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Asymmetric Heck Reaction. A Catalytic Asymmetric Synthesis of the Key Intermediate for Vernolepin

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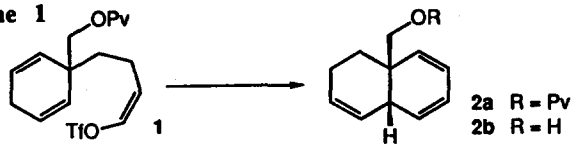
Abstract: *Enone **5a**, a functionalized decalin derivative, has been synthesized in up to 86% ee by an asymmetric Heck reaction starting with the allylic alcohol **3**. Enone **5a** was converted to a key intermediate for vernolepin.*

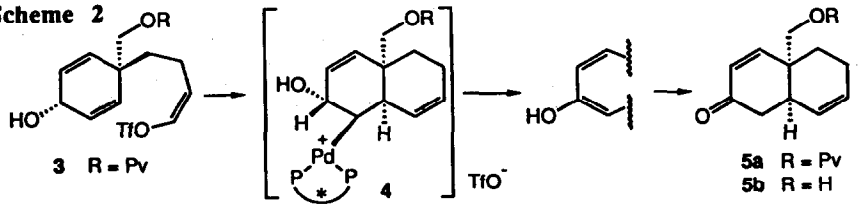
We have already demonstrated that the asymmetric Heck reaction is a powerful method for the synthesis of various optically active carbon skeletons including derivatives of decalin, hydrindan, and bicyclo[3.3.0]octane.[1,2] For example in the decalin system, we have observed high asymmetric induction (up to 91% ee) in the cyclization of **1** to **2a**.[1d] This triene **2a** has been functionalized, albeit with low efficiency, and because of our desire to develop highly functionalized chiral building blocks, we have examined bisallylic alcohols as substrates for the asymmetric Heck reaction. Here we would like to report a catalytic asymmetric synthesis of enone **5a** (86% ee), a decalin derivative similar to the Wieland-Miescher ketone,[3] and conversion of **5a** to a key intermediate **12** in the synthesis of vernolepin, an elemanolide sesquiterpene dilactone which has antitumor activity.[4]

Scheme 1



Our strategy is outlined in Scheme 2. Treatment of α-allylic alcohol **3** with a chiral palladium catalyst was expected to give intermediate **4** via oxidative addition of the vinyl triflate to palladium and enantioselective insertion of the alkenylpalladium to one of the allylic alcohol moieties. *Syn*-β-hydride elimination was then anticipated to generate enone **5a**, a compound which was expected to be amenable to further functionalization.

Scheme 2



Allylic alcohol **3** was readily prepared by allylic oxidation of **1** and stereoselective reduction of the resulting ketone.[5] Because aromatic solvents such as benzene and toluene have generally provided the best results in the asymmetric Heck reaction of triflates,[1d, 2c] initial reactions were run in benzene with $Pd(OAc)_2$ (4 mol %), K_2CO_3 (2 mol equiv) and a variety of chiral ligands (9 mol %).[6] The best conditions employed (*R*)-BINAP[7] and afforded the desired enone (+)-**5a** in 51% yield. Unfortunately, however, the enantiomeric excess of **5a** was only 28%, as determined by HPLC analysis (DAICEL CHIRALPAK AS, hexane-2-propanol, 4:1) of alcohol **5b**, obtained on treatment of **5a** with K_2CO_3 in MeOH at 60 °C (80%). Assignment of the absolute configuration was achieved by converting **5a** to known triene **2b**.[8, 1a]

Table 1. Catalytic Asymmetric Cyclization of Prochiral Triflate **3** Promoted by $Pd(OAc)_2$-(*R*)-BINAP Catalyst.[a]

entry	solvent	time (h)	yield of 5a (%)	ee (%)
1	DMSO	12	-[b]	-
2	CH_3CN	24	38	16
3	DMF	72	-[b]	-
4	THF	60	63	47
5	DME	78	49	24
6	dioxane	78	53	21
7	benzene	60	51	28
8[c]	toluene	70	49	28
9	mesitylene	70	36	46
10	$CHCl_3$	90	-[b]	-
11	$ClCH_2CH_2Cl$	144	37	76

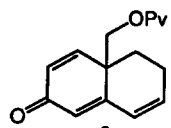
a) All reacions were carried out with $Pd(OAc)_2$ (4 mol %), (*R*)-BINAP (9 mol %), and K_2CO_3 (2 mol equiv)in the solvent shown at 60 °C under an argon atomosphere.
b) Complex mixture. c) $Pd(OAc)_2$ (5 mol %) and (*R*)-BINAP (15 mol %) were used.

Solvent effects were then examined (Table 1). In contrast to the results obtained with substrates such as **1**,[1d] cyclization of **3** was found to occur with the highest asymmetric induction (76% ee) in dichloroethane; however, the chemical yield of **5a** was not satisfactory. In order to improve this yield and the ee of **5a**, further investigations were carried out. The best conditions found employed $Pd_2(dba)_3$•$CHCl_3$ (9 mol% of Pd), (*R*)-BINAP (11.3 mol%) and ^{t}BuOH (11 equiv) as an additive (Table 2). With this catalyst and additive, cyclization of **3** proceeded cleanly in dichloroethane at 60 °C to yield **5a** in 86% ee and a chemical yield of

Table 2. Catalytic Asymmetric Cyclization of Prochiral Triflate **3** Promoted by $Pd_2(dba)_3$-(*R*)-BINAP Catalyst.[a]

entry	solvent	additive (11 equiv)	Pd/BINAP (mol %)	time (h)	yield of 5a (%)	ee (%)
1	$ClCH_2CH_2Cl$	-	9/9	24	72	73
2	$ClCH_2CH_2Cl$	-	9/11.3	76	58[b]	85
3	$ClCH_2CH_2Cl$	*t*-BuOH	9/9	18	83	78
4	$ClCH_2CH_2Cl$	*t*-BuOH	9/11.3	42	76	86
5	benzene	-	9/11.3	83	36[c]	42
6	*t*-BuOH	-	9/9	109	62	56

a) All reactions were carried out in the solvent shown at 60 °C under an argon atomosphere in the presence of K_2CO_3 (2 mol equiv). b) **6** was formed in 17% yield. c) **7** was formed in 15% yield.



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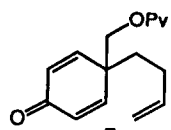
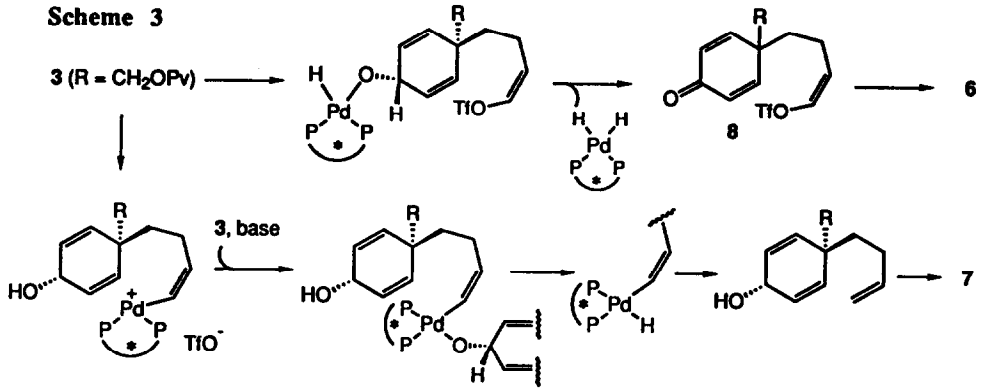


7

76%.[9]

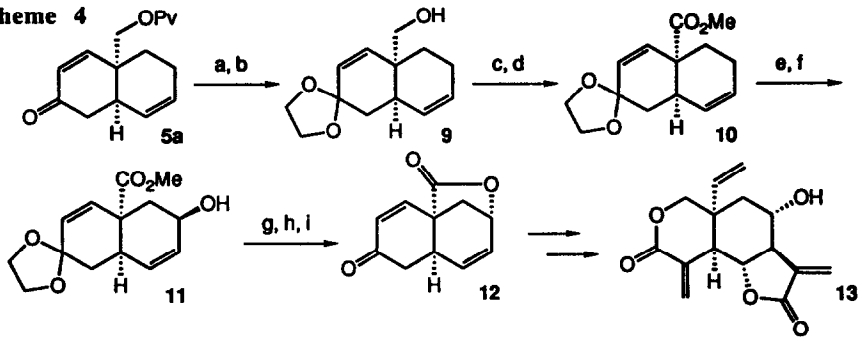
As can be seen addition of ^{t}BuOH improved the chemical yield of **5a**, and suppressed formation of ketone **6** and/or **7**. Formation of these by-products suggests that the bisallylic alcohol in **3** is oxidized either by oxidative addition of the O-H bond to Pd(0) or by nucleophilic attack of the alkoxide to Pd^+ followed by β-hydride elimination (Scheme 3).[10, 11] It is likely that ^{t}BuOH, an alcohol no β-hydrogens, prevents interaction of the substrate hydroxyl group with palladium, thereby suppressing oxidation.

Scheme 3



Having completed the asymmetric synthesis of enone **5a**, we have gone on to demonstrate the usefulness of this enone as a chiral building block. As shown in Scheme 4, (+)-**5a**: $[\alpha]_D^{24}$ +106 ° (c 1.00, $CHCl_3$) (86% ee) was converted in 9 steps to a key intermediate (-)-**12**: $[\alpha]_D^{24}$ -172 ° (c 0.47, $CHCl_3$) for Danishefsky's synthesis of vernolepin **13**.[12a] In spite of a variety of synthetic approaches and total syntheses of (±)-**13**, no asymmetric synthesis of (+)-**13** has been reported.[12] Thus, our asymmetric synthesis of **12** provides the first formal synthetic route to (+)-**13**.

Scheme 4



(a) ethylene glycol, TsOH, benzene, reflux, 3 h, 91%; (b) $LiAlH_4$, Et_2O, 0 °C, 0.5 h, 100%; (c) PDC, MS4A, CH_2Cl_2, 1.5 h, 80%; (d) i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (2 : 1), 1 h; ii) CH_2N_2, Et_2O, 79% (2 steps); (e) CrO_3, DMP, CH_2Cl_2, 0 °C, 9 h, 54% (SM Recovery 21%); (f) $NaBH_4$, $CeCl_3$, MeOH-THF (2 :1), -78 °C, 92%; (g) AcOH, PPh_3, DEAD, THF, 0 °C, 1h; (h) LiOH, MeOH-H_2O (3 : 1), 0.5h; 10% HCl; (i) Ac_2O, NaOAc, 34% (3 steps).

In conclusion, we have achieved a catalytic asymmetric synthesis of enone **5a** and **12**, the latter being an intermediate in the synthesis of vernolepin. It is our belief that enone **5a** will be a versatile chiral building block for the syntheses of a variety of natural products having the decalin skeleton.

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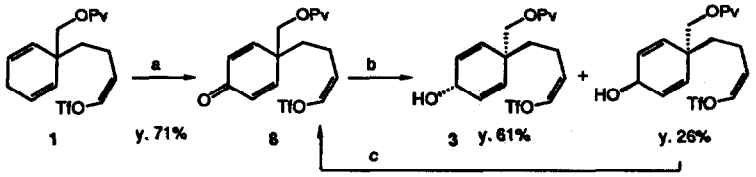
5 Alcohol **3** was prepared as shown. The β-alcohol was recycled by the oxidation to **8**.



(a) CrO_3, DMP, CH_2Cl_2, -20 °C, 1 h; (b) $NaBH_4$, $CeCl_3$, MeOH, -78 °C, 1 h; (c) PDC, MS4A, CH_2Cl_2, 0.5 h, 95%.

6 *(R, R)*-CHIRAPHOS and *(S, R)*-BPPFA gave a complex mixture of products. *(S, S)*-BPPM and *(R)*-DIOP afforded **5a** in 51% (1% ee) and 57% (8% ee) yields, respectively.

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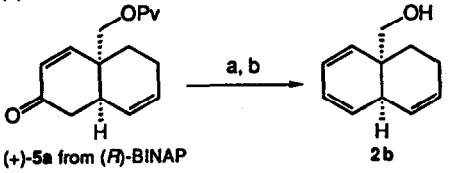
8 Transformation of (+)-**5a** to **2b** was effected as follows.



(+)-**5a** from *(R)*-BINAP **2b**

(a) i) Tf_2O, 2,6-di-*t*-Bu-Py, 1,2-dichloroethane, 60 °C, 20 min; ii) $Pd(OAc)_2$, PPh_3, HCO_2H, *i*-Pr_2NEt, DMF, 60 °C, 10 min, 53% (2 steps); (b) $LiAlH_4$, THF, 0 °C, 20 min, 63%

9 The representative experimental procedure is as follows : To a mixture of $Pd_2(dba)_3$•$CHCl_3$ (6.0 mg, 0.0058mmol), *(R)*-BINAP (9.0 mg, 0.0145 mmol) and K_2CO_3 (35.7 mg, 0.258 mmol) in 1, 2-dichloroethane (0.4 ml) was added a solution of **3** (53.3 mg, 0.129 mmol) in 1, 2-dichloroethane (1.3 ml). After degassing, *t*-BuOH (0.13 ml, 1.42 mmol) was added to the mixture. The reaction mixture was stirred at 60 °C under an argon atomosphere until the reaction was completed (42 h), diluted with ether, washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column (ether-hexane, 1:4) to give **5a** (25.6 mg, 76%) as a pale yellow oil.
Spectral data of **3** : IR (nujol) 3250, 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (s, 9 H), 1.4-1.6 (m, 3 H), 1.9-2.1 (m, 2 H), 3.92 (s, 2 H), 4.4-4.5 (m, 1 H), 5.21 (dt, *J* = 7.6, 5.6 Hz, 1 H), 5.63 (dd, *J* = 10.2, 1.7 Hz, 2 H), 6.06 (dd, *J* = 10.2, 3.3 Hz, 2 H), 6.49 (brd, *J* = 5.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.2, 27.1, 35.0, 38.9, 41.6, 62.3, 69.7, 118.5 (q, *J* = 321 Hz), 120.3, 130.4, 131.0, 135.4, 178.1; MS *m/z* 412 (M^+), 280, 91 (bp); Anal. Calcd. for $C_{17}H_{23}F_3O_6S$: C, 49.51; H, 5.62. Found : C, 49.53; H, 5.65. **5a** : IR (neat) 1731, 1687 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.13 (s, 9 H), 1.6-1.8 (m, 2 H), 2.0-2.1 (m, 2 H), 2.22 (dd, *J* = 15.8, 7.9 Hz, 1 H), 2.5-2.6 (m, 1 H), 2.65 (dd, *J* = 15.8, 5.3 Hz, 1 H), 3.90 (d, *J* = 10.9 Hz, 1 H), 4.14 (d, *J* = 10.9 Hz, 1 H), 5.4-5.5 (m, 1 H), 5.6-5.7 (m, 1 H), 5.95 (d, *J* = 10.2 Hz, 1 H), 6.56 (d, *J* = 10.2 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 22.1, 26.8, 27.1, 35.8, 38.9, 40.8, 67.6, 126.8, 128.5, 129.7, 152.6, 178.1, 198.5; MS *m/z* 262 (M^+), 161 (M^+-OPv), 57 (bp); Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.47, Found : C, 73.01; H, 8.53.

10 Cyclization of **8** proceeded rapidly under the same reaction conditions (29 h) shown in entry 2 (Table 2) to give **6** in 84% yield.

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