Improving Catalyst Scope: Use of Multiple Aniline Substrates To Optimize a Palladium-Catalyzed Bisdiene Cyclization
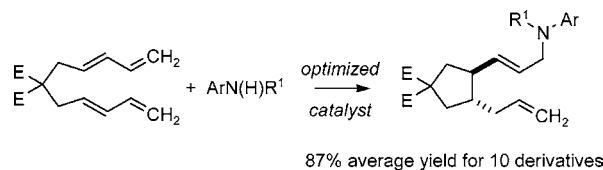
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ABSTRACT

87% average yield for 10 derivatives

Combinatorial screening of five catalyst precursors and nine ligands with three substituted aniline trapping reagents uncovered a catalyst system that promotes efficient palladium-catalyzed cyclization–trapping with a series of substituted anilines of varying steric and electronic character. The results of the parallel optimization study illustrate the interdependency of the key reaction variables.

Metal-catalyzed carbocyclization reactions have attracted much interest, leading to the development of a number of synthetically useful bond constructions.[1] We are interested in palladium-catalyzed cyclization reactions of bisdienes. Currently, our efforts are directed toward developing their potential for diversity-oriented synthesis through better control of reaction mode (e.g., cyclization–trapping, cycloaddition, cycloisomerization),[2] expanding their scope with respect to substrate and trapping reagent, and improving catalytic efficiency (i.e., turnover number and frequency).[3] Herein, we describe catalyst optimization studies which led to a catalyst exhibiting improved scope in cyclization–trapping reactions with substituted anilines.

Previous studies on palladium-catalyzed bisdiene cyclization via the cyclization-trapping mode largely focused on trapping with oxygen pronucleophiles. Most pharmaceuticals are nitrogen-containing compounds, and methods that efficiently introduce nitrogen, especially basic nitrogen, are of particular value in synthesis. We therefore turned our attention to the incorporation of nitrogen-trapping reagents. The bisdiene reaction is an intramolecular variant of the palladium-catalyzed linear dimerization of 1,3-dienes. The latter has been extensively studied with ammonia and alkylamines[4] and to a lesser extent with anilines,[5] sulfonamides,[6] and imides.[7]

We reasoned that the cyclization–trapping reaction of **1** with an aniline derivative **2** would serve as a good model for a variety of aryl- and heteroarylamine derivatives. A set

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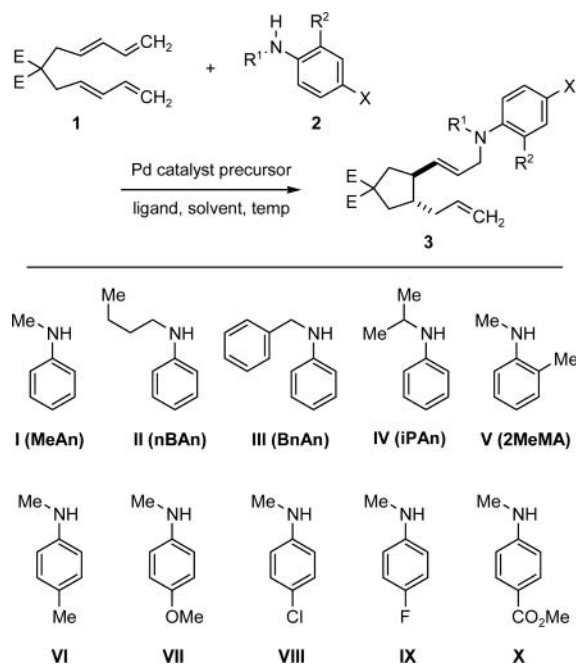
Figure 1. Palladium-catalyzed cyclization–trapping with a series of anilines selected to probe steric and electronic factors.

of substituted anilines was selected (Figure 1) to probe the scope of the reaction with respect to the trapping reagent, specifically, probing the effect of steric hindrance (**I**−**V**) and nucleophilicity (**VI**−**X**).

The trapping reagent plays several key roles in the reaction. A simplified mechanistic model, adapted from the widely accepted diene dimerization mechanism proposed by Jolly,[8] is shown in Figure 2. The active catalyst is thought to be a
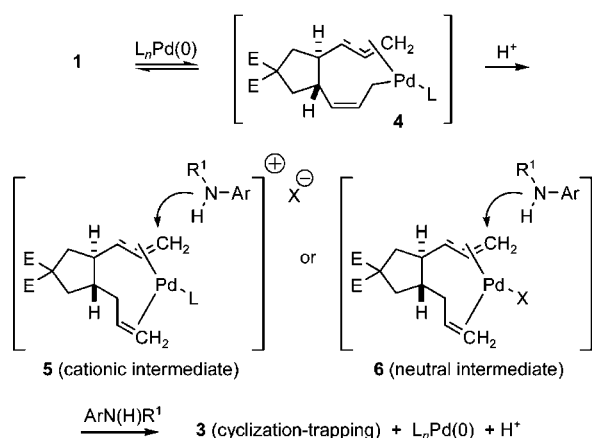

Figure 2. Mechanistic model for the palladium-catalyzed bisdiene cyclization–trapping with substituted anilines.

palladium(0) complex, and the key carbon–carbon bond formation is effected via formation of a metallacycle such as **4**. Protonation is expected to afford a chelated η^3-

Table 1. Reaction of Bisdiene **1** with Anilines **I**, **II**, and **IV**

(A) Influence of Catalyst Precursor on the Yield of the [PdX$_2$/2Ph$_3$P]-Catalyzed Reaction in THF				
aniline	Pd(OAc)$_2$	Pd(OTFA)$_2$	Pd(BF$_4$)$_2$	Pd(dba)$_2$
I (MeAn)	100	98	89	100
II (nBAn)	82	77	66	78
IV (iPAn)	54	31	48	23

(B) Effect of Solvent on the [Pd(OAc)$_2$/2Ph$_3$P]-Catalyzed Reaction					
aniline	tol	DCE	THF	MeCN	IPA	DMF
I (MeAn)	70	64	100	89	92	86
II (nBAn)	50	66	82	80	60	77
IV (iPAn)	63	60	54	82	22	34

allylpalladium(II) intermediate which, depending on the choice of counterion and/or ligand, might exist as a cationic complex (e.g., **5**) or a neutral intermediate (e.g., **6**). The trapping reagent subsequently adds to the η^3-allyl moiety affording **3**, regenerating the palladium(0) catalyst and releasing a proton required in the catalytic cycle.

The steric and electronic characteristics of the aniline should be important in the reaction. Sterically encumbered anilines could potentially slow the addition step and thereby impede the overall reaction and/or allow other reaction modes to compete. The nucleophilicity and basicity of the nitrogen should be similarly important. Three anilines, *N*-methyl- (**I**), *N*-butyl- (**II**), and *N*-isopropylaniline (**IV**), were selected to survey the effect of catalyst precursor and solvent on the efficiency of the cyclization reaction. Each reaction used 10 mol % palladium catalyst precursor and 2 equiv of triphenylphosphine per palladium (Table 1).[9]

All reactions in Table 1A were run in THF, the only difference being the nature of the palladium catalyst precursor employed. Two conclusions are apparent from the data. (1) The yield drops markedly in the series **I** > **II** ≫ **IV** indicating the reaction is very sensitive to steric effects. (2) The choice of catalyst precursor seems to play little or no role in determining the reaction efficiency.

Using [Pd(OAc)$_2$/2 PPh$_3$], the three trapping reagents were screened in eight solvents. Methanol and trifluoroethanol gave poor yields of aniline trapped product **3** even with the most reactive aniline, *N*-methylaniline (**I**); those alcohols compete effectively with aniline for trapping the bisdiene. 2-Propanol (IPA) also competes, but only with *N*-isopropylaniline (**IV**); in that case, the yield of **3** is low. The data for 2-propanol and the remaining solvents screened (THF, acetonitrile (MeCN), toluene (Tol), DMF, and 1,2-dichloroethane (DCE)) are summarized in Table 1B.

The solvent effects, while not very pronounced, could suggest that polar solvents are preferable to very nonpolar

(8) Jolly, P. W.; Mynott, R.; Raspel, B.; Schick, K. P. *Organometallics* **1986**, *5*, 473−481.

(9) All reactions were run at 65 °C for 4 h. The 4 h reaction time is arbitrary but selected to favor catalyst systems with higher turnover frequency, a key component of catalyst efficiency. The yield is determined by HPLC analysis of an aliquot taken from the crude reaction mixture.
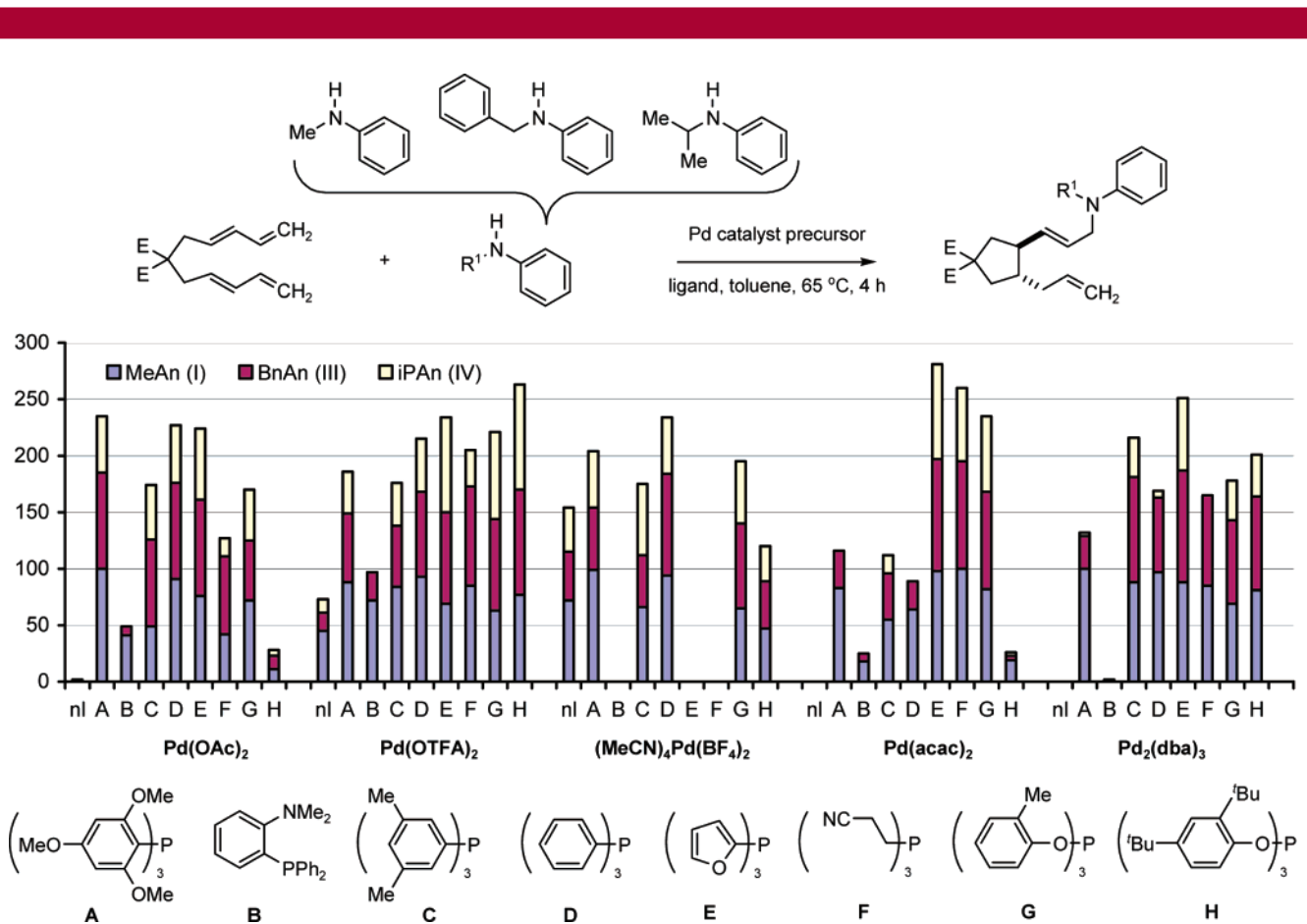
Figure 3. Catalyst optimization data arranged by catalyst precursor and ligand showing the cumulative yields obtained for the palladium-catalyzed cyclization−trapping of bisdiene **1** with anilines **I**, **III**, and **IV**.

ones (i.e., toluene and DCE), and had we focused on the results with *N*-methylaniline (**I**), [Pd(OAc)$_2$/2 Ph$_3$P] THF would have been selected as the optimal catalyst system for further study. However, we noticed that three solvents (i.e., toluene, DCE, and acetonitrile) gave less than 10% difference in yield between the three anilines, while the drop in yield due to increased steric hindrance was greater than 40% in THF and DMF. This led us to question whether our initial conclusion on steric hindrance was valid for all catalyst systems and reaction conditions or only some subset.

Chemists typically assume that most variables in a reaction are largely independent of each other and, therefore, independently optimize each. In the present case, the key intermediates likely participate in a complex series of equilibria during the course of the reaction.[10] Consequently, many of the key reaction variables are likely to be highly interdependent. Changing one variable at a time (as illustrated in Table 1) is unlikely to afford a well-optimized catalyst system. We therefore opted for a combinatorial approach to catalyst optimization[11] (Figure 3) in which we focused on varying the catalyst precursor and ligand. The choice of toluene as the reaction solvent was made, in part to complement a concurrent study.

In combinatorial studies, the components are selected in part based on precedent and in part on intuition. On the basis of the important role the counterion plays (see Figure 2), five common palladium catalysts precursors were selected: Pd(OAc)$_2$, Pd(OTFA)$_2$, (MeCN)$_4$Pd(BF$_4$)$_2$, Pd(acac)$_2$, and Pd$_2$(dba)$_3$. The selection of ligands was biased toward phosphines and phosphites, including five triarylphosphines of varying electronic nature and cone angle: tris(2,4,6-trimethoxyphenyl)phosphine (**A**), (2-dimethylaminophenyl)-diphenylphosphine (**B**), tris(3,5-dimethylphenyl)phosphine (**C**), triphenylphosphine (**D**), and tri(2-furanyl)phosphine (**E**). Among these, **A** and **B** had been used by others with great success in linear diene dimerizations.[12] Phosphine **C** was included as a more hindered analogue of triphenylphosphine, and **E** was included as a less electron rich analogue. One trialkylphosphine, tri(2-cyanoethyl)phosphine (**F**),[13] was included for comparison along with two phosphites. Tris-(2,4-di-*tert*-butylphenyl) phosphite (**H**) had been used with

(10) See a discussion of the related nickel-catalyzed reactions of 1,3-dienes: Tobisch, S.; Ziegler, T. *J. Am. Chem. Soc.* **2002**, *124*, 13290−13301.

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good success in cyclization−trapping reactions with *N*-hydroxyphthalimide,[2a] and tri(2-tolyl) phosphite (**G**) was included as a less hindered analogue.[14]

All combinations of the five catalyst precursors with ligands **A**−**H** and without added ligand (**nl**) were run separately with anilines **I**, **III**, and **IV**. Thus, 45 catalyst systems were screened with each aniline, for a total of 135 experiments.[15] The graph in Figure 3 summarizes the data as the sum of the yields for the three anilines with each ligand grouped by the catalyst precursor. In displaying the data in this manner, at least one conclusion is striking and inescapable; the 45 combinations selected exhibit widely diverse behavior.

The combination of Pd(acac)$_2$ and (2-furanyl)$_3$P (**E**) proved best from among the 45 catalyst systems screened giving a cumulative yield of 281% or an average yield of 93.7% for each the three anilines screened. Three other catalyst−ligand combinations gave high yields, Pd(OTFA)$_2$ and (2,4-di-tBuPhO)$_3$P (**H**) (87.7% average), Pd(acac)$_2$ and tri(2-cyanoethyl)phosphine (**F**) (86.7% average), and Pd$_2$(dba)$_3$ and **E** (83.7% average). No other combination gave an average yield above 80%.

Preparative reactions were run for all 10 aniline derivatives (**I**−**X**) using both the optimized catalyst system ([Pd(acac)$_2$/2(2-furanyl)$_3$P] in toluene, catalyst B) and [Pd(OAc)$_2$/2 Ph$_3$P] in THF (catalyst A) (Table 2). As anticipated, the optimized catalyst system proved much less sensitive to steric hindrance, and furthermore, we were delighted to find that it was also much less sensitive to electronic effects. The isolated yield for the 10 derivatives averaged above 87%, about 20% higher than that obtained with the Pd(OAc)$_2$-derived catalyst.

Had we only considered the results of our initial solvent and catalyst precursor survey (Table 1), we could reasonably have concluded that aniline trapping was limited to electron rich and sterically unencumbered anilines. However, using a combinatorial approach, we uncovered a catalyst system that works well for a relatively wide range of sterically and electronically differentiated aniline derivatives.

(14) Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J.-J.; Lee, T. H. *Eur. J. Org. Chem.* **2000**, 2991−3000.

(15) All reactions were run in toluene at 65 °C for 4 h. Approximately 20% of the combinations were run in duplicate, and from another 20% two aliquots were removed and analyzed separately as control experiments.

Table 2. Comparing Isolated Yields under the Original (A) and Optimized (B) Catalyst Systems for a Series of 10 Aniline Derivatives **2** (**I**−**X**)

2	R^1	R^2	X	catalyst A[a] (%)	catalyst B[b] (%)	Δ[c]
I	Me	H	H	92	91	−1
II	*n*Bu	H	H	70	93	23
III	Bn	H	H	66	89	23
IV	*i*-Pr	H	H	76	82	6
V	Me	Me	H	69	85	16
VI	Me	H	OMe	86	99	13
VII	Me	H	Me	72	94	22
VIII	Me	H	Cl	68	91	23
IX	Me	H	F	58	86	28
X	Me	H	CO$_2$Me	17	64	47
			avg	67.4	87.4	20

[a] Catalyst A: [Pd(OAc)$_2$/2Ph$_3$P] in THF at 65 °C (4 h). [b] Catalyst B: [Pd(acac)$_2$/2(2-furanyl)$_3$P] in toluene at 65 °C (4 h). [c] The difference in isolated yield obtained with catalysts A and B.

Why is the optimized catalyst successful? Given that the four best catalyst systems employ three different catalyst precursors (i.e., Pd(acac)$_2$, Pd(OTFA)$_2$, Pd$_2$(dba)$_3$) and ligands (i.e., triarylphosphine **E**, trialkylphosphine **F**, triaryl phosphite **H**), the answer is likely to be complicated. The ligand required innately depends on the catalyst precursor and the extent to which their interdependency influences the efficiency of this reaction is striking. The results highlight the challenge of designing catalyst systems exhibiting broad scope and the need for better algorithms for catalyst optimization. Further studies are in progress.

Supporting Information Available: Procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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