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A New Palladium Catalyst for Intramolecular Carbametalations of Enynes

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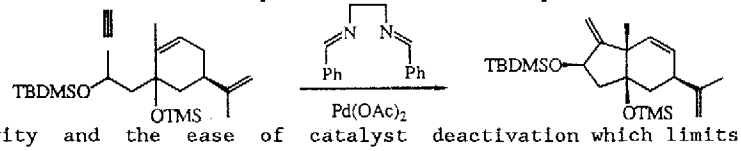
Summary. The combination of $(dba)_3Pd_2 \cdot CHCl_3$ plus a carboxylic acid effectively catalyzes cyclization of 1,6-enynes in which asymmetric induction may be achieved by use of enantiomerically pure carboxylic acids.

Chemical efficiency in a cyclization is optimized if such a process is simply an isomerization. The Pd(+2) cyclization of 1,6-enynes as represented by eq 1 is just such a process.[1-4] Limitations of the palladium acetate catalyst have included its



(1)

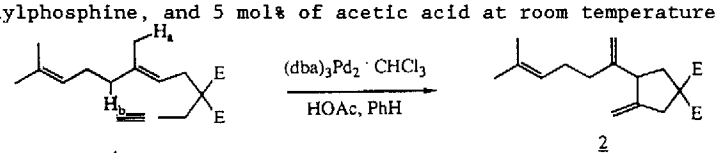
overreactivity and the ease of catalyst deactivation which limits the turnover number (mainly by reduction under the reaction conditions). While we could overcome such limitations in some cases[4] (e.g., the example of eq 1), we sought an alternative catalyst that might obviate such problems.

Consideration of the mechanistic picture of eq 2 suggested that we could effect the

(2)

desired cyclization if we generated a HPdX species. The generation of this species by the oxidative addition of HX to a palladium(0) complex is known for strong acids such as HCl,[5,6] but such a catalyst fails to effect cyclization. The contrast between palladium chloride, which fails to serve as a catalyst, and palladium acetate, which does serve as a catalyst, led us to consider the feasibility of employing a simple carboxylic acid even though an oxidative addition of acetic acid was unknown.[7]

In the event, treating a benzene solution of enyne 1 with 2.5 mol% of $(dba)_3Pd_2 \cdot CHCl_3$, 5 mol% of *o*-tolylphosphine, and 5 mol% of acetic acid at room temperature led to smooth



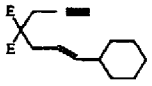
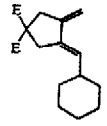
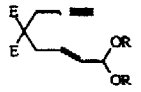
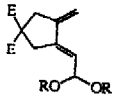
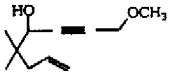
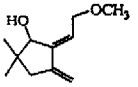
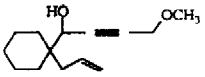
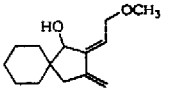
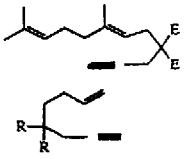
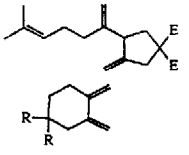
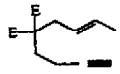
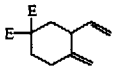
1 2

(3)

+ $(o\text{-}C_7H_7)_3P$ 69%

no ligand 86%

Table 1. Pd(0) + HOAc Catalyzed Enyne Cyclizations[a,b]

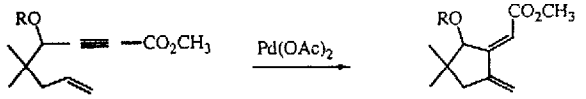
Entry	Enyne	Time	Product	Isolated Yield
1[e]		4h		95%
2[e]	 R = Ac	4h		75%
3[e]	R = CH_3	24h		86%
4		48h		78%
5		24h		76%
6[e]		2h		69% (86%)[c]
7[e]	R = E	6h		76%
8	R = SO_2Ph	5h		62%
9[e]		48h		54%[d]

a) All reactions were run by adding substrate to a benzene solution of the catalyst, comprised of 2.5 mol% of $(dba)_3Pd_2 \cdot CHCl_3$, 5 mol% of acetic acid, and 5 mol% of tri-*o*-tolylphosphine to give a substrate concentration of 0.06 - 0.2 M. b) All new compounds have been fully characterized spectrally and elemental composition established by high resolution mass spectroscopy. c) This run performed in the absence of tri-o-tolylphosphine. d) A 32% yield of a by-product, tentatively identified as the dimer formed by acetylenic coupling (ref 10), was obtained. e) E = CO_2CH_3.

cyclization to give the regioisomerically pure cyclopentane 2 (eq 3). Not only are phosphine ligands not required, but some improvement in yield can be seen in the absence of any ligands. Since a P/Pd ratio of greater than 2 and an increase in the ligating properties of a ligand toward Pd slows reaction, we have preferred the catalyst system stated in footnote *a* of Table 1. The many examples collated in Table 1 demonstrated the generality of this new catalyst system.

Several features are particularly noteworthy. Although a catalyst composed of Pd(0) and a triarylphosphine is well known to catalyze ionization of allyl acetates,[9] such a process does not compete with the enyne cyclization (entry 2). While there are many similarities between this catalyst system and that derived from palladium acetate, there are important differences too. The regioselectivity observed with the two catalyst systems closely parallels each other. For example, migration of H_a in substrate 1 (eq 3) dominates over H_b in both cases and a similar rationale may be invoked.[8] The presence of an allylic oxygen substituent (entries 2 and 3) or any branching at the allylic position that bears the hydrogen that must migrate to form a 1,4-diene (entry 1) leads to formation of the 1,3-diene instead with both catalytic systems.

On the other hand, the formation of six membered rings from relatively simple substrates occurs under these conditions (entries 7, 8, and 9). A particularly striking difference is the failure of substrates bearing a methoxycarbonyl group at the acetylenic terminus (such as 3) to cyclize under these conditions. In contradiction to this fact, the cyclization of substrate 3 succeeds with catalytic palladium acetate.[11] *Clearly, two different mechanisms*



(4)

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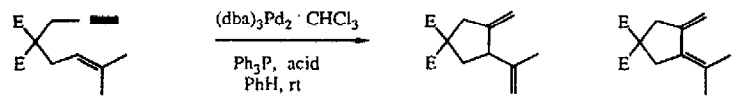
R = H (50%), TMS (70%), Ac (57%)

must be operating with the two different catalyst systems! While the mechanism for the palladium acetate catalyzed reaction remains undefined, the rationale outlined in eq 2 seems reasonable for the present case. Furthermore, it is clear that these seemingly closely related processes operate via multiple mechanistic pathways[12] - a fact that offers great opportunity in further developing this field.

The range of acids capable of effecting this transformation was examined for entry 8 of Table 1. Sulfonic acids such as camphorsulfonic acid or their pyridinium salts such as PPTS fail. *p*-Nitrophenol does generate some cyclic product but with many by-products. On the other hand, carboxylic acids appear to be quite general. A strong carboxylic acid like TFA[6] gives the cyclic product (63% yield) but the catalyst has a very limited lifetime as detected by the precipitation of palladium black. On the other hand, formic, mandelic, and camphoric acids effect the cyclization efficiently.

The ability to employ carboxylic acids in conjunction with Pd(0) as a catalyst has particular merit for exploring asymmetric induction for substrates that generate a 1,4-diene as a product. Eq 5 and Table 2 outlines our results. While the current results are modest, the notable success of binaphthoic acid as a chiral catalytic inducing element in such a simple carbon-carbon bond forming reaction at room temperature strongly encourages us.



(5)

4 5

Table 2. Asymmetric Induction in Enyne Cyclization

Entry	Optically Active Acid	Yield	Ratio 4:5	Optical Rotation[a]	%ee[b]
1	S(-)-binaphthoic	61%	3:1	+6.4°	33%
2	(+)-3S-methyl-2R-(nitromethyl)-5-oxo-3S-cyclopentaneacetic acid	59%	3.5:1	-0.54°	5-10%
3	(-)-2-pyrrolidone-5S-carboxylic acid	82%	3:1	N.D.	9%
4	S(-)-2-methoxy-2-trifluoromethyl-phenylacetic acid	60%	3:1	N.D.	8%
5	(+)-camphorcarboxylic acid	64%	3.2:1	N.D.	2-5%

a) At 23° using sodium D line in $CHCl_3$.
b) Obtained from chiral shift study using tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium in benzene-d_6.

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