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ASYMMETRIC INDUCTION IN PD CATALYZED ENYNE CYCLOISOMERIZATIONS

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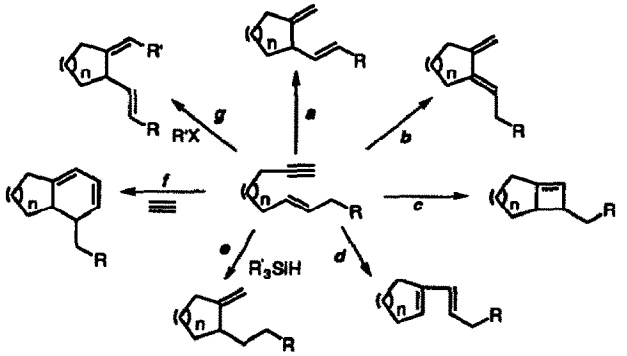
Summary: Asymmetric inductions up to 71% have been observed in a Pd catalyzed version of an intramolecular Alder ene reaction.

The thermal Alder ene reaction has had few applications in organic synthesis because of limitations in scope.[1] Metal catalyzed versions provide an opportunity to overcome such limitations, but also do much more. For example, Pd catalyzed cycloisomerizations of enynes[2] represent a flexible approach to a variety of products by simple manipulation of the catalyst as outlined in Scheme 1 (paths *a-d*), whereas a thermal process is limited to path *a* if it proceeds at all. Further variations become possible depending upon the addition of

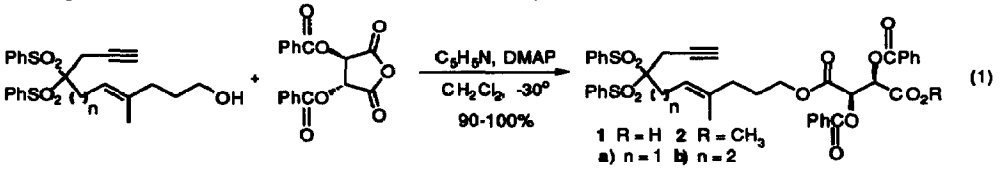
SCHEME 1. Pd Catalyzed Cycloisomerizations and Related Reactions of Enynes



various traps (Scheme 1 paths *e*[3] and *f*[4]) or initiators (Scheme 1, path *g*[5]). The excellent chemo-, regio-, and diastereoselectivity characteristics of the reactions make them suitable for application in the synthesis of complex natural products which include sterepolide,[6] petiodial,[7] merulidial,[8] dendrobine,[9] chokol C,[10] β-necredol,[11] phyllanthocin,[12] and vitamin D metabolites.[13] Another prospect for these metal catalyzed reactions is the ability to control absolute stereochemistry. While we focus on the Alder ene reaction, we hope what we learn will be extendable to the other processes illustrated in Scheme 1. In this letter, we communicate our efforts to explore tartaric acid derivatives and our recently described chiral ligands[14] as chiral inducing elements.

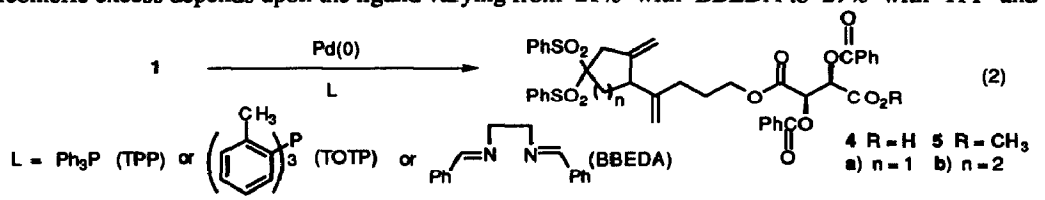
Since our previous work suggests that a free carboxylic acid substituent enhanced selectivity,[15] tartaric acid derivatives appear as potentially ideal chiral auxiliaries[16] since their functionality provides an easy point of attachment while maintaining a free carboxylic acid. Using dibenzoyltartaric anhydride,[17] the chiral auxiliary is readily attached to a substrate bearing an alcohol substituent as in eq. 1. Because the chiral auxiliary resides rather remotely from the newly forming stereogenic center, these substrates represent a rather severe test of the ability of the tartrate to function as a chiral auxiliary. Stirring a solution of substrate **1a**[18] with 3% $(dba)_3Pd_2{\cdot}CHCl_3$ (3) and 6% ligand in benzene-d_6 at ambient temperature give the cycloadduct usually in 60-

70% yields (eq. 2). The diastereomers of **4a**[18] are best analyzed after esterification with diazomethane. For **5a**,



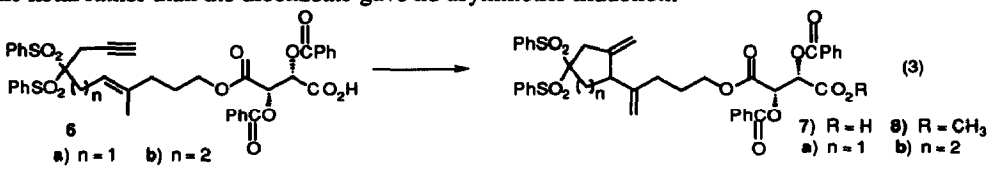
(1)

the signals for one of the tartrate unit's methine protons in the two diastereomeric products are readily resolved in C_6D_6 at δ 6.54 and 6.58 allowing the diastereomeric ratio to be determined by integration. The diastereomeric excess depends upon the ligand varying from 21% with BBEDA to 27% with TPP and 50%



(2)

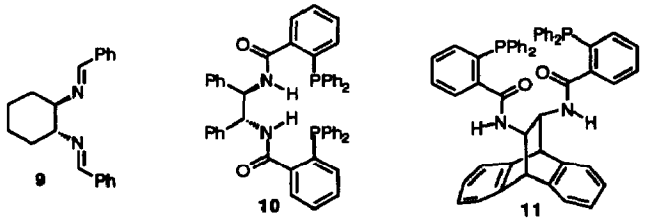
with TOTP. To verify that nothing unusual occurs, the *S,S*- tartaric ester substrate **6a** is also cycloisomerized (eq. 3). Under the same conditions, the mirror image diastereomer **7a** forms when TOTP is employed as ligand. Analysis of **8a**[18] reveals a 52% de. The choice of tartrate does make a diference. Derivatizing the tartrate diol as a cyclic ketal rather than the dibenzoate gave no asymmetric induction.



(3)

The effect of ring size on the asymmetric induction is explored using **1b**.[18] Interestingly, the conditions which give a 50% de for the cycloisomerization of **1a** (L = TOTP) yields a 71% de for the cycloisomerization of **1b** -- the product was also analyzed as its ester **2b**.[18] The ^{1}H nmr spectrum shows the methoxy groups as two singlets at δ 3.76 and 3.75 in $CDCl_3$. The importance of the free carboxylic acid is evident in both cyclizations. Treatment of the methyl esters **2a** or **2b** under these conditions give de's of 0-6%.

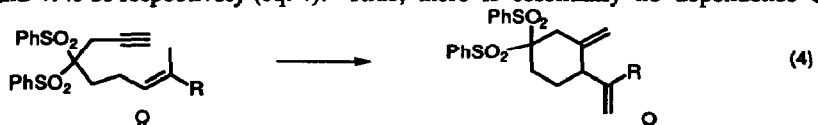
The question of double asymmetric induction employing a chiral ligand is examined by the use of ligands **9**,[18] **10**,[14] and **11**.[14] While neither an asymmetric version of BBEDA such as **9** nor the bis-amide **10** improves the de relative to achiral ligands, the bicyclic diamide **11** proves interesting since it generates as the major diastereomer what corresponds to the minor diastereomer in all the other cyclizations of **1a** and **1b**. Thus, from the same substrate **1b**, TOTP gives a 71% de favoring one diastereomer; whereas, **11** gives a 60% de favoring the one epimeric at the newly formed stereogenic center.



To establish that the ligand not the chiral auxiliary determines the sense of chirality in the cyclization,

the *S,S* substrates **6a** and **6b** are cyclized with both TOTP and **11** as the ligands. If the ligand controls the stereochemistry, there should be no reversal of the diastereoselectivity by switching from the achiral to chiral ligand in this case. Indeed, cyclization of **6a** gives 52% and 50% de and cyclization of **6b** gives 71% and 55% de for TOTP and **11** respectively wherein the same diastereomer dominated in all cases.

Ligand **11** operates independently of the chirality of the tartrate moiety. As a result, the simple succinate monoester **12**[18] should give similar results. Indeed, using 3% $(dba)_3Pd_2{\cdot}CHCl_3$ and 6% **11** at rt, it cyclizes to give **13**[18] with 50% ee (eq. 4) -- the same level of induction as with the chiral auxillary. What effect does the distance of the carboxylic acid from the newly forming stereogenic center have on the catalytic asymmetric induction? The two carboxylic acids **14a**[18] and **15**[18] address this issue. Their cyclizations using **11** give **16**[18] and **17**[18] of 42% and 47% ee respectively (eq. 4). Thus, there is essentially no dependence on the distance



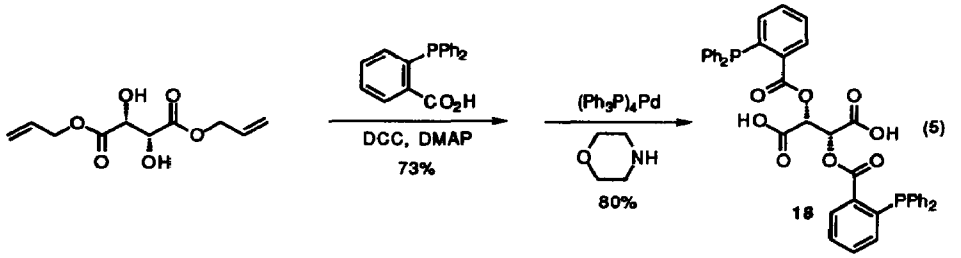
(4)

12 R = $(CH_2)_3OCCH_2CH_2CO_2H$
14a R = $CH_2CH_2CO_2H$
14b R = $CH_2CH_2CO_2C_2H_5$
15 R = CO_2H

13 R = $(CH_2)_3OCCH_2CH_2CO_2H$
16a R = $CH_2CH_2CO_2H$
16b R = $CH_2CH_2CO_2C_2H_5$
17 R = CO_2H

between the carboxylic acid and the newly forming stereogenic center. Nevertheless, the presence of a free acid does make a difference, albeit a smaller one than previously observed as is illustrated by the 24% ee obtained upon cyclizing the ethyl ester **14b** related to **14a** [3% $(dba)_3Pd_2{\cdot}CHCl_3$, 6% **11**, 10% HOAc, C_6D_6, rt].

The success of the C_2 symmetric diamide ligand **11** led to the exploration of incorporating both the 2-diphenylphosphinobenzoyl unit and a carboxylic acid[19] in the same C_2 symmetric ligand. A simple candidate **18**[18] derived from tartaric acid is readily available as outlined in eq. 5. Cycloisomerizations with this ligand

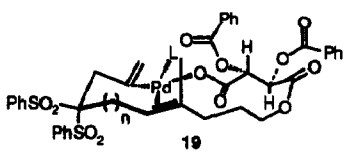


(5)

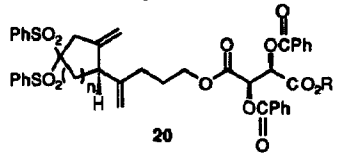
require temperatures of 60°C which likely decrease the enantioselectivity. Nevertheless, the cycloisomerization of the ester **2b**, which previously gave almost no asymmetric induction, now gives a 52% de. A smaller increase was observed in the ee (to 33%) in the cycloisomerization of **14b** -- the increase being compromised by the higher temperatures.

These results reveal several factors that appear useful to achieve asymmetric induction in Pd catalyzed cycloisomerizations of enynes. Dibenzoyltartrate is a useful chiral auxiliary, the level of induction being extraordinary considering the distance between the auxiliary and the newly formed stereogenic center. Gratifyingly, newly developed asymmetric ligands prove to be the most successful to date in achieving catalytic asymmetric induction. In both cases, the presence of a free carboxylic acid in the substrate enhances the level of induction. A model in which this carboxylic acid rigidifies the substrate by coordinating to the palladium in

the chiral discriminating step as depicted in **19** for substrates **1a** and **1b** may account for the ability to transmit



19



20

stereochemical information over such large distances. The illustrated folding places the benzoyloxy substituents outside the macrocyclic ring in this conformation and predicts the stereochemistry depicted in **20** for the major diastereomer. The ability of ligand **11** to override this control may stem from the fact that it serves as a bidentate ligand on palladium, thereby precluding bonding of the carboxylate to palladium as depicted in **19**. In such an event, the ligand stereochemistry, and not that of the chiral auxiliary determines the stereochemistry of the folding. Thus, this metal catalyzed cycloisomerization does offer promise as an approach for asymmetric synthesis using either chiral auxiliaries or catalytic asymmetric induction.

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