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Ligand and base additive effects on the reversibility of nucleophilic addition in palladium-catalyzed allylic aminations monitored by nucleophile crossover.

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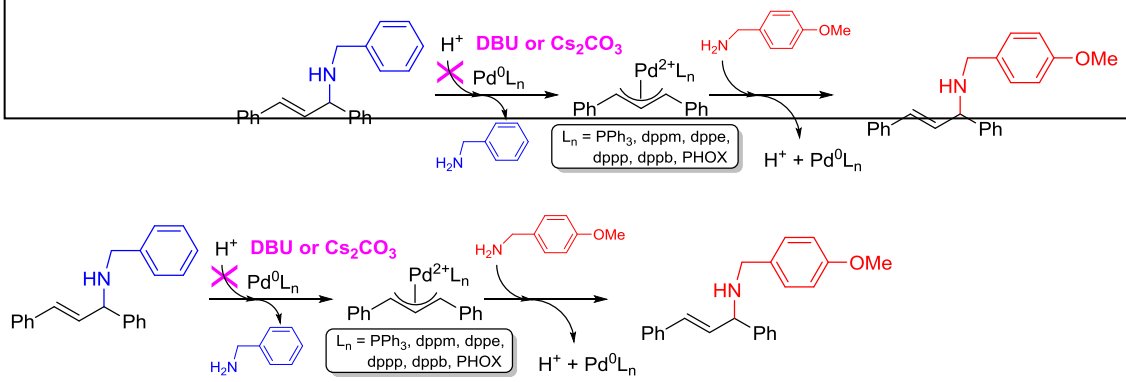

Tetrahedron Letters
journal homepage: www.elsevier.com

Ligand and base additive effects on the reversibility of nucleophilic addition in palladium-catalyzed allylic aminations monitored by nucleophile crossover.

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ARTICLE INFO

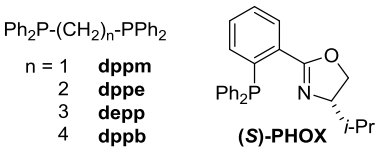
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Palladium catalysis
Allylic amination
Reversibility
Ligand effects
Elimination

ABSTRACT

A nucleophile crossover experiment was used to monitor the reversibility of nucleophilic addition of benzylamine to π-allylpalladium complexes. Dppe, dppp, dppb, and PHOX showed more crossover than PPh_3 and dppm in both DMF and dichloromethane. Crossover was inhibited by the addition of DBU or Cs_2CO_3, but much less elimination to diene side products was observed with Cs_2CO_3. Analysis of percent crossover vs. percent reaction completion using the PHOX ligand revealed that with added DBU or Cs_2CO_3 crossover only began occurring after 100% completion had been reached.

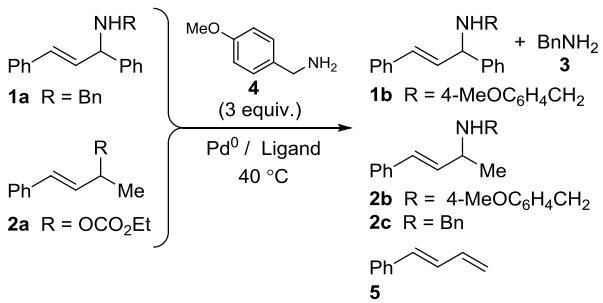
Palladium-catalyzed allylic aminations have been widely studied due to their synthetic utility[1] and the increasing availability of highly enantioselective versions.[2] We recently reported that reversible nucleophilic addition can lower the observed enantioselectivity of allylic amination reactions with a wide range of prototypical chiral ligands.[3] Amatore, Jutand, et al.[4a] have found that nucleophilic addition of amines was reversible with the bidentate ligand dppb but irreversible with the monodentate ligand PPh_3. Based on our interest in chiral ligand design and specific studies with PHOX ligands,[5,6] we wanted to investigate the key ligand, solvent, and base additive factors governing the reversibility of nucleophilic addition of amines.



Our previous study[3] of chiral ligands used time-dependent changes in the product ee to monitor the reversibility. Herein, we employed a nucleophile crossover experiment that provided a quantitative measure of product reversibility and allowed us to study both achiral and chiral ligands. Specifically, we isolated the back-reaction of **1a** to reform the π-allylpalladium intermediate (i.e., reverse of nucleophilic addition) and trapped it with a different amine nucleophile (Scheme 1). We focused on **1a** due to the widespread use of the 1,3-diphenylallyl system as a benchmark test reaction.[7] Phenyl methyl substrate **2a** was added as a co-reactant along with **1a** and **4** because our initial investigations established the necessity of an actively functioning catalyst to observe changes in the product ee. The reaction of **2a** also produced varying amounts of elimination[8] product **5** that depended on the reaction conditions and presence of added base[9]. In some cases we also observed formation of **2c**, which resulted either from reaction of newly formed **3** with **2a** or from "secondary" crossover of **2b**. Because **2c** was formed in very low amounts and only at longer reaction times, we defined the percent crossover and elimination in terms of **1a/b**, **2a/b**, and **5** only (eq. 1-2).[10] We quantified the amounts of all compounds by GC-MS.[11]

$$\text{Percent Crossover} = [\mathbf{1b} / (\mathbf{1a} + \mathbf{1b})] \times 100 \quad (1)$$

$$\text{Percent Elimination} = [\mathbf{5} / (\mathbf{2a} + \mathbf{2b} + \mathbf{5})] \times 100 \quad (2)$$



Scheme 1. Crossover reaction design.

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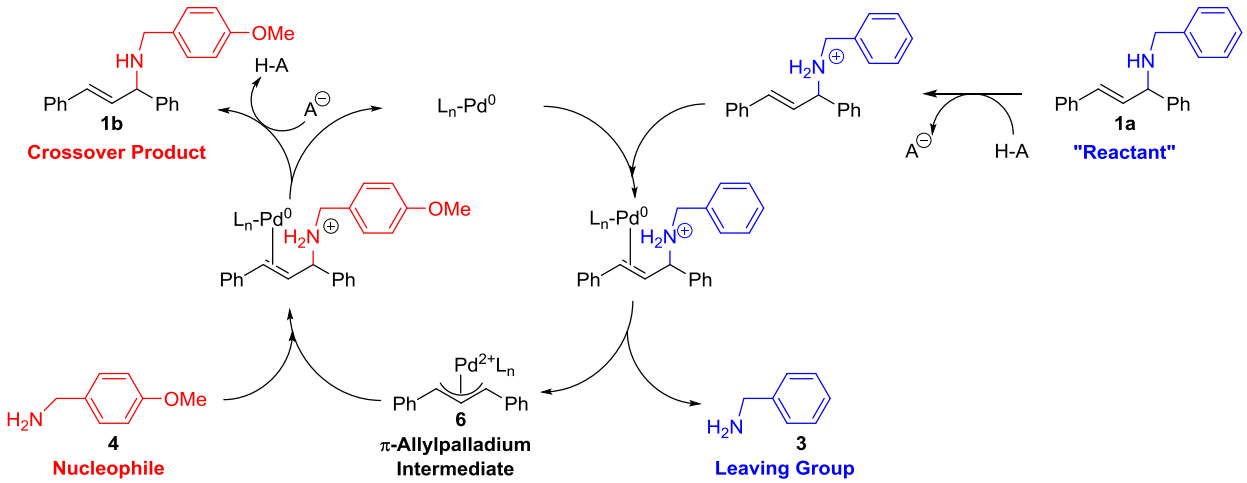


Scheme 2. Nucleophile crossover mechanism.

The crossover mechanism is outlined in Scheme 2. As with the metal-catalyzed isomerization of branched allylic amines to linear isomers elucidated by Yudin,[9,12] formation of **1b** and free benzylamine (**3**) are explained by **1a** re-entering the catalytic cycle to produce a catalytically active π-allylpalladium intermediate (**6**). Thus, detection of crossover products serves as a quantitative marker for the reversibility of an amination reaction that would have initially formed **1a** as a product. We also observed crossover in the other direction—starting with **1b** and **3** to produce **1a** and **4** as crossover products—to establish that this effect was not just a result of the methoxy group label.[13]

We initially studied PPh_3 and the series of bidentate analogs with one to four carbons in the tether (dppm to dppb) in both DMF and dichloromethane (DCM) (Table 1). The solvent choice had little impact on the trends in crossover or elimination. This result supports extending the kinetics findings of Amatore, Jutand, et al. in DMF[4a] to less polar solvents commonly employed in enantioselective reactions.[7] The amount of crossover, however, was very different among the ligands. Very little crossover was observed for PPh_3 and dppm in contrast to dppe, dppp, and dppb, which showed much higher levels of crossover. The dppm result was surprising based on the hypothesis that amination is irreversible with bidentate ligands.[4a]

Table 1.
Crossover and elimination with achiral ligands[a]

Ligand	Solvent	Crossover (%)	Elimination (%)
PPh_3	DMF	3	2
dppm	DMF	2	2
dppe	DMF	65	1
dppp	DMF	63	<1
dppb	DMF	83	2
PPh_3	DCM	4	5
dppm	DCM	4	6
dppe	DCM	43	<1
dppp	DCM	43	<1
dppb	DCM	79	<1

(a) Conditions: 40 °C, 4 h, 10% Pd; average of 3–6 trials.

When additional base (DBU or Cs_2CO), beyond the excess 4-methoxybenzylamine (**4**), was added to the reaction, crossover was almost completely suppressed (Table 2). Just as Yudin showed for amine isomerizations[9,14] and we proposed for enantioselective reactions,[3] added base limits protonation of **1a** and prevents it from re-entering the catalytic cycle that leads to crossover (Scheme 2). The impact of the added base on elimination, however, was more complex. With DBU the amount of elimination product (**5**) was increased in all cases, consistent with general finding that amine bases promote elimination from π-allylpalladium intermediates.[8] In contract, with Cs_2CO_3 increased elimination was only observed with PPh_3 and dppm, the two ligands that showed minimal crossover without added base. We believe this correlation is mechanistically significant and has a unifying explanation.

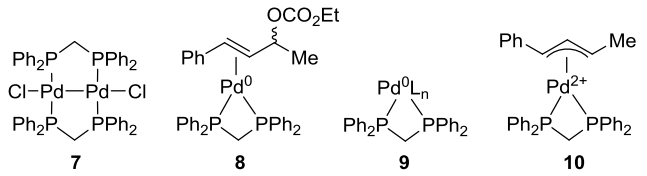
Table 2.
Crossover and elimination with achiral ligands in the presence of added bases[a]

Ligand	Solvent	Base[b]	Crossover (%)	Elimination (%)
PPh_3	DMF	DBU	<1	24
dppm	DMF	DBU	<1	21
dppe	DMF	DBU	<1	50
dppp	DMF	DBU	<1	27
dppb	DMF	DBU	<1	50
PPh_3	DCM	DBU	<1	30
dppm	DCM	DBU	<1	29
dppe	DCM	DBU	<1	31
dppp	DCM	DBU	<1	44
dppb	DCM	DBU	<1	86
PPh_3	DCM	Cs_2CO_3	<1	38
dppm	DCM	Cs_2CO_3	<1	27
dppe	DCM	Cs_2CO_3	<1	5
dppp	DCM	Cs_2CO_3	<1	5
dppb	DCM	Cs_2CO_3	<1	7

(a) Conditions: 40 °C, 4 h, 10% Pd, average of 3–6 trials. (b) 3.2 equivalents.

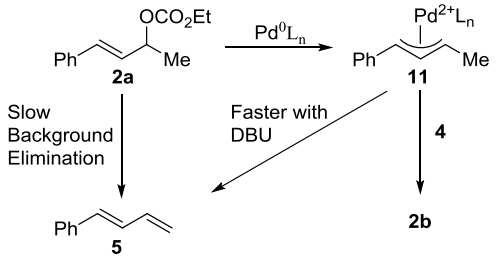
The amount of crossover observed with PPh_3 (low) and dppb (high) in the absence of added base are entirely consistent with the kinetic findings of Amatore, Jutand, et al. on amination reversibility.[4a] However their explanations—the higher nucleophilicity of alkyldiarylphosphinepalladium(0) complexes and the smaller bite angle of dppb favoring oxidative addition for steric reasons—do not account for the low levels of crossover observed with dppm, which is an alkyl diaryl phosphine and should have the smallest bite angle of the bidentate ligands. The

low crossover (i.e., reversibility) observed with dppm could be explained by the formation of off-cycle complexes that lower the concentration and thus net reactivity of the active catalyst. Dppm,[15] in contrast to dppe, dppp, and dppb, readily forms dinuclear palladium bridging complexes such as **7**.[16,17,18]



We conducted a crossover reaction with dppm in CD_2Cl_2 and monitored it by ^{31}P NMR to investigate possible off-cycle complexes. We observed a strong ^{31}P chemical shift at -3.0 ppm, along with a smaller peaks at 13.5 ppm and 25 ppm. The -3.0 ppm shift corresponds quite closely to the reported value[19] of -2.5 ppm for compound **7**. The 13.5 ppm shift (initially larger than the 25 ppm peak) was tentatively assigned to alkene complex **8**, the most likely resting state of the catalytic cycle.[4a,20] Other palladium complexes of the general form Pd(0)L_n (**9**) are possibly responsible for the 25 ppm shift, but we did not investigate them further. It is unlikely that these shifts arise from the π-allylpalladium complex (**10**) as the reported chemical shifts of the analogous dppe complex (phosphines not equivalent) are 46.3 and 49.0 ppm.[21] Formation of complex **7** (or other off-cycle palladium complexes) with dppm would result in a less active / slower ligand/catalyst system and explain the lower amount of crossover observed. This explanation is similar to what Amatore, Jutand, et al. proposed for PPh_3 due to steric factors.[4a]

The lower catalyst activity with PPh_3 and dppm also accounts for the unusual elimination results with Cs_2CO_3. Elimination to **5** can occur directly from **2a** or from π-allylpalladium intermediate[8] **11** prior to formation of amination product **2b** (Scheme 3). In the absence of additional base, the background elimination pathway is slower than the palladium-catalyzed amination pathway (data in Table 1). Soluble organic bases such as Et_3N[8a] and DBU[8b] are known to accelerate elimination from π-allylpalladium intermediates, which is consistent with our observations (data in Table 2). Added base also accelerates the amination of **11** by providing more unprotonated **4** in solution to serve as nucleophile.[22] With DBU these two pathways for **11** are more evenly competitive. With the heterogeneous Cs_2CO_3 base the amination pathway is accelerated more when dppe, dppe, or dppb are used as the ligand. Only with PPh_3 and dppm as ligands are higher levels of elimination observed. If these catalyst systems are slower, as hypothesized, then the background elimination reaction, also likely faster with added base, can become more significant compared to the net flux through **11**.



Scheme 3. Elimination pathways for **2a**.

The success of our crossover experiment at elucidating these subtle ligand and base effects prompted us to study crossover with the PHOX ligand as a prototypical, privileged[23] chiral ligand. As with the achiral ligands both DBU and Cs_2CO_3 effectively prevented crossover with the PHOX ligand (Table 3). Also as observed with the achiral ligands, use of Cs_2CO_3 results in much less elimination than DBU does. Elimination is not an issue for the canonical 1,3-diphenylallyl test substrate (i.e., reactions leading to **1a** as product), but for substrates that have β-hydrogens to eliminate, Cs_2CO_3 would be a much better base additive.

Table 3.
Crossover and elimination with PHOX[a]

Ligand	Solvent	Base[b]	Crossover (%)	Elimination (%)
PHOX	DMF	–	14	1
PHOX	DMF	DBU	<1	48
PHOX	DMF	Cs_2CO_3	<1	7
PHOX	DCM	–	29	1
PHOX	DCM	DBU	<1	64
PHOX	DCM	Cs_2CO_3	2	4

(a) Conditions: 40 °C, 4 h, 10% Pd.

In addition to providing insight into elimination issues, the conversion of **2a** to amine product **2b** and elimination product **5** (eq. 3) also provided a way to analyze the crossover data that offered additional insight into the catalyst behavior.

$$\text{Percent Conversion} = [(\mathbf{2b} + \mathbf{5}) / (\mathbf{2a} + \mathbf{2b} + \mathbf{5})] \times 100 \qquad (3)$$

We ran crossover reactions with the PHOX ligand for varying amounts of time (5 min to 4 h in DMF, 5 min to 36 h in DCM) to obtain a range of percent conversion values without and with added DBU or Cs_2CO_3. The graphs of percent crossover vs. percent conversion look generally similar in DMF (Figure 1) and DCM (Figure 2). Crossover products started appearing (> 1%) around 50% conversion and increased steadily thereafter. In the presence of either DBU or Cs_2CO_3 little to no crossover was observed prior to 100% conversion.

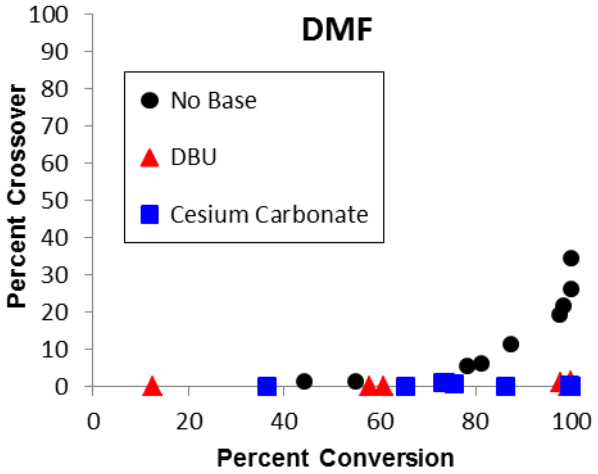


Figure 1. Correlation of of crossover with conversion with PHOX ligand in DMF with and without added bases. Reaction times 5 min to 4 h.

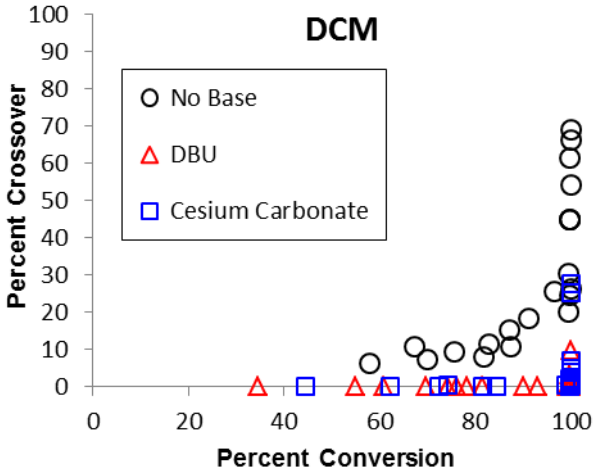


Figure 2. Correlation of of crossover with conversion with PHOX ligand in DCM with and without added bases. Reaction times 5 min to 36 h.

At 100% conversion, the amount of crossover was quite variable—the graph has no measure of how far or long past completion the reaction had proceeded. In DCM in particular we allowed several reactions to go long past (24-36 h) the time necessary for complete reaction of **2a**. In these cases much larger amounts of crossover were obtained, even in the presence of added base (although less crossover than without base). Based on the 3:1 net ratio of **4**/**3** in the reaction system, 70% crossover is likely close to the thermodynamic mixture of **1b**/**1a**.[24]

Overall, these conversion vs. crossover graphs provide a consistent picture of the PHOX catalyst behavior that extends what was learned from the achiral ligand experiments. The catalysts all prefer allyl carbonate **2a** to allyl amine **1a** as a substrate. In the presence of additional base (DBU or Cs_2CO_3) this preference is nearly absolute. In the absence of additional base or at very long reaction times, the catalysts will more slowly start converting **1a** to **1b** via π-allylpalladium intermediate **6**. These findings substantiate our explanation that added base can increase the observed enantioselectivity in allylic amination reactions by preventing product equilibration through reversible nucleophilic addition.[3] This effect is now clearly understood in terms of the crossover reaction mechanism which provides direct evidence for the reversibility of nucleophilic addition under similar reaction conditions. Finally, Cs_2CO_3 is a better base additive than DBU if substrate elimination to form unwanted diene side products is possible. We are currently using the crossover reaction to investigate the generality of these findings with other chiral ligands.

Acknowledgments

We thank the Donors of The Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE-071451) for support of this research. N. S. C., M. B. G., and I. N.-M. L. thank Middlebury College for summer financial support.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at doi.

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