Remote Substituent Effects on the Enantiomeric Excess of Intramolecular Asymmetric Palladium-Catalyzed Polyene Cyclizations

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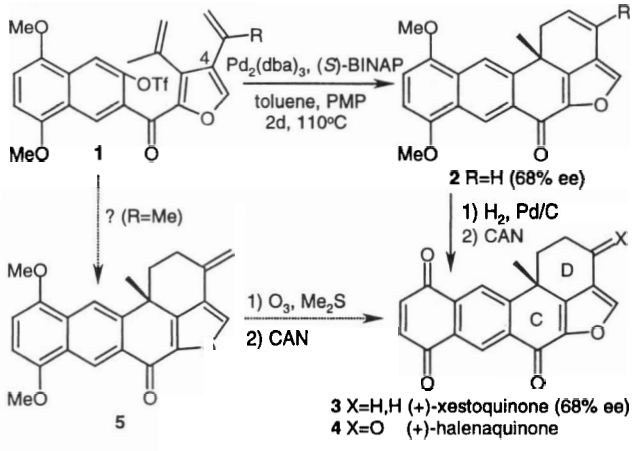
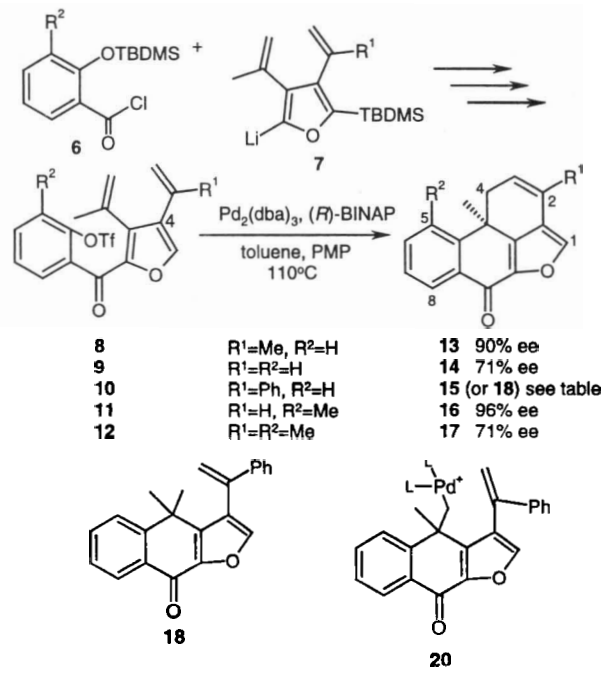
Abstract: Remote substituents show a profound influence on the enantiomeric excess of intramolecular palladium-catalyzed polyene cyclizations. An ee of 96% is obtainable by judicious placement of a methyl group.

Key words: asymmetric palladium-catalyzed polyene cyclizations, asymmetric Heck reactions, remote substituent effects

In 1996 we reported the first asymmetric synthesis of (+)-xestoquinone (**3**, 68% ee). The key step was an intramolecular asymmetric palladium catalyzed polyene cyclization of **1** (R = H) to give **2** (68% ee; R = H) in which the C and D rings and the stereogenic centre were formed in one step (Scheme 1).[1] Hydrogenation of **2** followed by a CAN oxidation gave (+)-xestoquinone (**3**). An alternative strategy was devised for the synthesis of (+)-halenaquinone (**4**). It was thought that conversion of the vinyl group of C-4 of the furan ring into a 2-propenyl group might cyclize under similar reaction conditions to give **5** with an exocyclic double bond. Subsequent oxidative cleavage of the double bond and CAN oxidation should afford (+)-halenaquinone (**4**). Treatment of model compound **8** with $Pd_2(dba)_3$ and *(R)*-BINAP (toluene, PMP, 2d, 110 °C) did not provide the expected compound with an exocyclic double bond, but gave **13** exclusively in 83% yield (Scheme 2). Surprisingly, the ee was 90%![2,3] This was in contrast to the results obtained with model furan **9**, which gave **14** with a modest ee of 71%. We therefore investigated the reaction further to attempt to understand how a group, which is on a double bond that becomes part of the second ring (at C-4 of the furan ring), influences the ee of the formation of the first ring in the polyene cyclization sequence. In addition, we also wanted to find a method for increasing the ee for the transformation of **9** into **14**. While there have been reports on how substituents on the alkene[4,5] and ligands[6] influence the stereoselectivity, ee and sense of chirality[7] in a Heck reaction, to our knowledge, the effect of remote substituents on the ee in polyene cyclizations has not been reported to date.[8]



Scheme 1



Scheme 2

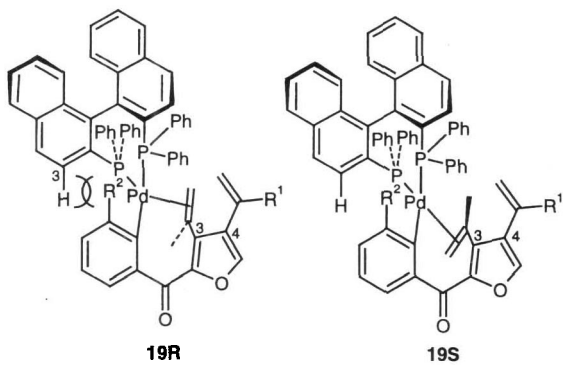
The starting triflates **8-12** were prepared in an analogous manner to **1** (R = H)[1a] by reacting a suitably substituted C-5 lithiated furan ring **7**[1a,9] with a substituted benzoyl chloride **6**. Functional group interconversion provided triflates **8-12** (Scheme 2). Table 1 summarizes the results from the polyene cyclizations performed on furans **8-12** under a variety of reaction conditions.[10] First, compound **9** was treated with a variety of commercially available chiral ligands (toluene, 110 °C, PMP); however, in all the cases tried the%ee ranged from 1-11%.[11] Only *(R)*-BINAP provided **14** with a reasonable ee of 71% (entry 1). Overman has reported[4] that in some intramolecular Heck cyclizations with triflates that a beneficial halide effect was observed

when Bu_4NBr was mixed with the triflate. Adding Bu_4NBr to triflate **9** in either toluene or *N,N*-dimethylacetamide resulted in a dramatic decrease in the ee (entries 2-4). Changing the base to K_2CO_3 did not noticeably change the ee with compound **9** (compare entries 1 and 5).

As mentioned above, when **8** was treated with *(R)*-BINAP compound **13** was formed with an ee of 90%. The only difference between **8** and **9** was the placement of a methyl group on the double bond at C-4 of the furan ring (entry 6). Using a less bulky catalyst like *(R,R)*-CHIRAPHOS with **8** resulted in a decrease in the ee of **13** to 24% (entry 7). In an attempt to try to understand why the ee increased in **13** relative to **14**, a series of PM3(tm) semi-empirical calculations[12] were done on the unsaturated palladium complexes **19R** and **19S** (Scheme 3). The energy difference between the C-3 rotamers **19R** and **19S** increased when $R^1 = H$ ($R^2 = H$) was changed to $R^1 = Me$ ($R^2 = H$) when *(R)*-BINAP was modeled. The calculations also indicated that a greater energy difference would be expected if $R^1 = Ph$ ($R^2 = H$). Thus if **10** was prepared, the ee of the cyclization might be higher than 90%.

Compound **10** was synthesized and subjected to a variety of polyene cyclizations. The cyclization proceeded smoothly with PPh_3 (entry 8) but problems occurred when *(R)*-BINAP was employed (entry 9). A 13:1 ratio of **18**:**15** (91%) was obtained and **15** could not be isolated in a pure form to measure the ee. The formation of **18** was unexpected and was always obtained as the major product when the reaction was repeated. Interestingly, changing the ligand to the smaller *(R,R)*-CHIRAPHOS resulted in the exclusive formation of **15** with an ee of 77% (entry 10). It was thought that the formation of **18** might be due to a hydride transfer from the PMP to an intermediate σ-palladium complex **20** (Scheme 2). Changing the base to K_2CO_3 with *(R)*-BINAP resulted in only the detection of starting material **10** and detriflated starting material (entry 11). Thus, the lack of formation of **15** when BINAP is used must be due to an unfavorable steric interaction within intermediate **20** that prohibits the palladium from coordinating to the second double bond (Scheme 2). Thus a hydride transfer occurs to provide **18** when PMP is used and the reaction stalls when K_2CO_3 is used and mainly SM and detriflated SM is recovered. Using a smaller chiral ligand presumably allows the intermediate **20** to coordinate to the second double bond and **15** is formed in moderate ee.

The PM3(tm) semi-empirical calculations[12] also indicated that as the size of the R^1 group increased, the hydrogen atom *ortho* to the palladium atom moved closer to the C-3 hydrogen on *(R)*-BINAP in **19R**, while in **19S** a similar steric interaction was not observed (Scheme 3). This steric interaction appeared to be responsible for the increase in the energy difference between **19R** and **19S** as the size of R^1 was increased. If the steric interaction between these two hydrogen atoms is truly giving rise to energy difference, then placement of a bulky group (i.e. methyl) *ortho* to the triflate should increase the ee further. Treatment of triflate **11** with $Pd_2(dba)_3$ and *(R)*-BINAP (toluene, PMP, 110 °C) resulted in **16** with an ee of 96% (entry 12). Finally, placement of a methyl group *ortho* to the triflate and on the furan C-4 double bond (i.e. **12**) resulted in a drop of the ee to 71% (entry 13). Presumably, the steric interactions of the two larger groups is counter-productive and the ee drops.



Scheme 3

Table 1: Polyene Cyclization Results with Compounds 8-12[a]

Entry	Compound	Additive	Ligand	Time (days)	Product (% ee)	% Yield	abs. stereochem.
1	**9**	PMP	(*R*)-BINAP	2	**14** (71)	83	*R*
2	**9**	PMP/Bu_4NBr	(*R*)-BINAP	2	**14** (16)	63	*R*
3[b]	**9**	PMP	(*R*)-BINAP	2	**14** (60)	60	*R*
4[b]	**9**	PMP/Bu_4NBr	(*R*)-BINAP	2	**14** (7)	54	*R*
5	**9**	K_2CO_3	(*R*)-BINAP	3	**14** (69)	74	*R*
6	**8**	PMP	(*R*)-BINAP	2	**13** (90)	78	*R*
7	**8**	PMP	(*R,R*)-CHIRAPHOS	3	**13** (24)	61	*S*
8	**10**	PMP	PPh_3	4	**15** (--)	57	-
9	**10**	PMP	(*R*)-BINAP	3	**18**:**15** (--)[c]	91	-
10	**10**	PMP	(*R,R*)-CHIRAPHOS	4	**15** (77)	66	*S*
11	**10**	K_2CO_3	(*R*)-BINAP	4	SM[d]	--	-
12	**11**	PMP	(*R*)-BINAP	3	**16** (96)	71	*R*
13	**12**	PMP	(*R*)-BINAP	3	**17** (71)	68	*R*

a) unless otherwise noted all reactions were done in toluene at 110°C. b) reaction performed in *N,N*-dimethylacetamide at 60°C. c) a 13:1 ratio of **18**:**15** was obtained by ^{1}H-NMR. d) only starting material and de-triflated starting material were detected by ^{1}H-NMR.

We have shown that either a remote substituent on the furan C-4 double bond or a group *ortho* to the triflate in systems like **9** result in a significant increase in the ee of a palladium-catalyzed polyene cyclization. Work is continuing to fine-tune our system for even higher ee's and for application towards the synthesis of xestoquinone (**3**), halenaquinone (**4**) and the viridin family of natural products.[13]

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(2) This work was first presented at the 80th Canadian Society for Chemistry Conference, Windsor, ON, Canada, in June 1997 and at the 16th International Congress of Heterocyclic Chemistry, Bozeman, MT, USA, in August 1997.

(3) The enantiomeric excesses were unequivocally determined by HPLC analysis using a DAICEL CHIRALCEL OJ column using *n*-hexane:ethanol (85:15) as the solvent system.

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(10) A typical experimental procedure is as follows: The catalyst solution was prepared by dissolving $Pd_2(dba)_3$ (5 mg, 0.011 mmol) and *(R)*-BINAP (14 mg, 0.022 mmol) in 1 mL of dry toluene and allowed to mix for 30 minutes under nitrogen. The triflate **9** (13 mg, 0.0337 mmol) was dissolved in 1 mL dry toluene and PMP (30 µL, 0.17 mmol) was added. The catalyst solution (153 µL, 5 mol% Pd) was added to the triflate/PMP solution, fitted with a reflux condenser and placed in a preheated oil bath at 110°C and stirred for 2 days under nitrogen. The solution was pre-filtered over silica gel and purified by preparative thin layer chromatography (3:1 hexanes:ethyl acetate) to afford the cyclized product **14** in 88% yield (7 mg, 0.0297 mmol). IR 1671 (C = O), 1600 (C = C) cm-1; ^{1}H NMR(200 MHz) (1.48 (s, 3H, CH_3), 2.53 (m, 1H, H-4a), 2.95 (ddd, 1H, $J_{4b,4a}$ = 16.6 Hz, $J_{4b,3}$ = 6.2 Hz, $J_{4b,2}$ = 0.7 Hz, H-4b), 6.07 (ddd, 1H, $J_{3,4a}$ = 2.4 Hz, $J_{3,4b}$ = 6.2 Hz, $J_{3,2}$ = 9.7 Hz, H-3), 6.62 (ddd, 1H, $J_{2,3}$ = 9.7 Hz, $J_{2,4b}$ = 0.7 Hz, $J_{2,4a}$ = 3.2 Hz, H-2), 7.40-7.65 (m, 3H, H-5, H-6, H-7), 7.56 (s, 1H, H-1), 8.37 (ddd, 1H, $J_{8,7}$ = 7.6 Hz, $J_{8,6}$ = 1.5 Hz, $J_{8,5}$ = 0.7 Hz, H-8); ^{13}C NMR(50 MHz) (29.7, 31.1, 34.6, 117.7, 120.8, 125.0, 127.0, 128.0, 128.3, 129.0, 130.9, 132.1, 141.3, 144.2, 149.9, 208.8; MS m/z 236 (100, M^+), 221 (60, M^+-Me).

(11) The chiral ligands tried with furan **9** and the corresponding ee's were: *(R,S)*-BPPFA, 9%; *(R,R)*-CHIRAPHOS, 11%; *(R)*-PROPHOS, 1%; *(R,S)*-PPFOMe, 8%; *(S,S)*-PPM, 3%.

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