Pergamon

Tetrahedron 57 (2001) 5067–5072

TETRAHEDRON

Rhodium-catalysed asymmetric ring opening reactions with carboxylate nucleophiles

Mark Lautens* and Keith Fagnou

Davenport Research Laboratories, Department of Chemistry, University of Toronto, Toronto, Ontario, M5S 3H6, Canada

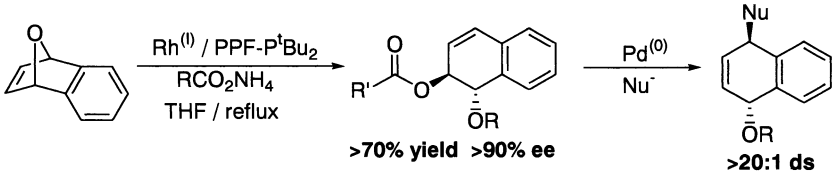
Dedicated to Professor Barry M. Trost, in honour of his contributions to research and teachings, on the occasion of his 60th birthday

Received 31 January 2001; revised 15 February 2001; accepted 19 February 2001

Abstract—We have developed an asymmetric ring opening reaction of oxabenzonorbornadiene with carboxylate nucleophiles to generate enantiomerically enriched hydronaphthalene products containing an allylic carboxylate moiety. These reactions occur in good yield and excellent enantioselectivity (>90% ee). The allylic carboxylate functionality was found to be stable towards reaction with the rhodium catalyst under the reaction conditions. In order to obtain these results, two advancements were required. First, the use of protic additives was necessary for good reactivity. Second, the exchange of the halide ligand on the catalyst from chloride to iodide was required to obtain high ee.

Allylic functionalisation through the intermediacy of π-allyl transition metal complexes remains an area of intense study. Palladium catalysts are the most thoroughly explored,[1] but other metals have been shown to exhibit useful properties.[2,3] We[4] and others[5] have been interested in exploring the reactivity of rhodium in analogous transformations and complementary reactivities have emerged when compared to the palladium 'benchmark'. While palladium catalysts will generally react with allylic acetates, the ability of rhodium catalysts to do so depends heavily on the nature of the ligands on the metal. It has been demonstrated that while rhodium–phosphite complexes will react with allylic acetates, analogous rhodium–phosphine complexes do not.[6] This led us to consider the use of carboxylate nucleophiles with rhodium catalysis as a means of generating enantioenriched allylic acetates for use in subsequent transformations. Herein, we report the realisation of this goal. Through the combined use of carboxylate nucleophiles, protic additives, and an intriguing halide effect on the rhodium catalyst, the asymmetric ring opening reaction (ARO) of oxabenzonorbornadiene to produce 1,2-dihydronaphthalenes in good yield and excellent ee (>90%) has been achieved. The resulting allylic carboxylate moiety was found to be inert towards further insertion under the reaction conditions. The utility of this methodology when coupled with palladium catalysis has been demonstrated in the preparation of 1,4-dihydronaphthalenes (Scheme 1).

Our initial investigations focused on determining whether carboxylates would be of sufficient nucleophilicity to participate in these reactions. We had previously uncovered a pKa effect with alcohol and phenol nucleophiles where the more acidic species reacted preferentially in competition experiments.[7] Since carboxylic acids are more acidic than phenols, we anticipated that this trend would continue. Unfortunately, reaction of **1** under previously established conditions in the presence of five equivalents acetic acid did not give any reaction (Table 1, Entry 1). Increasing the nucleophilicity by using sodium acetate also did not produce any reaction, in accord with our earlier findings with other nucleophiles that a proton source is essential

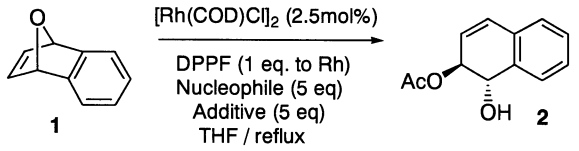


Scheme 1. Rhodium-catalysed ARO of oxabenzonorbornadiene with carboxylate nucleophiles.

Keywords: asymmetric catalysis; rhodium; carboxylate.
* Corresponding author. Fax: +1-416-978-1631; e-mail: mlautens@alchemy.chem.utoronto.ca

0040–4020/01/$ - see front matter
PII: S0040-4020(01)00351-9

Table 1. Development of ring opening reaction with acetate



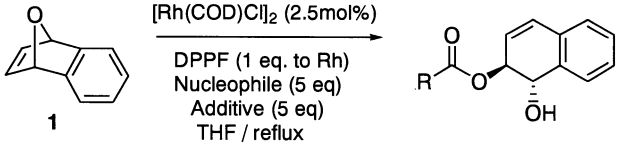
Entry	Nucleophile	Additive	Yield (%)[a]
1	AcOH	None	NR
2	AcONa	None	NR
3	AcONa	Et_3N·HCl	89
4	AcOH	Et_3N	89
5	$AcONH_4$	None	84

Conditions: $[Rh(COD)Cl]_2$ (2.5 mol%), dppf (5 mol%), nucleophile (5 eq.), additive (5 eq.), and **1** reacted in THF (0.1 M) at reflux.
[a] Isolated yield.

for the reaction to occur (Entry 2). We thus sought a method of maintaining both the increased nucleophilicity of an anionic carboxylate species and the presence of a proton source. In previous studies, we found that the addition of ammonium salts as protic additives could be used to increase the reactivity of aliphatic amines.[8] Since protonated amines did not negatively affect the catalyst activity, we reasoned that the combined use of sodium acetate and an amine hydrochloride might offer a solution.[9] This was indeed the case, since reaction of **1** in the presence of equimolar amounts of sodium acetate and triethylamine hydrochloride generated **2** in 89% yield (Entry 3).[10] Other methods of achieving the same result are through the combined use of equimolar amounts of acetic acid and triethylamine or by using ammonium acetate (Entries 4 and 5).

The scope of this reaction was found to be general with respect to the carboxylate nucleophile (Table 2). A variety of carboxylates effectively induce ring opening, including formate (Entries 3 and 4) and the potassium salt of ethyl malonate (Entry 7). Benzoate is also compatible despite its lower nucleophilicity and the higher propensity of the allylic benzoate moiety to undergo subsequent ionisation with transition metals (Entries 5 and 6). No appreciable changes in yields or reaction times were noted for the different conditions.

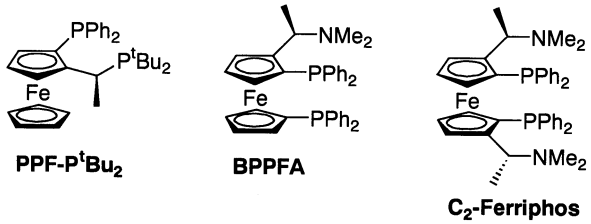
Table 2. Scope of ring opening with carboxylate nucleophiles



Entry	Nucleophile	Additive	Product	Yield (%)[a]
1	Propionic acid	Et_3N	**3**	72
2	Methacrylic acid	Et_3N	**4**	69
3	Sodium formate	Et_3N·HCl	**5**	69
4	Ammonium formate	None	**5**	73
5	Benzoic acid	Et_3N	**6**	70
6	Ammonium benzoate	None	**6**	81
7	Ethyl malonate potassium salt	Et_3N·HCl	**7**	79

Conditions: $[Rh(COD)Cl]_2$ (2.5 mol%), dppf (5 mol%), nucleophile (5 eq.), additive (5 eq.), and **1** reacted in THF (0.1 M) at reflux.
[a] Isolated yield.

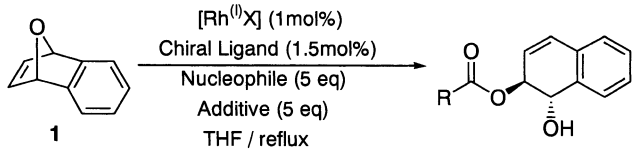
We have developed an efficient asymmetric version of this reaction through the correct combination of chiral phosphine ligand and halide ligand. While alcohols and phenols induce ring opening with ees in excess of 90% with a catalyst generated from PPF-P^{t}Bu$_2$ and $[Rh(COD)Cl]_2$, poor results were obtained with carboxylate nucleophiles (Table 3, Entries 1 and 5). Ees of 81% could be obtained by changing the chiral ligand to BPPFA or C_2-Ferriphos (Entries 2, 3 and 6, 7), but the best results were obtained by using PPF-P^{t}Bu$_2$ with a rhodium iodide complex prepared in situ from the rhodium chloride. Using this protocol, products **2** and **6** were obtained in >90% yield and 92% ee (Entries 4 and 8). The difference in the enantioselectivities between the chloro and the iodo complexes is particularly striking with benzoate as the nucleophile, where **6** was generated in only 31% ee when the Rh–Cl complex was used, and in 92% ee when the halide ligand was changed from Cl to I. These results, along with our earlier work with nitrogen nucleophiles,[8] underlines the importance of considering halide effects in asymmetric catalysis. Two other examples with methacrylic acid and propionic acid gave similar yields and ees (Entries 9 and 10).



The stability of the allylic carboxylate produced in these reactions was investigated under the ring opening conditions. An important question that needed to be answered was whether the rhodium catalyst was able to insert into the allylic carboxylate. When benzoate **6** was subjected to the reaction conditions with five equivalents of ammonium acetate as the nucleophile no reaction had occurred after 2 h and only **6** was detected in the crude ^{1}H NMR. In a second experiment, enantioenriched **2** (92% ee) was treated with rhodium and BPPFA as the chiral ligand (which gave **2** in only 78% ee). After 2 h the ee remained unchanged. This was also the case when enantioenriched **2** (78% ee) was subjected to the reaction conditions with the [RhI(PPF-P^{t}Bu$_2$)] catalyst (which gave **2** in 92% ee). It can be concluded based on these results that addition of the carboxylate nucleophile is irreversible and that the high enantioselectivities obtained with the rhodium iodide PPF-P^{t}Bu$_2$ catalyst are kinetic in origin and not the result of a reversible thermodynamically controlled process.

Preliminary studies of the utility of these ring opened products have been carried out. An initial goal was the development of a process which would rely on the differing chemoselectivities of rhodium and palladium to first create and then use an allylic carboxylate functionality for subsequent transformations. This goal has been attained[11] as exemplified by reaction of **8** with methyldiethyl malonate and a $Pd^{(0)}$ catalyst to generate **9** as the sole regioisomer in good yield [Eq. (1)]. The high regioselectivity is likely the result of the presence of the OTBS group adjacent to the π-allyl moiety that directs the nucleophilic attack to

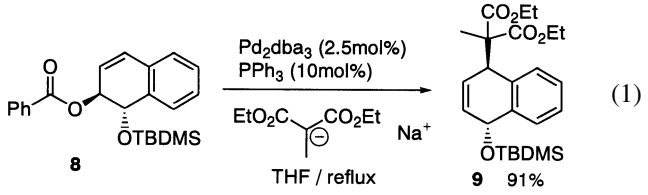
Table 3. ARO with carboxylate nucleophiles



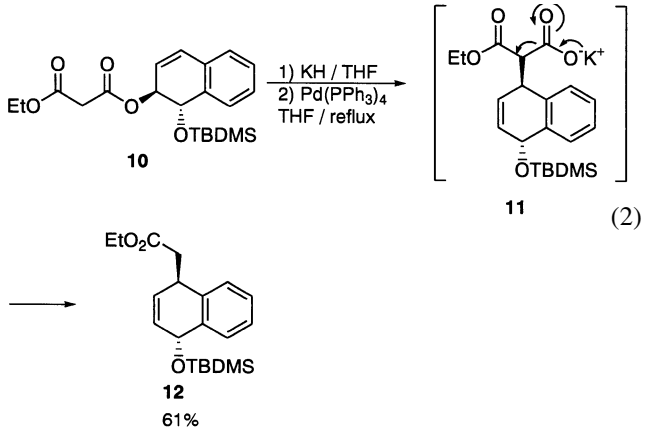
Entry	X ligand[a]	Chiral ligand	Nucleophile/additive	Product	Yield (%)[b]	Ee (%)[c]
1	Cl	PPF-P^{t}Bu$_2$	Ammonium acetate	**2**	81	61
2	Cl	BPPFA	Ammonium acetate	**2**	86	78
3	Cl	C_2-Ferriphos	Ammonium acetate	**2**	89	78
4	I	PPF-P^{t}Bu$_2$	Ammonium acetate	**2**	93[d]	92
5	Cl	PPF-P^{t}Bu$_2$	Ammonium benzoate	**6**	72	31
6	Cl	BPPFA	Ammonium benzoate	**6**	75	81
7	Cl	C_2-Ferriphos	Ammonium benzoate	**6**	74	81
8	I	PPF-P^{t}Bu$_2$	Ammonium benzoate	**6**	91[d]	92
9	I	PPF-P^{t}Bu$_2$	Propionic acid/Et_3N	**3**	75	91
10	I	PPF-P^{t}Bu$_2$	Methacrylic acid/Et_3N	**4**	71	91

[a] Conditions (X ligand=Cl): $[Rh(COD)Cl]_2$ (0.5 mol%), ligand (1.5 mol%), nucleophile (5 eq.), additive (5 eq.), and **1** reacted in THF (0.1 M) at reflux. Conditions (X ligand=I): $[Rh(COD)Cl]_2$ (0.5 mol%), ligand (1.5 mol%) added to flask followed by addition of AgOTf (2 mol%) then Bu_4NI (4 mol%). To this was added **1**. The nucleophile (5 eq.) and additive (5 eq.) were added to this solution in THF (0.1 M) at reflux.
[b] Isolated yield.
[c] Ee determined by CSP HPLC with a Chiralcel OD collumn.
[d] These reactions were run on a 1 g scale.

the distal position.[12] The intramolecular process was also examined. Treatment of **10** with base and catalytic $Pd(PPh_3)_4$ causes rearrangement to **11** and subsequent decarboxylation to give **12** in 61% yield [Eq. (2)]. This rearrangement does not occur after 2 h in the absence of the palladium catalyst. The 1,4-dihydronaphthalene products obtained through the sequential application of rhodium and palladium catalysis are synthetically interesting and belong to a biologically important class of compounds.[13]



(1)



(2)

In conclusion, we have shown that carboxylate nucleophiles can be effectively used to induce ring opening reactions of oxabenzonorbornadiene in good yield and excellent enantioselectivity (>90% ee). In order to achieve this goal, two changes to our earlier protocols were made. First, the combined use of a carboxylate nucleophile with a protic additive is vital to induce reaction. If the carboxylic acid is not deprotonated or if a proton source is not available, no reaction occurs. Second, an intriguing halide effect on the rhodium catalyst must be utilised to obtain high enantioselectivity.

It was established that no reaction of the allyl carboxylate occurred with the rhodium catalyst under the reaction conditions and that the high enantioselectivities are not the result of a reversible addition/insertion process. The utility of these products has been demonstrated through their application in the preparation of 1,4-dihydronaphthalenes. The hydronaphthalene products of these reactions constitute an important molecular scaffold in medicinal chemistry and can be found in a wide range of natural and synthetic compounds possessing a large diversity of biological activities. We are currently exploring the application of this methodology to other ring systems.

1. Experimental

1.1. General

All flasks were flame-dried under a stream of nitrogen or argon and cooled before use. Solvents and solutions were transferred with syringes and cannulae using standard inert atmosphere techniques. ^{1}H NMR spectra were recorded at 400 MHz using a Varian XL400 spectrometer with $CDCl_3$ as reference standard (δ 7.24 ppm) or some other suitable solvent. Spectral features are tabulated in the following order: chemical shift (δ, ppm); number of protons; multiplicity (s-singlet, d-doublet, t-triplet, q-quartet, m-complex multiplet); coupling constants (J, Hz). ^{13}C NMR spectra were recorded at 100 MHz with $CDCl_3$ as reference standard (δ=77.0 ppm) or some other suitable solvent. IR spectra were obtained using a Nicolet DX FT-JR spectro-

meter as a KBr pellet or neat film between KBr plates. High resolution mass spectra were obtained from a VG 70-250S (double focusing) mass spectrometer at 70 eV. Melting points were taken on a Fisher–Johns melting point apparatus and are uncorrected. HPLC analysis was performed on a Waters 600E with Chiralcel OD or OJ columns. Analytical TLC was performed using EM Separations precoated silica gel 0.2 mm layer UV 254 fluorescent sheets. Column chromatography was performed as 'Flash Chromatography' as reported by Still[14] using (200–400 mesh) Merck grade silica gel. THF was distilled from sodium benzophenone ketyl immediately prior to use. The PPF-P^{t}Bu$_2$ ligand was donated by Solvias. Oxabenzonorbornadiene **1**,[15] BPPFA, and C$_2$-Ferriphos were prepared according to literature procedure. All other reagents were obtained from Aldrich and used as received unless otherwise stated.

1.2. Representative procedure for the in situ exchange of chloride to iodide ligands

To a flame-dried round bottomed flask under inert atmosphere was added [Rh(COD)Cl]$_2$ (5 mg, 0.01 mmol) and (*S*,*R*)-PPF-P^{t}Bu$_2$ (12 mg, 0.022 mmol), which was dissolved in 2 mL THF and stirred at room temperature for 5 min to produce a dark red solution. In a separate flame-dried round bottomed flask was added AgOTf (11 mg, 0.04 mmol). The rhodium–phosphine solution was transferred to the flask containing the AgOTF via cannula resulting in the formation of a white precipitate. This heterogeneous mixture was stirred at room temperature for 5 min prior to its transfer to a flame-dried flask containing TBAI (22 mg, 0.06 mmol). After stirring for 5 additional minutes, this red–brown solution was ready for use.

1.3. Representative procedure for the asymmetric ring opening reaction with carboxylate nucleophiles

To a round bottom flask containing the rhodium iodide (*S*,*R*)-PPF-P^{t}Bu$_2$ complex (1 mol% to **1**) was added **1** (100 mg, 0.694 mmol). The red–brown solution was then heated to reflux followed by addition of ammonium acetate (267 mg, 3.47 mmol). The reaction was allowed to stir at reflux until **1** was consumed as determined by TLC analysis. Upon completion, the crude mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted three times with ethyl acetate. The organic layers were combined, dried over Na_2SO_4 and concentrated. The resulting solid was purified by flash chromatography.

1.3.1. (1*S*,2*S*)-Acetic acid 1-hydroxy-1,2-dihydronaphthalen-2-yl-ester (2). Following the general procedure, **2** was obtained as a crystalline solid (93% yield). The ee was determined to be 92% using HPLC analysis on a Chiralcel OD column, 10% isopropanol in hexanes, λ=254 nm. Retention times were 8.0 min and 11.3 min (major). $[\alpha]_D^{25}$=+1.2 (c=11.3, $CHCl_3$); R_f=0.26 on silica gel (20% ethyl acetate:hexanes); mp 67–68° (Et_2O); IR (KBr, cm^{-1}): 3620 (br), 3048 (w), 2977 (w), 1744 (s), 1454 (m), 1370 (s), 1235 (s), 1057 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.53 (1H, m), 7.29–7.24 (2H, m), 7.10–7.08 (1H, m), 6.50 (1H, dd, *J*=3.9, 1.3 Hz), 5.85 (1H, dd, *J*=9.9, 3.1 Hz), 5.59 (1H, ddd, *J*=9.0, 2.8, 1.9 Hz), 4.92 (1H, d, *J*=9.0 Hz), 2.64 (1H, s), 2.12 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 135.2, 131.5, 129.5, 128.3, 126.7, 126.0, 125.4, 75.3, 71.7, 21.2. HRMS calcd for $C_{12}H_{12}O_3$ (M^+): 204.0786. Found: 204.0791.

1.3.2. (1*S*,2*S*)-Propionic acid 1-hydroxy-1,2-dihydronaphthalen-2-yl-ester (3). Following the general procedure, **3** was obtained as a white crystalline solid (75%). The ee was determined to be 91% using HPLC analysis on a Chiralcel OD column, 10% isopropanol in hexanes, λ=254 nm. Retention times were 6.7 min and 11.0 min (major). $[\alpha]_D^{25}$=+124 (c=20.1, $CHCl_3$); R_f=0.24 on silica gel (20% ethyl acetate:hexanes); mp 55–56° (Et_2O); IR (KBr, cm^{-1}) 3491 (br), 3048 (w), 2984 (w), 1739 (s), 1454 (m), 1363 (w), 1182 (s), 1083 (m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.52 (1H, m), 7.29–7.24 (2H, m), 7.11–7.08 (1H, m), 6.50 (1H, dd, *J*=10.0, 2.0 Hz), 5.85 (1H, dd, *J*=12.8, 2.8 Hz), 5.61 (1H, ddd, *J*=9.2, 2.8, 2.0 Hz), 4.93 (1H, d, *J*=9.2 Hz), 2.40 (2H, qd, *J*=7.6, 1.2 Hz), 1.16 (3H, t, *J*=7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 135.3, 131.5, 129.4, 128.3, 128.3, 126.7, 125.9, 125.5, 75.2, 71.9, 27.7, 9.0. HRMS calcd $C_{13}H_{14}O_3$ (M^+): 218.0943. Found: 218.0938.

1.3.3. (1*S*,2*S*)-2-Methyl acrylic acid 1-hydroxy-1,2-dihydronaphthalen-2-yl-ester (4). Following the general procedure, **4** was obtained as a white crystalline solid (71%). The ee was determined to be 91% using HPLC analysis on a Chiralcel OD column, 10% isopropanol in hexanes, λ=254 nm. Retention times were 6.4 min and 9.6 min (major). $[\alpha]_D^{25}$=+141 (c=8.7, $CHCl_3$); R_f=0.32 on silica gel (20% ethyl acetate:hexanes); mp 80–82° (Et_2O); IR (KBr, cm^{-1}) 3450 (br), 3030 (w), 2928 (w), 1722 (s), 1637 (m), 1454 (m), 1289 (m), 1163 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.55 (1H, m), 7.29–7.24 (2H, m), 7.10–7.09 (1H, m), 6.51 (1H, dd, *J*=9.9, 1.9 Hz), 6.15 (1H, s), 5.87 (1H, dd, *J*=9.9, 3.0 Hz), 5.67 (1H, ddd, *J*=9.3, 2.1, 2.1 Hz), 5.61 (1H, s), 5.01 (1H, dd, *J*=9.0, 5.7 Hz), 2.74 (1H, d, *J*=6.1 Hz), 1.96 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 135.9, 135.3, 131.5, 129.4, 128.3, 128.2, 126.6, 126.4, 125.8, 125.5, 75.9, 71.9, 18.3. HRMS calcd $C_{14}H_{12}O_2$ (M^+–H_2O): 212.0837. Found: 212.0831.

1.3.4. (1*S,2*S**)-Formic acid 1-hydroxy-1,2-dihydronaphthalen-2-yl-ester (5).** Following the general procedure, **5** was obtained as a white crystalline solid (73%). R_f=0.25 on silica gel (30% ethyl acetate:hexanes); mp 133–135° (Et_2O); IR (KBr, cm^{-1}) 3146 (br), 2935 (w), 1720 (s), 1482 (w), 1186 (s), 1049 (m), 968 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (1H, d, *J*=0.8 Hz), 7.52–7.50 (1H, m), 7.29–7.27 (2H, m), 7.13–7.11 (1H, m), 6.54 (1H, dd, *J*=9.6, 1.6 Hz), 5.88 (1H, dd, *J*=9.6, 2.8 Hz), 5.71–5.68 (1H, m), 4.96 (1H, d, *J*=8.8 Hz), 2.8 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 134.8, 131.4, 130.0, 128.5, 126.9, 126.1, 124.6, 74.8, 71.4. HRMS calcd for $C_{11}H_{10}O_3$ (M^+): 190.0630. Found: 190.0625.

1.3.5. (1*S*,2*S*)-Benzoic acid 1-hydroxy-1,2-dihydronaphthalen-2-yl-ester (6). Following the general procedure, **6** was obtained as a white crystalline solid (91%). The ee was determined to be 92% using HPLC analysis on a Chiralcel OD column, 10% isopropanol in hexanes,

λ=254 nm. Retention times were 9.0 min and 11.1 min (major). R_f=0.3 on silica gel (10% ethyl acetate:hexanes); mp 107–109° (Et_2O); $[\alpha]_D^{25}$=+299 (c=11.3, $CHCl_3$); IR (KBr, cm^{-1}) 3619 (br), 3071 (w), 2977 (w), 1724 (s), 1451 (m), 1324 (m), 1265 (s), 1110 (s). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, J=7.6 Hz), 7.64–7.59 (2H, m), 7.48–7.45 (2H, m), 7.34–7.32 (2H, m), 7.13–7.11 (1H, m), 6.55 (1H, d, J=10.0 Hz), 5.97 (1H, dd, J=9.8, 2.9 Hz), 5.86 (1H, ddd, J=9.8, 2.0, 2.0 Hz), 5.11 (1H, d, J=9.0 Hz), 2.84 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 135.3, 133.3, 131.6, 129.9, 129.8, 129.7, 128.4, 128.4, 128.4, 126.8, 126.1, 125.5, 76.1, 71.9. HRMS calcd for $C_{17}H_{14}O_3$ (M^+): 266.0943. Found: 266.0938.

1.3.6. (1*S,2*S**)-Malonic acid ethyl ester (1-hydroxy-1,2-dihydronaphthalen-2-yl) ester (7).** Following the general procedure, **7** was obtained as a colourless oil (79%). R_f=0.29 on silica gel (30% ethyl acetate:hexanes); IR (KBr, cm^{-1}) 3470 (br), 2983 (w), 1731 (s), 1453 (w), 1370 (m), 1150 (s), 1031 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.56–7.54 (1H, m), 7.27–7.21 (2H, m), 7.08–7.06 (1H, m), 6.48 (1H, dd, J=9.9, 2.1 Hz), 5.83 (1H, dd, J=9.7, 2.8 Hz), 5.70 (1H, ddd, J=9.7, 2.5, 2.2 Hz), 4.97 (1H, d, J=9.5 Hz), 4.18 (2H, q, J=7.2 Hz), 3.43 (2H, dd, J=23.6, 15.9 Hz), 3.21 (1H, s), 1.25 (3H, t, J=7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.5, 135.0, 131.5, 129.6, 128.3, 128.1, 126.6, 125.6, 125.1, 77.0, 71.6, 61.9, 41.6, 14.0. HRMS calcd for $C_{15}H_{14}O_4$ (M^+–H_2O): 258.0892. Found: 258.0899.

1.3.7. (1*S*,2*S*)-Benzoic acid 1-(tert-butyl-dimethyl-silanyloxy)-1,2-dihydronaphthalen-2-yl ester (8). In a dried round bottom flask, **6** (266 mg, 1.0 mmol), imidazole (134 mg, 1.96 mmol), and dimethylaminopyridine (6 mg, 0.05 mmol) were dissolved in dichloromethane (4 mL). Tert-butyldimethylsilyl chloride (222 mg, 1.47 mmol) was then added portionwise and allowed to react for 24 h. The reaction was then quenched with water, extracted with dichloromethane, dried over Na_2SO_4 and concentrated *in vacuo*. Flash chromatography (10% ethyl acetate in hexanes) gave a colourless oil **8** (365 mg, 96%). R_f=0.48 on silica gel (10% ethyl acetate:hexanes). $[\alpha]_D^{25}$=+314 (c=19.9, $CHCl_3$); IR (KBr, cm^{-1}) 2983 (w), 1731 (s), 1453 (w), 1370 (m), 1150 (s), 1031 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (2H, d, J=7.8 Hz), 7.60–7.52 (1H, m), 7.50–7.40 (3H, m), 7.30–7.22 (2H, m), 7.14–7.06 (1H, m), 6.53 (1H, d, J=8.2 Hz), 5.96–5.86 (2H, m), 5.19 (1H, d, J=9.4 Hz), 0.88 (9H, s), 0.11 (3H, s), 0.05 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 136.5, 133.0, 132.3, 130.3, 129.8, 129.2, 127.9, 127.8, 126.5, 126.5, 126.0, 75.7, 72.1, 25.8, 18.1, −4.3, −4.4. HRMS calcd $C_{19}H_{19}O_3Si$ (M^+–C_4H_9): 323.1103. Found: 323.1100.

1.3.8. 2-[4-(tert-Butyl-dimethyl-silanyloxy)-1,4-dihydronaphthalen-1-yl]-2-methyl-malonic acid diethyl ester (9). To a flame-dried round bottomed flask was added $Pd_2(dba)_3$ (2.3 mg, 0.002 mmol) and triphenylphosphine (2.6 mg, 0.01 mmol) followed by the addition of THF (2 mL). The solution was stirred at room temperature for 5 min then **8** (50 mg, 0.13 mmol) was added. In a separate flask, methyl diethylmalonate (35 mg, 0.2 mmol) was dissolved in THF (1 mL) followed by the addition of NaH (5 mg, 0.2 mmol) and stirring for 5 min. This sodium methyl diethyl malonate solution was then transferred to the first flask via cannula. The combined solution was heated at reflux for 2 h then poured into water and extracted with ethyl acetate. The combined extracts were dried over Na_2SO_4 and concentrated. The resulting crude oil was purified by flash chromatography (5% ethyl acetate in hexanes) to give a colourless oil **9** (51 mg, 91%). R_f=0.27 on silica gel (5% ethyl acetate:hexanes); IR (KBr, cm^{-1}) 3036 (w), 2956 (s), 1735 (s), 1472 (m), 1257 (s), 1077 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, J=8.1 Hz), 7.32–7.24 (1H, m), 7.20–7.12 (2H, m), 6.19–6.10 (2H, m), 5.18–5.13 (1H, m), 4.50–4.45 (1H, m), 4.28–4.10 (4H, m), 1.30–1.24 (6H, m), 1.10 (3H, s), 0.98 (9H, s), 0.22 (3H, s), 0.16 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 140.9, 135.9, 127.8, 127.0, 126.7, 126.3, 125.8, 77.2, 65.7, 61.5, 60.9, 44.5, 25.9, 18.2, 15.1, 14.0, 13.9, –4.2, −4.6. HRMS calcd $C_{20}H_{27}O_5Si$ (M^+–C_4H_9): 375.1628. Found: 375.1626.

1.3.9. (1*S,2*S**)-Malonic acid (1-tert-butyldimethyl-siloxy-1,2-dihydronaphthalen-2-yl) ester ethyl ester (10).** To a dried round bottom flask, **7** (270 mg, 0.98 mmol), imidazole (134 mg, 1.96 mmol), and dimethyl-aminopyridine (6 mg, 0.05 mmol) were dissolved in dichloromethane (4 mL). Tert-butyldimethylsilyl chloride (222 mg, 1.47 mmol) was then added portionwise and allowed to react for 24 h. The reaction was then quenched with water, extracted with dichloromethane, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (10% ethyl acetate in hexanes) gave a colourless oil **10** (343 mg, 90%). R_f=0.34 on silica gel (10% ethyl acetate: hexanes). IR (KBr, cm^{-1}) 2983 (w), 1731 (s), 1453 (w), 1370 (m), 1150 (s), 1031 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.39 (1H, m), 7.24–7.22 (2H, m), 7.07–7.05 (1H, m), 6.47 (1H, dd, J=9.9, 1.8 Hz), 5.83 (1H, dd, J=9.7, 2.7 Hz), 5.60 (1H, ddd, J=9.3, 2.9, 2.0 Hz), 5.00 (1H, dd, J=9.3, 0.5 Hz), 4.22–4.15 (2H, m), 3.40 (2H, dd, J=19.6, 16.0 Hz), 1.57 (1H, s), 1.25 (3H, t, J=7.1 Hz), 0.92 (9H, s), 0.13 (3H, s), 0.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 166.2, 136.2, 132.1, 129.4, 128.0, 127.9, 126.5, 125.9, 125.7, 76.4, 71.6, 61.6, 41.7, 25.8, 18.1, 14.0, −4.3, −4.5. HRMS calcd for $C_{17}H_{21}O_5Si$ (M^+–C_4H_9): 333.1158. Found: 333.1149.

1.3.10. [4-(tert-Butyl-dimethyl-silanyloxy)-1,4-dihydronaphthalen-1-yl]-acetic acid ethyl ester (12). To a dried round bottom flask, **10** (100 mg, 0.256 mmol) was dissolved in THF (4 mL). Potassium hydride (11.3 mg, 0.28 mmol) was then added portionwise and allowed to react for five minutes at room temperature. Triphenylphosphine (34.1 mg, 0.13 mmol) was then added followed by $Pd(PPh_3)_4$ (14.8 mg, 0.013 mmol). The reaction was then heated to reflux for 2 h. The solvent was then removed in vacuo and the resulting oil purified by flash chromatography (5% ethyl acetate in hexanes) giving **12**, a colourless oil (54 mg, 61%). R_f=0.27 on silica gel (5% ethyl acetate:hexanes); IR (KBr, cm^{-1}) 3036 (w), 2956 (s), 1735 (s), 1472 (m), 1257 (s), 1077 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (1H, m), 7.30–7.23 (3H, m), 6.09 (1H, ddd, J=2.4, 4.6, 10.2 Hz), 6.02 (1H, ddd, J=10.2, 2.0, 0.5 Hz), 5.22–5.21 (1H, m), 4.15 (2H, q, J=7.2 Hz), 3.92–3.87 (1H, m), 2.62 (1H, dd, J=15.7, 5.7 Hz), 2.39 (1H, dd, J=15.2, 9.0 Hz), 1.25 (3H, t,

J=7.2 Hz), 0.98 (9H, s), 0.21 (3H, s), 0.15 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 138.3, 136.1, 131.8, 128.2, 127.2, 127.0, 126.9, 126.6, 65.3, 60.5, 42.7, 36.5, 25.9, 18.2, 14.2, −4.2, −4.5. HRMS calcd $C_{17}H_{21}O_5Si$ (M^+–C_4H_9): 289.1260. Found: 289.1257.

Acknowledgements

We would like to thank AstraZeneca (Montreal), NSERC, the ORDCF and the University of Toronto for valuable support of this research program. We thank Solvias AG for generously supplying us with the PPF-P^{t}Bu$_2$ ligand used in these studies. K. F. would like to thank AstraZeneca and NSERC for an industrial postgraduate scholarship (IPS) and an NSERC PGS.

References

1. For a review on allylic alkylation, see: Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395 and pertinent references therein. For a review on allylic amination, see: Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689 and pertinent references therein. For a general review of palladium chemistry, see: Tsuji, J. *Palladium Reagents and Catalysis*; John Wiley and Sons: Toronto, 1995.
2. For references regarding the regioselectivity, see: Mo: (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1987**, *109*, 1469. (b) Dvorak, D.; Stary, I.; Kocovsky, P. *J. Am. Chem. Soc.* **1996**, *118*, 897 W. (c) Trost, B. M.; Tometzki, G. B.; Hung, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 2176. Ir: (d) Takeuchi, R.; Kashio, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 263. Rh: (e) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. Ru: (f) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.-A.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945. Fe: (g) Xu, Y.; Zhou, B. *J. Org. Chem.* **1987**, *52*, 974.
3. For references pertaining to enantioselective variants, see: Mo: (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104. (b) Trost, B. M.; Hidebrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416. W: (c) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 462. Ir: (d) Janssen, J. P.; Helchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025.
4. We have found that rhodium can be used to effect the asymmetric ring opening of oxabicyclic alkenes with alcohols, phenols and amines, see: (a) Lautens, M.; Fagnou, K.; Rovis, T. *J. Am. Chem. Soc.* **2000**, *122*, 5650. (b) Lautens, M.; Fagnou, K.; Taylor, M. *Org. Lett.* **2000**, *2*, 1677. For a full account of the development of these transformations, see: (c) Lautens, M.; Fagnou, K. *J. Organomet. Chem.* in press. Rhodium will also catalyse the diastereoselective ring opening of vinyl epoxides, see: (d) Fagnou, K.; Lautens, M. *Org. Lett.* **2000**, *2*, 2319.
5. For the first reports of a rhodium-catalysed allylic transformation, see: (a) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1984**, *25*, 5157. (b) Minami, I.; Shimizu, I.; Tsuji, J. *J. Organomet. Chem.* **1985**, *296*, 269. See also: (c) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581. (d) Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761. (e) Evans, P. A.; Leahy, D. *J. Am. Chem. Soc.* **2000**, *122*, 5012.
6. Takeuchi, R.; Kitamura, N. *New J. Chem.* **1998**, 659.
7. For example, when a competition experiment was run with isopropanol and hexafluoroisopropanol (HFIP), only HFIP was incorporated in the product. Analogously, reaction in the presence of both 4-methoxyphenol and 4-hydroxyacetophenone resulted in a 16:1 product mixture with addition of 4-hydroxyacetophenone constituting the major product. See Refs. 4b and 4c.
8. Lautens, M.; Fagnou, K. Submitted for publication.
9. Since the pKa of acetic acid is lower than that of the conjugate acid of aliphatic amines, sodium acetate will remain deprotonated even when 1 equivalent Et_3N·HCl is added.
10. The relative stereochemistry for the acetate adduct was proven by deprotection of the acetate moiety, and dimethylation with iodomethane. This dimethoxy-1,2-dihydronaphthalene was identical to authentic *trans*-dimethoxy-1,2-dihydronaphthalene prepared via an alternative method.
11. A full account of this work will be reported elsewhere in due course.
12. The directing effect of an oxygen functionality adjacent to the π-allyl palladium moiety has been found in other systems. See: (a) Genet, J. P.; Piau, F.; Ficini, J. *Tetrahedron Lett.* **1980**, *21*, 3183. (b) Genet, J. P.; Balabane, M.; Charbonnier, F. *Tetrahedron Lett.* **1982**, *23*, 5027. (c) Akermark, B.; Ljungqvist, A.; Panunzio, M. *Tetrahedron Lett.* **1981**, *22*, 1055. (d) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc.* **1981**, *103*, 5969. (e) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett.* **1981**, *22*, 2575.
13. The hydronaphthalene core can be found in a variety of natural and synthetic compounds possessing a wide range of biological activities. See: (a) Johnson, B. M.; Chang, P.-T. L. *Analytical Profiles of Drug Substances and Excipients* **1996**, *24*, 443. (b) Freeman, J. P.; Michalson, E. T.; D'Andrea, S. V.; Baczynskyj, L.; VonVoigtlander, P. F.; Lahti, R. A.; Smith, M. W.; Lawson, C. F.; Scahill, T. A.; Mizsak, S. A.; Szmuszkovicz, J. *J. Med. Chem.* **1991**, *34*, 1891. (c) Jones, J. H.; Anderson, P. S.; Baldwin, J. J.; Clineschmidt, B. V.; McClure, D. E.; Lundell, G. F.; Randall, W. C.; Martin, G. E.; Williams, M.; Hirshfield, J. M.; Smith, G.; Lumma, P. K. *J. Med. Chem.* **1984**, *27*, 1607. (d) Snyder, S. E. *J. Med. Chem.* **1995**, *38*, 2395. (e) Kamal, A.; Gayatri, L. *Tetrahedron Lett.* **1996**, *37*, 3359. (f) Welch, W. M.; Kraska, A. R.; Sarges, R.; Keo, B. K. *J. Med. Chem.* **1984**, *27*, 1508. (g) Wyrick, S. D.; Booth, R. G.; Myers, A. M.; Owens, C. E.; Kula, N. S.; Baldessarini, R. J.; McPhail, A. T.; Mailman, R. B. *J. Med. Chem.* **1993**, *36*, 2542. (h) Johansson, A. M.; Arvidsson, L.-E.; Hacksell, U.; Nilsson, J. L. G.; Svensson, K.; Carlsson, A. *J. Med. Chem.* **1987**, *30*, 602. (i) Snyder, S. E.; Aviles-Garay, F. A.; Chakraborti, R.; Nichols, D. E.; Watts, V. J.; Mailman, R. B. *J. Med. Chem.* **1995**, *38*, 2395. (j) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiatti, V.; Chiglieri, A.; Giovoni, S. *J. Med. Chem.* **1995**, *38*, 942. (k) New, S. J.; Yevich, J. P.; Eison, M. S.; Taylor, D. P.; Eison, A. S.; Riblet, L. A.; VanderMaelen, C. P.; Temple, Jr., D. L. *J. Med. Chem.* **1986**, *29*, 1476. (l) Hallinan, K. O.; Honda, T. *Tetrahedron* **1995**, *51*, 12211. (m) Saito, A.; Kayama, Y.; Watanabe, T.; Fukushima, H.; Hara, T. *J. Med. Chem.* **1980**, *23*, 1364. (n) Sobti, A.; Kim, K.; Sulikowski, J. A. *J. Org. Chem.* **1996**, *61*, 6. (o) Davis, F. A.; Clark, C.; Kumar, A.; Chem, B.-C. *J. Org. Chem.* **1994**, *59*, 1184. (p) Kaneko, T.; Wong, H. *Tetrahdron Lett.* **1987**, *28*, 517. (q) Kamal, A.; Gayatri, N. L. *Tetrahedron Lett.* **1996**, *37*, 3359.
14. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1989**, *54*, 5667.
15. Stiles, M.; Miller, R. G. *Can. J. Chem.* **1965**, *43*, 1599.