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Controlling Mode Selectivity in Palladium-Catalyzed Bisdiene Carbocyclizations: Optimizing for Cyclization-Trapping over Cycloisomerization

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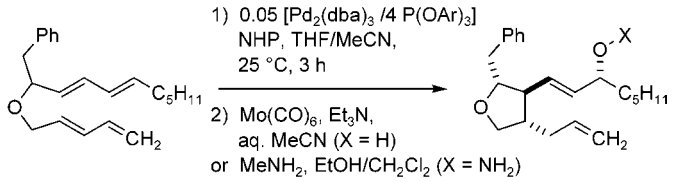
ABSTRACT



Screening combinations of five catalyst precursors with 13 phosphorus ligands identified cyclization catalysts that favor carbocyclization-trapping with *N*-hydroxyphthalimide over a competing cycloisomerization mode.

Efficient palladium-mediated carbocyclizations define a variety of novel strategies for assembling structurally complex ring systems.[1] We are interested in palladium-catalyzed reactions of 1,3-dienes,[2,3] specifically, the intramolecular reactions of acyclic substrates containing two 1,3-diene moieties within their structure (i.e., bisdienes). Two of the reaction modes exhibited by such substrates, (i) cyclization with trapping by a pronucleophile[4] and (ii) cycloisomerization to a cyclized enediene,[5] are particularly relevant to the present study.

The cyclization-trapping and cycloisomerization modes often compete, particularly in the case of substituted bisdienes. In the cyclization of **1**, for example, the ratio of cyclization-trapping product **2** to cycloisomerization product **3** varies widely (Table 1). The cyclization-trapping mode can be favored by high concentration of trapping reagent or by rendering the trapping agent intramolecular,[6] and of course, the cycloisomerization mode is favored in the absence of trapping reagent. The goal of the present study is to find a combination of a trapping reagent, catalyst precursor, ligand, and reaction conditions that favors cyclization-trapping with a synthetic equivalent to "OH" over bisdiene cycloisomerization.

A working model for the mechanism of the palladium-catalyzed cyclization, one consistent with that proposed for the related intermolecular 1,3-diene linear dimerization-

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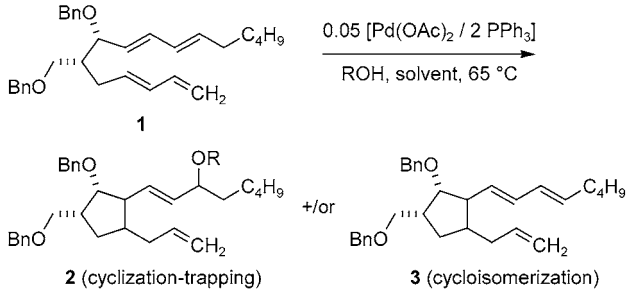
Table 1. Competing Reaction Modes: Cyclization-Trapping versus Cycloisomerization with ROH Trapping Reagents



trapping agent (conditions)	**2**:**3**	yield (%)
MeOH (as solvent)	90:10	90
H_2O (Na_2CO_3, CO_2, THF)	70:30	68
(p-$MeOC_6H_4$)CH_2OH (THF)	30:70	72
TBDMSiOH (THF)	0:100	92

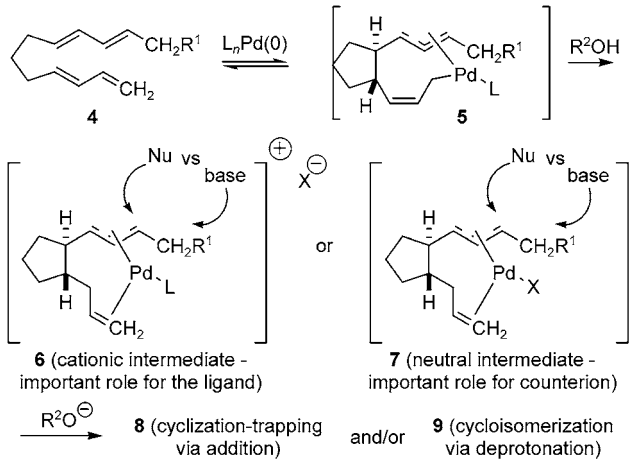


Figure 1. A mechanistic model, showing potential roles for the counterion (X, catalyst precursor), ligand (L), and trapping agent (R^2OH).

trapping (telomerization) reactions,[7,8] is shown in Figure 1. Palladium(0)-mediated oxidative coupling of the bisdiene **4** to palladacycle **5** is followed by protonation. The proton is presumably supplied by the trapping reagent to generate intermediates such as **6** and/or **7**. The two differ in that **6** is cationic and complexed with ligand (L), whereas **7** is neutral and associated with counterion X, not L. We reported that cycloisomerization products likely arise via deprotonation of **6** or **7**,[5,9] and thus, the tendencies of **6** and **7** to preferentially add nucleophile or deprotonate is potentially a key to controlling the cyclization mode.

Several reaction variables are likely to be particularly important in partitioning between the two cyclization modes. Cationic and neutral catalysts show significant differences in the linear dimerization-trapping of butadiene.[10,11] Thus, the nature of the counterion and, by extension, the choice of catalyst precursor (e.g., PdX_2 or $Pd(0)L_n$) are important variables. The nature and quantity of the ligand are equally important in diene dimerizations.[2,12] The trapping reagent serves both as a proton donor and, afterward, either as a nucleophile adding to the η^3-allyl to afford the cyclization-trapping product **8** or alternatively as a base, deprotonating the η^3-allyl to afford the cycloisomerization product **9**.

The trapping reagent should possess a relatively low pK_a as the pronucleophile and be strongly nucleophilic as the conjugate base. Once having added, it should not readily revert to a π-allylpalladium(II) intermediate via oxidative addition, and it must be easily deprotected to afford the desired allylic alcohol. A number of trapping reagents were screened under the (then) standard reaction conditions (0.1 [$Pd(OAc)_2$/2PPh_3], THF, 65 °C, 12 h). *N*-Hydroxyphthalimide (**10**, NHP) emerged as a promising candidate. Its reaction with bisdiene **11** gives the cyclized-trapped product **12** in about 50% yield in several solvents (65 °C, 4 h). At the time of our studies, the use of NHP had not been reported in diene dimerization-trapping reactions or in palladium-catalyzed allylic substitution reactions. Takemoto recently reported palladium-catalyzed *O*-allylic substitutions of other hydroxylamine derivatives bearing an *N*-electron-withdrawing substituent.[13]

Using **11** (bisdiene substrate), NHP (trapping reagent), and 1:1 THF/acetonitrile (solvent), the catalyst precursor and ligand were varied in a parallel optimization mode (Figure 2). Five catalyst precursors were selected, $(Pd(OAc)_2$, $Pd(TFA)_2$, $Pd(acac)_2$, $Pd(hfa)_2$ (hfa = hexafluoroacetyl acetonate), and $Pd_2(dba)_3$. With the exception of $Pd(hfa)_2$, each had frequently been used in bisdiene carbocyclizations or diene linear dimerizations. Thirteen phosphorus ligands, spanning a wide range of steric and electronic characteristics, were selected for screening (Figure 2, **A**−**M**).

Many of the ligands selected had previously been used to effect bisdiene carbocyclizations or diene dimerizations (e.g., tricyclohexylphosphine (**A**),[14] triphenylphosphine (**B**), tri(*o*-tolyl)phosphine (**C**), tris(2,4,6-trimethoxy-phenyl) phosphine (**D**),[15] tri(*o*-tolyl) phosphite (**G**),[16] 2′-(diphenylphosphino)-*N*,*N*-dimethyl-[1,1′-biphenyl]-2-amine (**K**)[10]). Others are included for various reasons. In the absence of trapping reagent, tri(2-furanyl)phosphine (**F**) does not efficiently

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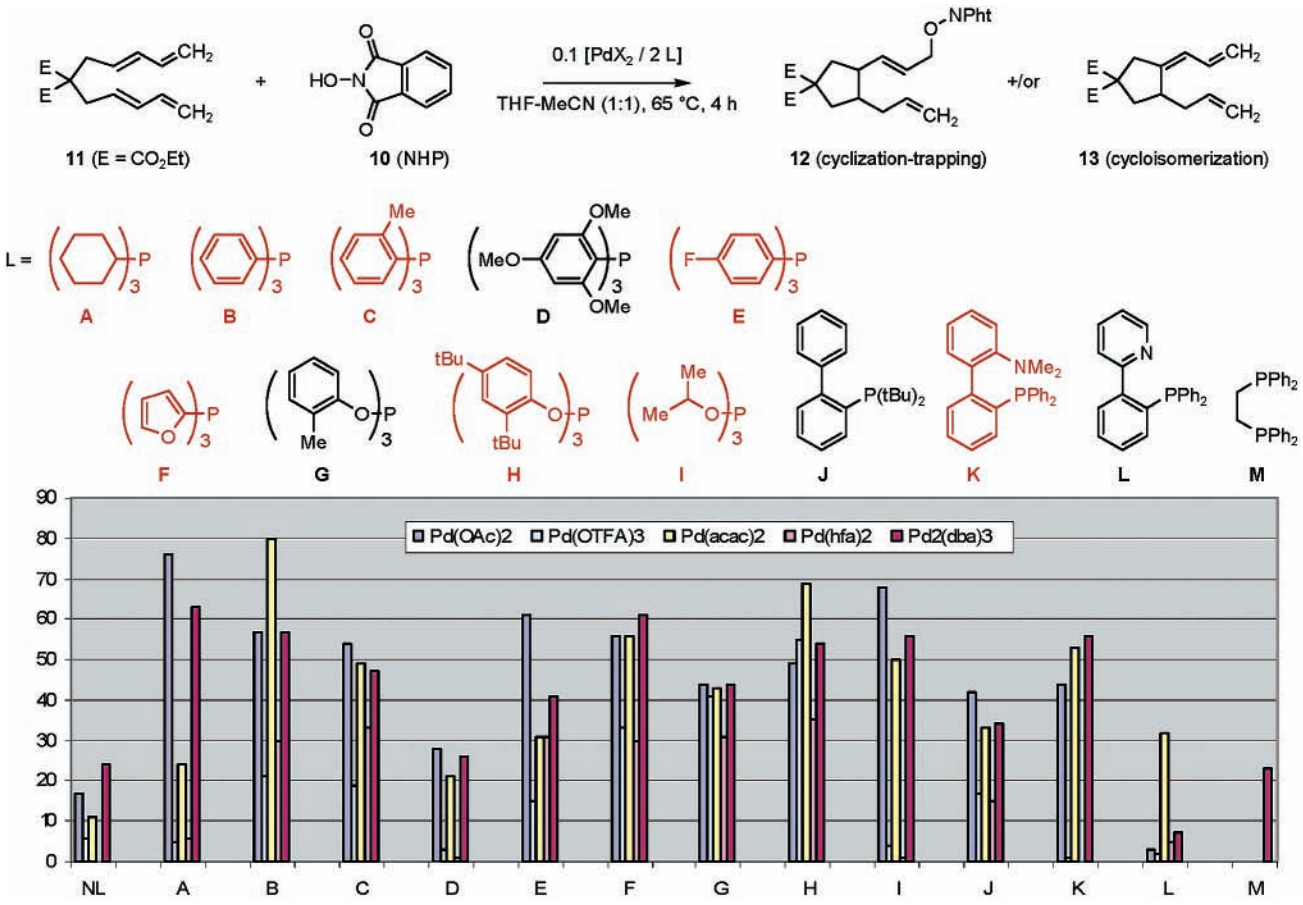

Figure 2. The palladium-catalyzed cyclization of bisdiene **11** with NHP. HPLC yields of cyclization-trapping product **12** as a function of ligand (ligands **A**−**M**; NL = no added ligand) and catalyst precursor ($Pd(OAc)_2$, $Pd(TFA)_2$, $Pd(acac)_2$, $Pd(hfa)_2$, $Pd_2(dba)_3$).

promote (the undesired) bisdiene cycloisomerization.[5] (2,4-Di-*tert*-butylphenyl) phosphite (**H**, DTBPP), triisopropyl phosphite (**I**), and 2-(di-*tert*-buylphosphino)biphenyl (**J**) form catalysts exhibiting high turnover numbers in palladium-catalyzed cross-coupling reactions.[17,18] 2-(Diphenylphosphino)pyridine (**L**) is included because several *P*,*N*-ligands form very active catalysts for the reaction of butadiene with methanol.[19] Diphosphines are occasionally used in diene dimerizations,[14] and one chelating diphosphine (**M**, dppe) is included. Each catalyst precursor is also screened in the absence of added ligand (Figure 2, NL = no ligand added).

The results of the parallel optimization study are summarized graphically in Figure 2.[20] The reaction is surprisingly sensitive to the precise combination of catalyst precursor and ligand. Few trends are apparent. $Pd(hfa)_2$ and $Pd(OTFA)_2$ are the least successful catalyst precursors. Eight ligands in the screening set (those highlighted in red) give at least one catalyst yielding 50% or greater. The combination of $Pd(acac)_2$ and Ph_3P gives the overall highest yield (80%).

The substituted bisdiene **14a** was prepared. Its reaction with NHP using the old standard catalyst system, i.e., [$Pd(OAc)_2$/2 PPh_3], gives the cyclized-trapped product **15a** in only 10% yield; the major product is **16**. The cyclization-trapping of bisdiene **14a** with NHP was screened using all combinations of the three best catalyst precursors ($Pd(OAc)_2$, $Pd(acac)_2$, $Pd_2(dba)_3$) and six of the best ligands (**A**, **B**, **F**, **H**, **I**, **K**). The results are shown graphically in Figure 3. The yield of **15a** varied widely. Nonetheless, four combinations give HPLC yields greater than 60%; three of these employed DTBPP (**H**), a ligand that had not been previously been used in palladium-catalyzed bisdiene carbocyclizations.

The combination of $Pd_2(dba)_3$ and DTBPP was studied further. In THF or acetonitrile alone the yield is lower than in the 1:1 solvent mixture. A 2:1 L:Pd ratio was used the screening experiments, but the [$Pd_2(dba)_3$/DTBPP] catalyst is insensitive to L:Pd ratios ranging from 1:1 to 10:1. Although the screening reactions were run at 65 °C (4 h),

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(20) The series was carried out twice, first by two students working as a team and then repeated (albeit with a few substitute ligands) by a third student. Although the absolute yields varied (ca. ±5%), the trends were quite consistent between the runs. The second data set are shown in Figure 2.

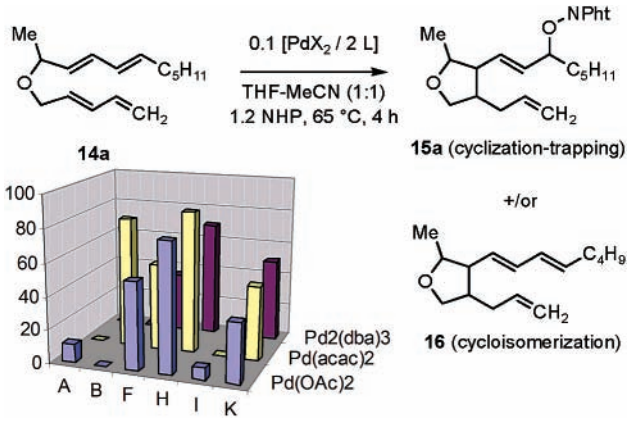
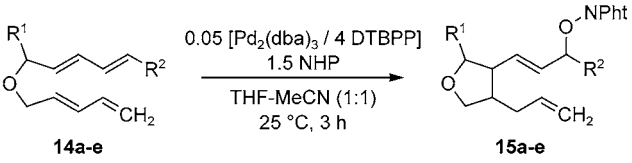


Figure 3. The palladium-catalyzed cyclization of bisdiene **14a** with NHP. HPLC yields as a function of ligand (**A**, **B**, **F**, **H**, **I**, **K**) and catalyst precursor ($Pd(OAc)_2$, $Pd(acac)_2$, $Pd_2(dba)_3$).

the [$Pd_2(dba)_3$/DTBPP] catalyst proceeds readily at room temperature (3 h). With this modest refinement, bisdienes **14a**−**e** give products **15a**−**e** in 67−90% yield (Table 2).

Table 2. Preparative Cyclization-Trapping of Bisdienes **14a**−**e**



compound	R^1	R^2	yield (%)
15a	Me	n-C_5H_{11}	68
15b	i-Pr	n-C_5H_{11}	79
15c	i-Pr	Me	90
15d	Bn	n-C_5H_{11}	67
15e	Bn	Me	86

Three new tetrahedral stereocenters and a disubstituted alkene are formed in the cyclization of bisdiene **14**. Thus, 16 diastereomers of **15** are possible, but essentially one is formed. Compound **15d** crystallized readily, and its crystal structure is shown in Figure 4. A regioisomer, wherein the NHP moiety is allylically transposed, is also formed (10 ± 5%). The allylic alcohol **17** (78%) is obtained by cleavage of the N−O bond with $Mo(CO)_6$ using a modification of the procedure by Goti.[21] NHP has an added benefit as a

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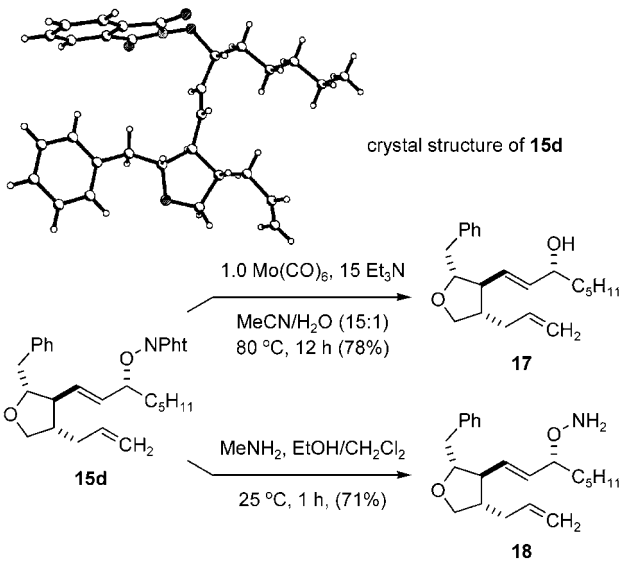

Figure 4. The crystal structure of **15d** and its conversion to allylic alcohol **17** and the hydroxylamine derivative **18**.

trapping reagent; *O*-allyl hydroxylamines are themselves useful functionalities[22] and **18** is readily obtained by treatment with *N*-methylamine.[23,24]

Palladium-catalyzed bisdiene carbocyclizations proved very sensitive to the choice of catalyst precursor, ligand, and reaction conditions. Using a parallel optimization strategy we achieved our goal of obtaining good yields of cyclized-trapped products from substituted bisdienes. The conditions obtained from optimizing a simple substrate provided a useful starting point for the more complicated one. The catalyst system identified via screening gives good preparative yields for five related bisdienes. Further studies into the reasons for its success are in progress.

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Supporting Information Available: Procedures and spectral data for **14a**−**e**, **15a**−**e**, **17**, and **18** and details for the crystal structure of **15d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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