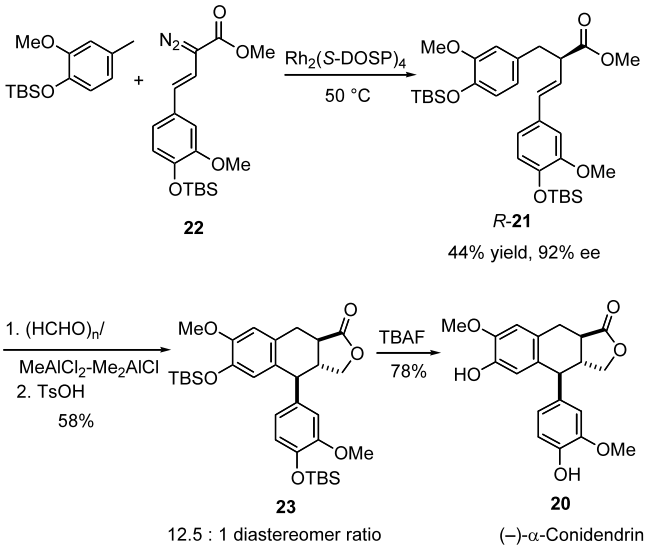
The total synthesis of (−)-α-conidendrin combines C–H activation with a cascade of reactions (Scheme 3). The Prins reaction followed by electrophilic substitution has been previously established in model studies.[10] $Rh_2(S\text{-DOSP})_4$ catalyzed decomposition of **22** in the presence of **11** at 50°C generates (*R*)-**21** in 44% yield with 92% ee. Treatment of (*R*)-**21** with formaldehyde in a Lewis acid catalyzed Prins reaction/electrophilic substitution sequence followed by treatment with *p*-toluenesulfonic acid afforded TBS protected (−)-α-conidendrin **23** as the major diastereomer (12.5:1 mixture of tricyclic products). Desilylation using TBAF affords the natural product **20** in 78% yield. The specific rotation value of **20** ($[\alpha]_D^{25}$ −50.4 (*c* 0.90, acetone)) is in agreement with the literature value[9b] ($[\alpha]_D^{25}$ −52.5 (*c* 1.05, acetone)).

3. Conclusions

In summary, we have demonstrated that effective C–H activation of benzylic methyl groups can be achieved as long as the aromatic ring is at least *p*-disubstituted. The aromatic functionalization sterically protects the ring from electrophilic attack by the rhodium carbenoid intermediates. Thus, the C–H activation strategy we have presented herein offers exciting new options for total synthesis as illustrated in the very concise routes to (+)-imperanene and (−)-α-conidendrin.



Scheme 2.



Scheme 3.

4. Experimental

4.1. General

^1H NMR spectra were run at either 400 or 500 MHz and ^{13}C NMR at 75 or 125 MHz with the sample solvent being $CDCl_3$ unless otherwise noted. Mass spectral determinations were carried out at 70 eV. IR spectra were obtained using a Nicolet Impact series 420 IR. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Column chromatography was carried out on silica gel 60 (230–400) mesh. Enantiomeric excess was determined by HPLC using a Chiralcel OD-H, Chiralpak AD-RH or (*R*,*R*)-Whelk-O 1 chiral analytical column (UV detection at 254 nm). Melting points were measured on an Electrothermal melting point apparatus and are uncorrected. Degassing was carried out by bubbling Ar gas through the solution for 5–10 min. 2,2-Dimethylbutane was distilled from Na after passing through a pad of activated silica gel. Decalin was purchased from Aldrich as anhydrous grade, used directly. Methylaluminum sesquichloride was prepared by mixing equimolar amounts of methylaluminum dichloride (1 M in hexanes) and dimethylaluminum chloride (1 M in hexanes).

4.2. General procedure for C–H insertion

To a degassed, refluxing solution of aromatic compound (5 mmol) and $Rh_2(S\text{-DOSP})_4$ (0.005 mmol) in 2,2-dimethylbutane (2 mL) was added a solution of methyl *p*-bromophenyldiazoacetate (0.5 mmol) in 2,2-dimethylbutane (5 mL) in 45 min using syringe-pump. The mixture was heated under reflux for an additional 15 min. The solvent was removed in vacuo and the residue was subjected to flash chromatography.

4.3. (*R*)-Methyl 2-(4-bromophenyl)-3-(4-methoxyphenyl)-propionate, 10a

The reaction was carried out at 0°C on 0.5 mmol scale. Purified by flash chromatography on silica gel (6:1 pentane/ether) to afford product **10a** (120 mg, 69% yield) as a colorless oil: R_f 0.31 (5:1 pentane/ether); $[\alpha]_D^{25}$ −106.3 (*c* 2.20, $CHCl_3$); FTIR (film) 3000, 2951, 2837, 1735, 1611, 1512, 1488, 1440, 1295, 1248, 1160, 1034, 1012, 823, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, $J=8.2$ Hz, 2H), 7.15 (d, $J=8.2$ Hz, 2H), 6.98 (d, $J=8.5$ Hz, 2H), 6.75 (d, $J=8.5$ Hz, 2H), 3.80–3.72 (m, 1H), 3.73 (s, 3H), 3.59 (s, 3H), 3.31 (dd, $J=13.7$, 8.2 Hz, 1H), 2.92 (dd, $J=13.7$, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 158.1, 137.5, 131.6, 130.4, 129.8, 129.7, 121.2, 113.7, 55.0, 53.2, 52.0, 38.8; MS (EI) *m*/*z* (relative intensity) 121.1 (100), 348.0 (M^+, 3); HRMS (EI) *m*/*z* calcd for $[C_{17}H_{17}BrO_3]^+$: 348.0356. Found: 348.03299. HPLC analysis: 83% ee (Chiralpak AD-RH, 0.5% *i*-PrOH in hexane, 0.8 mL/min, $\lambda=254$ nm, $t_R=14.3$ min, minor; $t_R=15.6$ min, major). Anal. calcd for $C_{17}H_{17}BrO_3$: C, 58.47; H, 4.91. Found: C, 58.72; H, 4.93%.

4.4. (*R*)-Methyl 3-(4-methoxyphenyl)-2-phenylpropionate, 10b[11]

The reaction was carried out at rt on 0.5 mmol scale. Purified by flash chromatography on silica gel (5:1 pentane/ether) to afford product **10b** (91 mg, 67% yield) as a light yellow oil: R_f 0.33 (5:1 pentane/ether); $[\alpha]_D^{25}$ −85.1 (*c* 1.50, $CHCl_3$); FTIR (film) 3060, 3029, 3001, 2951, 2837, 1735, 1611, 1512, 1445, 1350, 1297, 1248, 1217, 1159, 1110, 1034, 827, 733, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30–7.20 (m, 5H), 7.01 (d, $J=8.6$ Hz, 2H), 6.75 (d, $J=8.6$ Hz, 2H), 3.80 (dd, $J=8.8$, 6.6 Hz, 1H), 3.72 (s, 3H), 3.57 (s, 3H), 3.34 (dd, $J=13.9$, 8.8 Hz, 1H), 2.95 (dd, $J=13.9$, 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 158.0, 138.6, 131.0, 129.8, 128.5, 127.9, 127.3, 113.6, 55.0, 53.8, 51.9, 38.9; HPLC analysis: 79% ee (Chiralpak AD-RH, 0.5% *i*-PrOH in hexane, 1.0 mL/min, $\lambda=254$ nm, $t_R=10.2$ min, minor; $t_R=11.0$ min, major).

Following the procedure described in the literature,[7] a mixture of **10b** (27 mg, 0.1 mmol), acetic acid (1 mL) and hydrochloride acid (2N, 0.35 mL) was stirred for 3 h at 120°C. Purified by flash chromatography on silica gel (4:1 pentane/ether, 0.5% acetic acid) to afford (*R*)-3-(4-methoxyphenyl)-2-phenylpropionic acid (22 mg, 87% yield) as a white solid: $[\alpha]_D^{25}$ −82.3 (*c* 1.40, CH_2Cl_2) (lit.:[7] $[\alpha]_D^{22}$ −62.0 (*c* 1.0, CH_2Cl_2, 93% ee); FTIR (film) 3500–2500, 1706 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.29 (br, s, 1H), 7.32–7.24 (m, 5H), 7.01 (d, $J=8.5$ Hz, 2H), 6.75 (d, $J=8.5$ Hz, 2H), 3.80 (dd, $J=8.3$, 7.0 Hz, 1H), 3.75 (s, 3H), 3.34 (dd, $J=13.7$, 8.3 Hz, 1H), 2.97 (dd, $J=13.7$, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.1, 158.2, 138.0, 130.7, 129.9, 128.7, 128.1, 127.6, 113.8, 55.2, 53.7, 38.4.

4.5. (*R*)-Methyl 2,3-bis(4-methoxyphenyl)propionate, 10c

The reaction was carried out at 50°C in 0.5 mmol scale. Purified by flash chromatography on silica gel (6:1 pentane/ether) to afford product **10c** (53 mg, 35% yield) as a white solid: mp 77–79°C; R_f 0.33 (3:1 pentane/ether); $[\alpha]_D^{25}$ −73.3 (*c* 2.10, $CHCl_3$); FTIR ($CHCl_3$) 3033, 2998, 2952, 2934, 2835, 1735, 1612, 1584, 1512, 1463, 1441, 1301, 1249, 1178, 1156, 1035, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, $J=8.5$ Hz, 2H), 7.01 (d, $J=8.5$ Hz, 2H), 6.83 (d, $J=8.5$ Hz, 2H), 6.76 (d, $J=8.5$ Hz, 2H), 3.80-3.72 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.59 (s, 3H), 3.31 (dd, $J=13.7$, 8.5 Hz, 1H), 2.93 (dd, $J=13.7$, 6.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.1, 158.8, 158.0, 131.1, 130.7, 129.8, 128.9, 113.9, 113.6, 55.2, 55.1, 52.9, 51.9, 39.0; MS (CI) *m*/*z* (relative intensity) 121.1 (28), 135.1 (100), 136.1 (50), 137.1 (75), 195.1 (41), 241.1 (29), 266.9 (34), 300.1 (M^+, 5), 301.1 (M^++H, 9); HRMS (CI) *m*/*z* calcd for $[C_{18}H_{20}O_4]^+$: 300.1356. Found: 300.13556. HPLC analysis: 67% ee (Chiralcel OD-H, 1.0% *i*-PrOH in hexane, 0.8 mL/min, $\lambda=254$ nm, $t_R=15.6$ min, major; $t_R=19.8$ min, minor). Anal. calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.76; H, 6.91%.

4.6. (*R*)-Methyl 2-(4-bromophenyl)-3-(4-*tert*-butyldimethylsilyloxy-3-methoxyphenyl)propionate, 12a

The reaction was carried out at 50°C in 0.5 mmol scale. Purified by flash chromatography on silica gel (9:1 pentane/ether) to afford product **12a** (193 mg, 80% yield) as a colorless oil: R_f 0.37 (5:1 pentane/ether); $[\alpha]_D^{25}$ −74.8 (*c* 8.60, $CHCl_3$); FTIR (film) 2952, 2930, 2856, 1737, 1605, 1585, 1514, 1488, 1464, 1282, 1255, 1237, 1158, 901, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, $J=8.2$ Hz, 2H), 7.13 (d, $J=8.2$ Hz, 2H), 6.71 (d, $J=7.9$ Hz, 1H), 6.52 (dd, $J=7.9$, 1.5 Hz, 1H), 6.47 (d, $J=1.5$ Hz, 1H), 3.74 (*pseudo* t, $J=7.7$ Hz, 1H), 3.68 (s, 3H), 3.60 (s, 3H), 3.28 (dd, $J=13.7$, 8.2 Hz, 1H), 2.91 (dd, $J=13.7$, 7.6 Hz, 1H), 0.98 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 150.5, 143.4, 137.5, 131.9, 131.5, 129.7, 121.2, 121.0, 120.7, 112.8, 55.2, 53.2, 51.9, 39.5, 25.6, 18.4, −4.76, −4.77; HPLC analysis: 77% ee (Chiralpak AD-RH, 0.5% *i*-PrOH in hexane, 1.0 mL/min, $\lambda=254$ nm, $t_R=4.6$ min, minor; $t_R=6.6$ min, major); LCMS (ESI) *m*/*z* (relative intensity) 501 ($M+Na^+$, 100), 463 ($M+H^+$, 36), 419 (60), 251 (39), 221 (70). Anal. calcd for $C_{23}H_{31}BrO_4Si$: C, 57.61; H, 6.52. Found: C, 57.97; H, 6.54%.

4.7. (*R*)-Methyl 3-(4-*tert*-butyldimethylsilyloxy-3-methoxyphenyl)-2-phenylpropionate, 12b

The reaction was carried out at 50°C in 0.5 mmol scale. Purified by flash chromatography on silica gel (8:1 pentane/ether) to afford product **12b** (160 mg, 80% yield) as a colorless oil: R_f 0.37 (5:1 pentane/ether); $[\alpha]_D^{25}$ −58.4 (*c* 1.38, $CHCl_3$); FTIR (film) 2952, 2929, 2856, 1736, 1604, 1585, 1514, 1464, 1453, 1282, 1255, 1236, 1157, 1126, 1039, 906, 839, 781, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.18 (m, 5H), 6.70 (d, $J=8.0$ Hz, 1H), 6.55 (dd, $J=8.0$, 1.8 Hz, 1H), 6.47 (d, $J=1.8$ Hz, 1H), 3.77 (*pseudo* t, $J=7.7$ Hz, 1H), 3.65 (s, 3H), 3.57 (s, 3H), 3.31 (dd, $J=13.7$, 8.2 Hz, 1H), 2.94 (dd, $J=13.7$, 7.2 Hz, 1H), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8 (C), 150.4 (C), 143.3 (C), 138.6 (C), 132.4 (C), 128.5 (CH), 127.9 (CH),

127.2 (CH), 121.0 (CH), 120.6 (CH), 112.9 (CH), 55.2 (CH_3), 53.8 (CH), 51.8 (CH_3), 39.6 (CH_2), 25.6 (CH_3), 18.3 (C), −4.8 (CH_3); GC-MS (EI) m/z (relative intensity) 179 (100), 251 (12), 343 (M^+−Bu^t, 32); HPLC analysis: 75% ee (Chiralcel OD-H, 0.5% *i*-PrOH in hexane, 0.8 mL/min, $\lambda=254$ nm, $t_R=8.9$ min, major; $t_R=9.7$ min, minor). Anal. calcd for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05. Found: C, 68.89; H, 8.13%.

4.8. (*R*)-Methyl 3-(4-*tert*-butyldimethylsilyloxy-3-methoxyphenyl)-2-(4-methoxyphenyl)propionate 12c

The reaction was carried out at 50°C in 0.5 mmol scale. Purified by flash chromatography on silica gel (5:1 pentane/ether) to afford product **12c** (171 mg, 71% yield) as a colorless oil: R_f 0.26 (5:1 pentane/ether); $[\alpha]_D^{25}$ −59.0 (*c* 1.70, $CHCl_3$); FTIR (film) 2997, 2953, 2930, 2856, 1736, 1610, 1584, 1513, 1464, 1282, 1250, 1179, 1157, 1126, 1038, 901, 839, 806, 782 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (d, $J=8.5$ Hz, 2H), 6.83 (d, $J=8.5$ Hz, 2H), 6.71 (d, $J=7.9$ Hz, 1H), 6.55 (dd, $J=7.9$, 1.8 Hz, 1H), 6.51 (d, $J=1.8$ Hz, 1H), 3.78 (s, 3H), 3.74 (*pseudo* t, $J=7.8$ Hz, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.29 (dd, $J=13.6$, 8.4 Hz, 1H), 2.92 (dd, $J=13.6$, 7.2 Hz, 1H), 0.98 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 158.8, 150.5, 143.3, 132.5, 130.7, 129.0, 121.0, 120.6, 113.9, 112.9, 55.3, 55.2, 53.0, 51.9, 39.7, 25.7, 18.4, −4.7; LC-MS (ESI) m/z (relative intensity) 371 (8), 431 (M^++H, 12), 453 (M^++Na, 74); HPLC analysis: 67% ee (Chiralpak AD-RH, 0.5% *i*-PrOH in hexane, 1.0 mL/min, $\lambda=254$ nm, $t_R=6.6$ min, minor; $t_R=10.1$ min, major). Anal. calcd for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96. Found: C, 66.80; H, 8.04%.

4.9. (*R*)-Methyl 2-(4-bromophenyl)-3-(4-di-*p*-tolylaminophenyl)propionate, 14

To a degassed solution of tritolylamine (2.5 mmol) and Rh_2(*S*-DOSP)$_4$ in decalin (2 mL) was added a solution of methyl *p*-bromophenyldiazoacetate (0.5 mmol) in 2,2-dimethylbutane (5 mL) at 35°C in 45 min using syringe-pump. The mixture was stirred for additional 15 min. The solvent was removed in vacuo, and the residue was subject to flash chromatography on silica gel (20:1–10:1 pentane/ether) to afford product **14** (136 mg, 53% yield) as a white solid: mp 45–48°C; R_f 0.42 (10:1 pentane/ether); $[\alpha]_D^{25}$ −105.1 (*c* 5.90, $CHCl_3$); FTIR ($CHCl_3$) 3025, 2949, 2920, 1737, 1606, 1506, 1488, 1320, 1291, 1275, 1157, 1011, 815, 757 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, $J=8.4$ Hz, 2H), 7.17 (d, $J=8.4$ Hz, 2H), 7.03 (d, $J=8.2$ Hz, 4H), 6.95–6.87 (m, 8H), 3.78 (*pseudo* t, $J=7.8$ Hz, 1H), 3.62 (s, 3H), 3.31 (dd, $J=13.7$, 8.5 Hz, 1H), 2.92 (dd, $J=13.7$, 7.1 Hz, 1H), 2.29 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.5, 146.6, 145.3, 137.6, 132.2, 131.8, 131.6, 129.8, 129.7, 129.4, 124.2, 122.9, 121.3, 53.0, 52.1, 39.0, 20.8; HPLC analysis: 81% ee (Chiralpak AD-RH, 5.0% *i*-PrOH in hexane, 1.0 mL/min, $\lambda=254$ nm, $t_R=6.4$ min, minor; $t_R=7.8$ min, major). Anal. calcd for $C_{30}H_{28}BrNO_2$: C, 70.04; H, 5.49; N, 2.72. Found: C, 69.96; H, 5.32; N, 2.70; LCMS (ESI) m/z (relative intensity) 536 (M+Na$^+$, 100), 514 (M+H$^+$, 52), 413 (22), 286 (18).

4.10. (*R*)-Methyl 2-(4-bromophenyl)-3-(4-methylphenyl)-propionate, 16

The reaction carried out at 50°C in 0.5 mmol scale. Purified by flash chromatography on silica gel (20:1–10:1 pentane/ether) to afford product **16** (116 mg, 70% yield) as a colorless oil: R_f 0.60 (5:1 pentane/ether); $[\alpha]_D^{25}$ −99.0 (*c* 5.00, $CHCl_3$); FTIR (film) 3021, 2950, 2920, 1737, 1515, 1488, 1435, 1215, 1157, 1011, 811 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, $J=8.4$ Hz, 2H), 7.15 (d, $J=8.4$ Hz, 2H), 7.02 (d, $J=7.9$ Hz, 2H), 6.96 (d, $J=7.9$ Hz, 2H), 3.78 (*pseudo* t, $J=7.9$ Hz, 1H), 3.85 (s, 3H), 3.33 (dd, $J=13.7$, 8.4 Hz, 1H), 2.94 (dd, $J=13.7$, 7.0 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 137.5, 135.9, 135.3, 131.6, 129.7, 129.0, 128.7, 121.2, 53.0, 52.0, 39.2, 21.0; HPLC analysis: 74% ee ((*R*,*R*)-Whelk-O 1, 1.0% *i*-PrOH in hexane, 0.8 mL/min, $\lambda=254$ nm, $t_R=10.4$ min, major; $t_R=12.3$ min, minor). Anal. calcd for $C_{17}H_{17}BrO_2$: C, 61.28; H, 5.14. Found: C, 61.50; H, 5.26%.

4.11. (*R*)-(*E*)-Methyl 3-(4-bromophenyl)-2-(4-methoxybenzyl)but-3-enoate, 18a

The reaction carried out at rt in 0.48 mmol scale. Purified by flash chromatography on silica gel (5:1 pentane/ether) to afford product **18a** (96 mg, 53% yield) as a white solid: mp 66–68°C; R_f 0.24 (5:1 pentane/ether); $[\alpha]_D^{25}$ −130.6 (*c* 1.60, $CHCl_3$); FTIR ($CHCl_3$) 3026, 3001, 2949, 2837, 1734, 1612, 1585, 1512, 1488, 1441, 1295, 1248, 1163, 1072, 1034, 1013, 968, 831, 809 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, $J=8.4$ Hz, 2H), 7.17 (d, $J=8.4$ Hz, 2H), 7.07 (d, $J=8.5$ Hz, 2H), 6.80 (d, $J=8.5$ Hz, 2H), 6.31 (d, $J=15.9$ Hz, 1H), 6.21 (dd, $J=15.9$, 8.8 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.41 (*pseudo* q, $J=7.9$ Hz, 1H), 3.10 (dd, $J=13.7$, 7.9 Hz, 1H), 2.86 (dd, $J=13.7$, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.6, 158.2, 135.6, 131.6, 131.4, 130.3, 130.0, 127.8, 127.6, 121.3, 113.7, 55.1, 51.9, 51.6, 38.0; MS (EI) m/z (relative intensity) 121.1 (100), 122.1 (54), 374.1 (M^++H, 3); HRMS (EI) m/z calcd for $[C_{19}H_{19}BrO_3]^+$: 374.0512; Found: 374.05051. HPLC analysis: 94% ee (Chiralcel OD-H, 2.0% *i*-PrOH in hexane, 1.0 mL/min, $\lambda=254$ nm, $t_R=10.1$ min, major; $t_R=12.3$ min, minor). Anal. calcd for $C_{19}H_{19}BrO_3$: C, 60.81; H, 5.10. Found: C, 61.05; H, 5.28%.

4.12. (*R*)-(*E*)-Methyl 2-(4-methoxybenzyl)-4-phenylbut-3-enoate, 18b

The reaction carried out at rt at 0.5 mmol scale. Purified by flash chromatography on silica gel (5:1 pentane/ether) to afford product **18b** (79 mg, 53% yield) a white solid: mp 50–54°C; R_f 0.34 (5:1 pentane/ether); $[\alpha]_D^{25}$ −141.5 (*c* 0.90, $CHCl_3$); FTIR (film) 3027, 3002, 2950, 2838, 1734, 1611, 1511, 1444, 1296, 1249, 1161, 1111, 1033, 967, 830, 743, 695 cm^{-1}; ^{1}H

NMR (500 MHz, $CDCl_3$) δ 7.33 (d, $J=7.4$ Hz, 2H), 7.29 (t, $J=7.4$ Hz, 2H), 7.24–7.19 (m, 1H), 7.09 (d, $J=8.5$ Hz, 2H), 6.80 (d, $J=8.5$ Hz, 2H), 6.40 (d, $J=15.9$ Hz, 1H), 6.22 (dd, $J=15.9$, 8.8 Hz, 1H), 3.76 (s, 3H), 3.64 (s, 3H), 3.43 (*pseudo* q, $J=8.0$ Hz, 1H), 3.10 (dd, $J=13.7$, 7.9 Hz, 1H), 2.88 (dd, $J=13.7$, 7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8, 158.1, 136.7, 132.5, 130.5, 130.0, 128.5, 127.6, 126.9, 126.3, 113.7, 55.1, 51.8, 51.6, 38.1; MS (EI) m/z (relative intensity) 121.1 (100), 122.1 (62), 237.1 (10), 296.2 (M^+, 16); HRMS (EI) m/z calcd for $[C_{19}H_{20}O_3]^+$: 296.1407. Found: 296.14096. HPLC analysis: 92% ee (Chiralcel OD-H, 2% *i*-PrOH in hexane, 1.0 mL/min, $\lambda=254$ nm, $t_R=10.1$ min, major; $t_R=13.2$ min, minor). Anal. calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.71; H, 6.90.

4.13. (*E*)-Methyl (4-*tert*-butyldimethylsilyoxy-3-methoxyphenyl)vinyldiazoacetate, 22

To a cloudy solution of 4-*tert*-butyldimethylsilyoxy-3-methoxybenzylaldehyde[8b] (7.42 g, 27.8 mmol) and 3-carboxypropyl-triphenylphosphonium chloride[12] (15.50 g, 41.8 mmol) in anhydrous THF (90 mL) was added a solution of *t*-BuOK (9.75 g, 84.0 mmol) in anhydrous THF (20 mL) in 50 min using cannula at 0°C. The mixture was stirred for an additional 1 h after addition then quenched with CH_3I (18 mL, 270.0 mmol). The resulting mixture was stirred overnight. Water was added to make a clear solution and the mixture was extracted with Et_2O (3×30 mL), then dried over $MgSO_4$. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel (10:1 petroleum ether/ether) to give methyl (4-*tert*-butyldimethylsilyoxy-3-methoxyphenyl)vinyl-acetate (2.49 g, 26% yield) as a yellow oil: R_f 0.30 (5:1 pentane/ether); FTIR (film) 3035, 2952, 2894, 2857, 1740, 1599, 1577, 1512, 1465, 1414, 1282, 1257, 1160, 1036, 964, 905, 840, 802, 788 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.82 (d, $J=8.4$ Hz, 1H), 6.78 (d, $J=8.4$ Hz, 1H), 6.42 (d, $J=15.9$ Hz, 1H), 6.15 (dq, $J=15.9$, 7.0 Hz, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 3.23 (d, $J=7.0$ Hz, 1H), 1.00 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 150.9, 144.8, 133.3, 130.7, 120.8, 119.47, 119.41, 109.4, 55.3, 51.8, 38.1, 25.6, 18.4, –4.7. DBU (1.33 mL, 8.9 mmol) was added quickly to a stirring mixture of methyl (4-*tert*-butyldimethylsilyoxy - 3 - methoxyphenyl)vinylacetate (2.49 g, 7.4 mol) and *p*-acetamidobenzenesufonyl azide (2.13 g, 8.9 mmol) in CH_3CN (30 mL) at 0°C. After 2 h, aqueous NH_4Cl (40 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2×30 mL). The combined organic extract was washed with brine then dried over $MgSO_4$. The crude product was dissolved in pentane/ether (1:1) and passed through a pad of silica gel. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel (10:1 pentane/ether) to afford the product **22** (1.88 g, 70% yield) as a purple solid: R_f 0.47 (5:1 pentane/ether); FTIR (CH_2Cl_2) 2954, 2930, 2857, 2079, 1708, 1627, 1698, 1574, 1512, 1437, 1310, 1280, 1248, 1110, 906, 840, 804, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.82–6.77 (m, 2H), 6.29 (d, $J=16.2$ Hz, 1H), 6.13 (d, $J=16.2$ Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H), 0.99 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 151.1, 144.6, 130.8, 123.2, 120.9, 119.0, 109.0, 108.8, 55.4, 55.2, 25.6, 18.4, –4.7 (C=N_2 is missing); MS (ESI) m/z (relative intensity) 191.1 (58), 335.2 (M^+-N_2+H, 56), 363.3 (M^++H, 46); HRMS (ESI) m/z calcd for $[C_{18}H_{27}N_2O_2Si]^+$ (M^++H): 363.1735. Found: 363.17426.

4.14. (*S*)-(*E*)-Methyl 2-(4-*tert*-butyldimethylsilyoxy-3-methoxybenzyl)-4-(4-*tert*-butyldimethylsilyloxy-3-methoxyphenyl)but-3-enoate, (*S*)-21

Under an argon atmosphere, to a refluxing degassed solution of **11** (1.26 g, 5 mmol) and Rh_2(*S*-DOSP)$_4$ (9.5 mg, 1 mol%) in 2,2-dimethylbutane (2 mL), was added a degassed solution of diazo compound **22** (181 mg, 0.5 mmol) in 2,2-dimethylbutane (5 mL) in 45 min using syringe-pump. The reaction mixture was refluxed for additional 15 min then cooled to rt. The solvent was removed and the residue was purified by flash chromatography on silica gel (10:1–5:1 pentane/ether) to afford product (*S*)-**21** (130 mg, 44% yield) as a yellow oil: R_f 0.32 (5:1 pentane/ether); $[\alpha]_D^{25}$ –85.1 (*c* 6.50, $CHCl_3$); FTIR (film) 2953, 2929, 2857, 1737, 1601, 1578, 1513, 1281, 1252, 1158, 1126, 1038, 902, 839, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.82–6.78 (m, 2H), 6.76 (d, $J=7.6$ Hz, 1H), 6.67 (d, $J=1.8$ Hz, 1H), 6.64 (dd, $J=8.2$, 1.8 Hz, 1H), 6.31 (d, $J=15.6$ Hz, 1H), 6.09 (dd, $J=15.6$, 8.8 Hz, 1H), 3.82 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 3.41 (*pseudo* q, $J=7.9$ Hz, 1H), 3.10 (dd, $J=13.4$, 8.1 Hz, 1H), 2.86 (dd, $J=13.4$, 7.0 Hz, 1H), 1.01 (s, 9H), 1.00 (s, 9H), 0.16 (s, 6H), 0.14 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 150.9, 150.5, 144.9, 143.4, 132.4, 132.1, 130.6, 124.8, 121.2, 120.8, 120.6, 119.4, 113.1, 109.6, 55.35, 55.31, 51.8, 38.9, 25.66, 25.65, 18.39, 18.36, –4.72, –4.74, –4.75; MS (ESI) m/z (relative intensity) 105.0 (57), 119.1 (100), 301.2 (54), 609.6 (M^++Na, 95); HRMS (ESI) m/z calcd for $[C_{32}H_{50}NaO_6Si_2]^+$ (M^++Na): 609.3038. Found: 609.30151. HPLC analysis: 92% ee (Chiralcel OD-H, 1.0% *i*-PrOH in hexane, 0.8 mL/min, $\lambda=254$ nm, $t_R=7.5$ min, major; $t_R=10.7$ min, minor). Anal. calcd for $C_{32}H_{50}O_6Si_2$: C, 65.49; H, 8.59. Found: C, 65.75; H, 8.73%.

(*R*)-**21** (127 mg, 43% yield) was obtained following the same procedure as (*S*)-**21** except using Rh_2(*R*-DOSP)$_4$ as catalyst: $[\alpha]_D^{25}$ +91.0 (*c* 6.35, $CHCl_3$); The IR, ^1H and ^{13}C NMR spectra are consistent with those of compound (*S*)-**21**; HPLC analysis: 91% ee (Chiralcel OD-H, 1.0% *i*-PrOH in hexane, 0.8 mL/min, $\lambda=254$ nm, $t_R=7.8$ min, minor; $t_R=10.5$ min, major).

4.15. (+)-Imperanene, 19[8b,c]

Under an argon atmosphere, to a stirred solution of **21** (127 mg, 0.22 mmol) in THF (4 mL) was added LAH (0.22 mL, 1 M in THF) dropwise at –40°C. The mixture was stirred for 30 min at –40°C then quenched with aqueous NH_4Cl. The organic phase was separated and the aqueous layer was extracted with ether. The

combined organic extract was dried over $MgSO_4$. The crude product thus obtained was near pure and was used directly in the next step without purification. FTIR (film) 3374 (br), 2954, 2929, 2857, 1601, 1578, 1513, 1471, 1417, 1281, 1254, 1234, 1158, 1128, 1039, 906, 840, 806, 782 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.83 (d, $J=1.5$ Hz, 1H), 6.80 (dd, $J=8.0$, 1.5 Hz, 1H), 6.76 (d, $J=8.0$ Hz, 1H), 6.66 (d, $J=1.8$ Hz, 1H), 6.63 (dd, $J=7.9$, 1.8 Hz, 1H), 6.34 (d, $J=15.9$ Hz, 1H), 5.93 (dd, $J=15.9$, 8.2 Hz, 1H), 3.81 (s, 3H), 3.74 (s, 3H), 3.66 (dd, $J=10.7$, 4.7 Hz, 1H), 3.54 (dd, $J=10.7$, 7.3 Hz, 1H), 2.75–2.60 (m, 2H), 0.99 (s, 9H), 0.98 (s, 9H), 0.15 (s, 6H), 0.13 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.9, 150.5, 144.6, 143.2, 133.1, 132.0, 131.1, 128.7, 121.3, 120.8, 120.6, 119.0, 113.3, 109.7, 65.2, 55.4, 47.5, 37.6, 29.6, 25.7, 18.39, 18.35, –4.7. The crude was dissolved in THF (4 mL), and TBAF (0.45 mL, 1 M in THF) was added. The resulting mixture was stirred for 20 min at rt then quenched with aqueous NH_4Cl. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic extract was dried over $MgSO_4$. The crude product was purified by flash chromatography on silica gel (1:2 pentane/ether) to afford the product (+)-imperanene **19** (62 mg, 87%) as a white solid: $[\alpha]_D^{25}$ +115.2 (*c* 1.05, $CHCl_3$); FTIR (film) 3423 (br), 3013, 2935, 2848, 1600, 1514 1463, 1450, 1429, 1370, 1271, 1236, 1154, 1033, 754 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 3H), 6.82 (d, $J=8.2$ Hz, 1H), 6.70–6.66 (m, 2H), 6.35 (d, $J=16.0$ Hz, 1H), 5.92 (dd, $J=16.0$, 8.3 Hz, 1H), 5.64 (br s, 1H), 5.51 (br s, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.67 (dd, $J=10.7$, 4.9 Hz, 1H), 3.56 (dd, $J=10.7$, 7.2 Hz, 1H), 2.77–2.68 (m, 2H), 2.68–2.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.6, 146.3, 145.2, 143.8, 132.1, 131.5, 129.7, 128.3, 121.8, 119.6, 114.4, 114.2, 111.7, 108.2, 65.2, 55.83, 55.81, 47.5, 37.6; HPLC analysis: 92% ee (Chiralcel OD-H, 30.0% *i*-PrOH in hexane, 1.0 mL/min, $\lambda=254$ nm, $t_R=13.8$ min, minor; $t_R=16.6$ min, major).

4.16. (–)-α-Conidendrin, 20[13]

To a stirred suspension of paraformaldehyde (40 mg, 1.32 mmol) in a solution of (*R*)-**21** (130 mg, 0.22 mmol) in CH_2Cl_2 (5 mL) was added methylaluminum sesquichloride (1.32 mL, 1 M in hexanes) at 0°C. The resulting mixture was allowed to stir for 1 h then quenched with water. The mixture was extracted with ether, washed with brine then dried over Na_2SO_4. This crude product was treated with $TsOH{\cdot}H_2O$ (6 mg, 0.03 mmol) in CH_2Cl_2 for 1 h at rt. Water (5 mL) was added and extracted with ether. The organic extract was washed with brine then dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel (10:1–5:1 pentane/ether) to afford product **23** (75 mg, 58% yield) as a white solid: R_f 0.41 (1:1 pentane/ether); FTIR ($CDCl_3$) 2954, 2958, 2856, 1783, 1511, 1292, 1255, 902, 839 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.80 (d, $J=8.0$ Hz, 1H), 6.64 (s, 1H), 6.60 (dd, $J=8.0$, 1.4 Hz, 1H), 6.52 (br s, 1H), 6.28 (s, 1H), 4.19 (dd, $J=8.5$, 6.4 Hz, 1H), 4.00 (dd, $J=10.7$, 8.5 Hz, 1H), 3.84 (d, $J=10.7$ Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.20 (dd, J=15.5, 5.0 Hz, 1H), 2.96 (dd, $J=15.5$, 11.6 Hz, 1H), 2.58 (ddd, $J=13.5$, 11.6, 5.0 Hz, 1H), 2.51 (dtd, $J=13.5$, 10.7, 6.4 Hz, 1H), 0.99 (s, 9H), 0.86 (s, 9H), 0.14 (s, 6H), 0.00 (s, 3H), –0.03 9s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.1, 151.3, 149.7, 144.1, 143.5, 135.9, 131.0, 127.8, 121.5, 121.0, 120.8, 112.5, 111.4, 71.9, 55.56, 55.40, 49.7, 47.4, 41.8, 29.2, 26.0, 25.7, 25.6, 18.4, 18.3, –4.70, –4.72, –4.73, –4.74; MS (FAB) *m*/*z* (relative intensity) 251.1 (54), 347.1 (21), 527.2 ($M^+-{}^t$Bu, 100), 584.3 (M^+, 11), 607.2 (M^++Na, 58); HRMS (FAB) *m*/*z* calcd for $[C_{32}H_{48}NaO_6Si_2]^+$ (M^++Na): 607.2882. Found: 607.28830.

TBAF (0.25 mL, 1 M in THF) was added to a stirred solution of **23** (66 mg, 0.11 mmol) in THF (5 mL) at rt. The resulting solution was stirred for 30 min at rt then quenched with saturated aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. The solvent was removed in vacuo and the crude product was purified by flash chromatography on silica gel (1:1–1:2 pentane/ether then 1:1 ether/CH_2Cl_2) to afford (–)-α-conidendrin **20** (32 mg, 78% yield) as a white solid: mp 255°C (lit[14] mp 256°C); R_f 0.65 (1:1 ether/CH_2Cl_2); $[\alpha]_D^{25}$ –50.4 (*c* 0.90, acetone); ^1H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, $J=8.0$ Hz, 1H), 6.64 (br s, 2H), 6.54 (s, 1H), 6.40 (s, 1H), 5.57 (s, 1H), 5.41 (s, 1H), 4.23 (dd, $J=8.5$, 6.1 Hz, 1H), 4.01 (*pseudo* t, $J=9.5$ Hz, 1H), 3.89 (s, 3H), 3.85 (d, $J=10.0$ Hz, 1H), 3.82 (s, 3H), 3.21 (dd, J=15.6, 4.5 Hz, 1H), 2.98 (dd, $J=15.6$, 11.0 Hz, 1H), 2.62–2.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$, three drops of DMSO-d_6 was added to dissolve the sample) δ 176.9, 147.2, 145.8, 145.0, 144.4, 133.7, 131.3, 125.6, 121.1, 115.4, 114.8, 111.4, 110.5, 71.7, 55.74, 55.70, 49.5, 47.2, 41.6, 29.0.

Acknowledgements

Financial support of this work by the National Science Foundation (CHE 0092490) and the National Institutes of Health (CA85641) is gratefully acknowledged.

References

1. For reviews on other methods for C–H activation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879; (b) Dyker, G. *Angew. Chem.; Int. Ed. Engl.* **1999**, *28*, 1698; (c) Arndsten, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970; (d) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633; (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731; (f) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
2. For recent representative examples of C–H activation, see: (a) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995; (b) Waltz, K. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 11358; (c) Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900; (d) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856; (e) Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115; (f) Saaby, S.; Bayon, P.; Aburel, P. S.; Jorgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4352; (g) Tan,

K. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2002**, *124*, 3202; (h) Zhong, H. A.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **2002**, *124*, 1378.

3. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp. 112–162.
4. (a) Scott, L. T.; DeCicco, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 322; (b) Ambramovitch, R. A.; Roy, J. *J. Chem. Soc., Chem. Commun.* **1965**, 542; (c) Adams, J.; Poupart, M.-A.; Greainer, L.; Schaller, C.; Quimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749; (d) Callott, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, *23*, 4321; (e) Callott, H. J.; Metz, F. *Nouv. J. Chim.* **1985**, *9*, 167; (f) Domenceau, A.; Noels, A. F.; Costa, J. L.; Hubert, A. *J. Mol. Catal.* **1990**, *58*, 21.
5. (a) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075; (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233; (c) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383; (d) Davies, H. M. L.; Hansen, T.; Hopper, D.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509; (e) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063; (f) Davies, H. M. L.; Antoulinakis, E. G. *Org. Lett.* **2000**, *2*, 4153; (g) Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2071; (h) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2001**, *3*, 1773; (i) Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587; (j) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951; (k) Davies, H. M. L.; Walji, A. M.; Townsend, R. J. *Tetrahedron Lett.* **2002**, *43*, 4981; (l) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2197; (m) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165.
6. For recent reviews, see: (a) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617–618*, 45; (b) Davies, H. M. L. *J. Mol. Catal. A* **2002**, *189*, 125.
7. Camps, P.; Gilmenez, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1227.
8. (a) Matsunaga, K.; Shibuya, M.; Ohzumi, Y. *J. Nat. Prod.* **1995**, *58*, 138; (b) Shattuck, J. C.; Shreve, C. M.; Solomon, S. E. *Org. Lett.* **2001**, *3*, 3021; (c) Doyle, M. P.; Hu, W.; Valenzuela, M. V. *J. Org. Chem.* **2002**, *67*, 2954.
9. (a) Herrick, F. W.; Hergert, H. L. *Recent Advances in Photochemistry*; Plenum Press: New York, 1977; pp. 443–515; (b) Boissin, P.; Dhal, R.; Brown, E. *Tetrahedron Lett.* **1989**, *30*, 4371; (c) Dantzig, A.; LaLonde, R. L.; Ramdayal, F.; Shepard, R. L.; Yanai, K.; Zhang, M. *J. Med. Chem.* **2001**, *44*, 180.
10. Snider, B. B.; Jackson, A. C. *J. Org. Chem.* **1983**, *48*, 1471.
11. Schauble, J. H.; Walter, G. J.; Morin, J. G. *J. Org. Chem.* **1974**, *39*, 755.
12. Denney, D. B.; Smith, L. C. *J. Org. Chem.* **1962**, *27*, 3404.
13. Miller, R. W.; McLaughlin, J. L.; Powell, R. G.; Plattner, R. D.; Weisleder, D.; Smith, C. R. *J. Nat. Prod.* **1982**, *45*, 78.
14. Freudenburg, K.; Knof, L. *Chem. Ber.* **1957**, *90*, 2857.