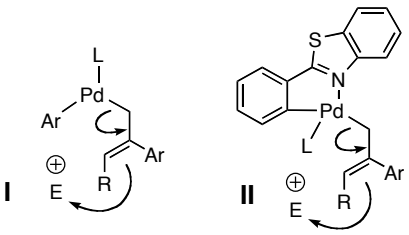
FINAL REPORT FOR: DE-FG02-06ER15792

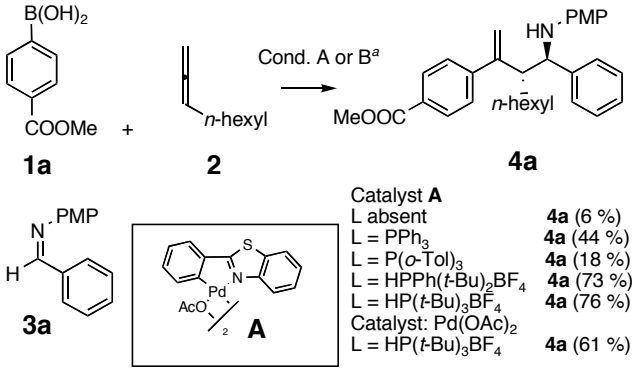
(a) Description of the results

(I) Application of cyclopalladated complexes as catalysts for a three-component coupling reaction for the preparation of homoallylic amines has been developed.



Allyl(aryl)palladium(II) complex **I** has been proposed to operate as a catalytic nucleophilic allyl transfer reagent in the reactions catalyzed by $Pd(OAc)_2/PR_3$ system. We envisioned that a cyclopalladated complex, for example compound **II** could operate as an analogous more stable catalytic intermediate. We explored the scope and limitations of our novel three-component coupling reaction catalyzed by palladium(II) complex **A** and its derivatives seeking to asses structure-activity effects in the cyclopalladated Pd(II) dimers bearing C-X (X = N, S, P) chelates.

The reaction of boronic acid **1a**, allene **2** and imine **3a** catalyzed by cyclopalladated dimer **A** was studied (Scheme 1). Indeed, the application of cyclopalladated catalyst **A** afforded the product **4a** in improved yields (76%), comparing to the original $Pd(OAc)_2/P(t\text{-}Bu)_3$ catalyst (61%). Unexpectedly, the presence of additional phosphine ligand along with catalyst **A** was required, and $HP(t\text{-}Bu)_3BF_4$ and $HPPh(t\text{-}Bu)_2BF_4$ afforded the best yields of amine **4a** (76% and 73%, respectively).



[a] Cond. A: **1a** : **2** : **3a** = 2 : 5 : 1 (mol equiv.), THF, 40 ºC, 16 h, 10 mol% Pd as complex A, L (PR_3) (10 mol%), CsF (4 equiv). Cond. B: same as Cond. A except 10 mol% Pd as $Pd(OAc)_2$, $HP(t\text{-}Bu_3)BF_4$ (10 mol%)

Scheme 1

The initially unexpected need for additional phoshine ligands in reactions catalyzed by the cyclopalladated catalyst **A** could be rationalized by the involvement of both the phosphine ligand (L) and the imine (L) in a series of ligand exchange equilibriums featuring the allylpalladium(II) intermediates **II** ultimately providing the optimum concentration of the η^1-bonded allylpalladium(II) complex **II** (L = PR_3) necessary for the nucleophilic allyl transfer.

Next, the performance of a series of cyclopalladated dimer complexes **B-L** (Fig. 1) as catalysts for the preparation of amine **4a** under the conditions optimized with the pallada(II)cycle **A** was evaluated (Table 1). In general, cyclopalladated complexes **A-H** possessing the C-N chelate in the auxiliary ligands proved to be viable catalysts affording amine **4a** in yields higher than 50% (entries 2, 3 and 5-9, Table 1). However, none of the complexes performed better than complex **A** or the originally reported $Pd(OAc)_2$.

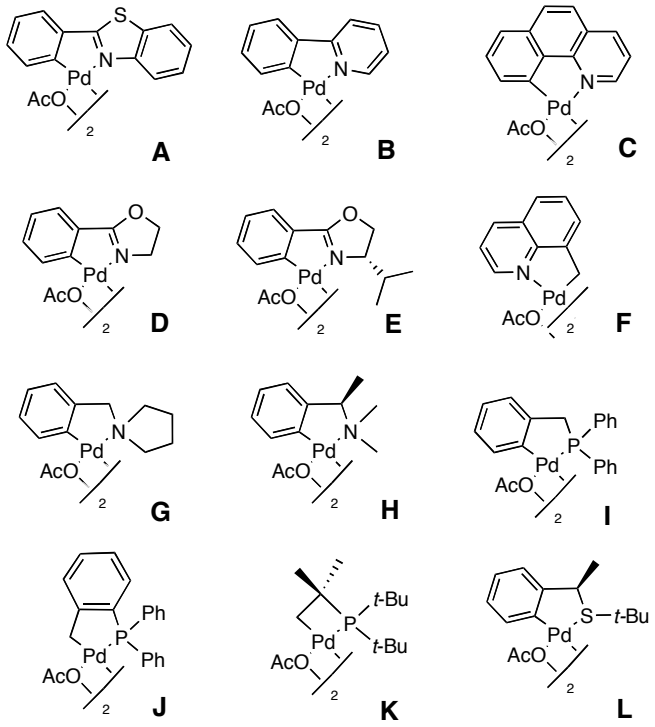
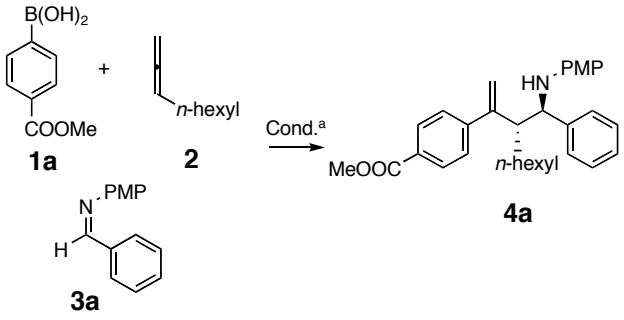


Figure 1

The lack of catalytic activity of complex **K** is significant when considering the reactive species involved in the catalytic cycle of reactions catalyzed by $Pd(OAc)_2/P(t\text{-}Bu)_3$ system, since under the reaction conditions, palladation of the phosphine ligand giving rise to a four-membered cyclopalladated ligand present in the complex **K** should be facile Disappointingly, attempts at realizing the asymmetry transfer from chiral nonracemic cyclopalladated complexes **E**, **H** and **L** did not afford enantiomerically enriched product **4a** (entries 6, 9 and 13, Table 1).

Table 1. Comparison of different pallada(II)cycles as catalysts



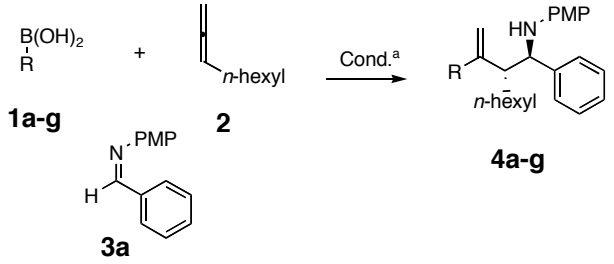
entry	catalyst	yield of **4a** (%)
1	$Pd(OAc)_2$	61
2	**A**	76
3	**B**	61
4	**C**	21
5	**D**	55
6	**E**	67 (3.1)[b]
7	**F**	50
8	**G**	58
9	**H**	56 (2.0)[b]
10	**I**	34
11	**J**	16
12	**K**	29
13	**L**	20 (0)

[a] Cond. **1a** : **2** : **3a**, 2 : 5 : 1 (mol equiv), THF, 40 ºC, 24 h, Pd catalyst (10 mol%), $HP(t\text{-}Bu)_3BF_4$ (10 mol%), CsF (4 equiv). [b] Enantiomeric excess (%) measured by chiral phase HPLC.

(II) The synthetic scope of the Pd-catalyzed three-component reaction for the preparation of homoallylic amines has been expanded.

The effectiveness of the catalyst **A** (Scheme 1, Table 1) in the three-component coupling reactions of selected boronic acids **1a-g** bearing heteroatom-containing substituents (methoxy, methylcarbonyl, cyano, fluoro, chloro) and the methyl group in the *para* position was investigated. Indeed catalyst **A** afforded amines **4a-e** bearing methoxy, cyano, fluoro and methylcarbonyl groups in the aromatic ring arising from the boronic acid component in yields moderately improved (8-34%) in comparison to the results with the originally reported $Pd(OAc)_2$ catalyst, thus extending the scope of the three-component coupling reactions. The cyclopalladated catalyst **A** appears to better tolerate substitution with groups significantly effecting the electron density in the aromatic ring of the boronic acids. Under these conditions a broader range of the rates of B to Pd transmetalation in the step leading to the key allylpalladium(II) intermediate **II** bearing the cyclometalated auxiliary ligand is tolerated.

Table 2. The reaction scope with substituted boronic acids



entr	substrate **1** (R)	catalyst	prdt **4**	yield (%)
1	4-$MeOOCC_6H_4$- *p*-methoxycarbonyl-phenyl	$Pd(OAc)_2$	**4a**	61
2		**A**		76 (+15)
3	4-$MeOC_6H_4$- *p*-methoxyphenyl	$Pd(OAc)_2$	**4b**	48
4		**A**		64 (+16)
5	4-$MeCOC_6H_4$- *p*-methylcarbonyl-phenyl	$Pd(OAc)_2$	**4c**	43
6		**A**		77 (+34)
7	4-CNC_6H_4- *p*-cyanophenyl	$Pd(OAc)_2$	**4d**	30
8		**A**		54 (+24)
9	4-FC_6H_4- *p*-fluorophenyl	$Pd(OAc)_2$	**4e**	29
10		**A**		37 (+8)
11	4-ClC_4H_4- *p*-chlorophenyl	$Pd(OAc)_2$	**4f**	54
12		**A**		56 (+2)
13	4-MeC_6H_4- *p*-methylphenyl	$Pd(OAc)_2$	**4g**	56
14		**A**		58 (+2)

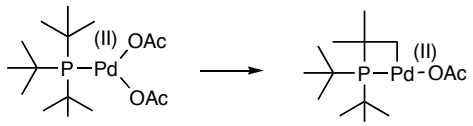
[a] Cond. **1a** : **2** : **3a**, 2 : 5 : 1 (mol equiv), THF, 40 ºC, 16 h, Pd catalyst (10 mol%), $HP(t\text{-}Bu)_3BF_4$ (10 mol%), CsF (4 equiv).

*(III) Investigation of the mechanism of the reactions catalyzed by the palladium acetate and the cyclopalladated complex **A**.*

We have performed ^{31}P NMR studies on the reaction mixtures from reactions catalyzed by both the cyclopalladated complex **A** and $Pd(OAc)_2$ in the presence of the optimized phosphine ligands under the optimized conditions.

The results of the ^{31}P NMR studies indicated that *distinct catalytic intermediates operate in reactions catalyzed by the cyclopalladated catalyst **A** in contrast to the reactions catalyzed by $Pd(OAc)_2$/ $(t\text{-}Bu)_3P$.*
The ^{31}P NMR studies on the $Pd(OAc)_2/HP(t\text{-}Bu)_3BF_4$-catalyzed reaction revealed that a cyclometalation of the $P(t\text{-}Bu)_3$ ligand might be occurring ultimately giving rise to a cyclometalated complex **III** (Figure 2). Since we observed that an analogous

cyclopalladated complex **K** (Figure 1) did not function as a successful catalyst for the synthesis of amine **4a**, we conclude that an in situ cyclopalladateion of the P(*t*-Bu)$_3$ ligand is likely limiting the performance of our originally discovered Pd(OAc)$_2$ catalytic system.



III

Figure 2

Despite an extensive effort, we were *unable extend* the previously demonstrated nucleophilic transfer of a simple C3-allyl group from the pinene-derived bis-π-allylpalladium complex (spectroscopically characterized in situ) to an imine (unpublished results) to the *transfer of the same simple C3-allyl fragment from the in situ generated allyl-Pd(II) complex bearing the cyclopalladated ligand* to an imine yielding the homoallylic amine (Figure 3).

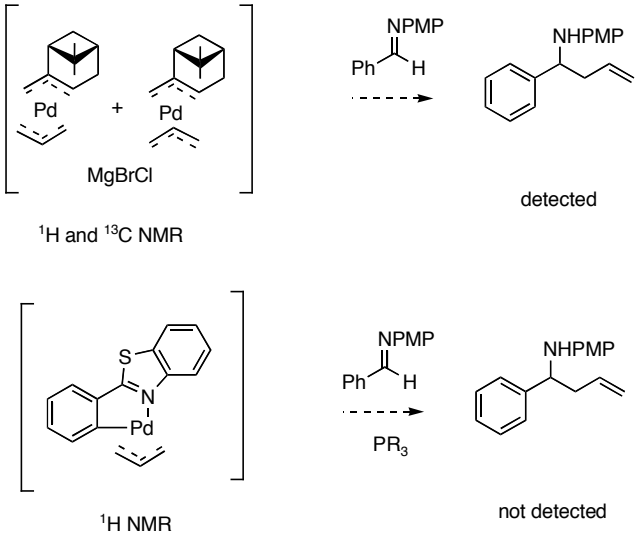


Figure 3