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Reversible nucleophilic addition can lower the observed enantioselectivity in palladium-catalyzed allylic amination reactions with a variety of chiral ligands

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ABSTRACT

Palladium-catalyzed allylic amination is an important synthetic reaction that is also frequently used as a benchmark for the design and evaluation of new chiral ligands. The effect of reversible nucleophilic addition on the reaction of benzylamine with (*E*)-1,3-diphenylallyl ethyl carbonate (**1**) in CH_2Cl_2 was examined with 12 different chiral ligands across a range of scaffolding types. In 8 out of 12 cases the observed ee was significantly higher when DBU or Cs_2CO_3 was added to suppress the proton-driven reversibility. For chiral ligand screening with this test reaction, adding DBU or Cs_2CO_3 provides a better measure of the ligand's inherent enantioselectivity.

Enantioselective allylic substitutions have proven very effective for synthesizing chiral molecules,[1] and palladium-catalyzed allylic aminations, in particular, have been widely studied due to their utility.[2] During our ongoing Hammett studies of electronically modified phosphinooxazoline (PHOX) ligands,[3,4] we noted some unusual and inconsistent enantioselective results with palladium-catalyzed benzyl amine additions to 1,3-diphenylallyl substrates that led us to believe that reversible product formation was lowering the observed enantioselectivities. Previous mechanistic studies by Amatore and Jutland[5] have established the reversibility of product formation with secondary amine nucleophiles and achiral bidentate ligands. Additionally, regiospecific formation and isomerization during palladium-catalyzed synthesis of unsymmetrical allylic amine products (branched vs linear) have demonstrated that the reaction conditions have a large impact on the reversibility of product formation.[6–8] Yudin[6a,g] showed that adding 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), but few other bases they screened,[9] significantly increased the reaction selectivity for the kinetically favored, branched allyl amine isomer by preventing or greatly reducing its proton-driven isomerization to the linear product that proceeds via reformation of the π-allylpalladium intermediate.

Because of our own observations with modified PHOX ligands and the widespread use of allylic amination as a benchmark test reaction for asymmetric catalysis and chiral ligand design,[10] we undertook a wider study of enantioselective palladium-catalyzed allylic aminations. Herein, we present the first examples of asymmetric palladium catalysis in which the reversible nucleophilic addition of benzylamine can lower the observed enantioselectivity. We found that DBU and Cs_2CO_3, a base not previously examined, can mitigate these effects with most of the chiral ligands tested.

Initially, we examined the enantioselectivity obtained with the (*S*)-PHOX ligand (**4**) as a function of reaction time using racemic carbonate **1** and benzylamine as the nucleophile (Scheme 1). We employed CH_2Cl_2 as the solvent because it showed a greater propensity than THF for product isomerization[6a] and we wanted to test the enantioselectivity under potential 'worst case' conditions. We found that in the absence of added base the observed ee of (*R*)-**3** dropped significantly over time (Fig. 1). In contrast, when 3.2 equiv of DBU or Cs_2CO_3 were employed as a base additive for the reaction, the observed ee remained both high and constant over time. Based on TLC and GC/MS analysis, the reaction with ligand **4** went to completion in 2–3 h without added base and 15–30 min with added base.[11] Consequently, the 0.25 h and 1 h time points without DBU or Cs_2CO_3 are particularly notable because they show significant erosion of the product ee before the reaction is even complete.

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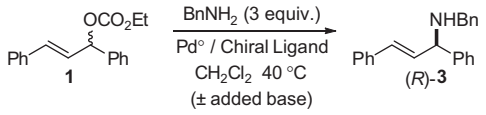


Scheme 1. Standard test reaction for enantioselective amination.

The observed ee with no base at 24 h has a larger standard deviation because the catalyst does not always remain active well beyond the time necessary for the reaction to go to completion. Once the active catalyst 'dies' (formation of palladium black or other catalytically inactive species), the ee stays fixed at that value regardless of the length of time the reaction is allowed to proceed. Control reactions in which isolated samples of (*R*)-**3** were resubjected to the reaction conditions without additional starting material (**1**) did not show any change in the ee. However, when a small amount of **1** was included, the ee of **3** decreased by much more than could be accounted for by the additional amount of **3** produced in the reaction (data not shown). Thus, an actively functioning catalyst is necessary to observe the back reaction of **3**, which lowers the ee. We found that the rigorous exclusion of oxygen using strict purge/backfill protocols with argon helped maintain the active catalyst lifetime. The general robustness of π-allylpalladium chemistry to air and water can obscure this point, as indeed, such measures are not typically necessary.[12]

The racemization mechanism that equilibrates (*R*)-**3** and (*S*)-**3** is shown in Scheme 2. With ligand **4**, for example, the π-allylpalladium complex (**2**) initially forms (*R*)-**3**-H$^+$ with high enantioselectivity. The discrete Pd(0)–alkene complex has been omitted from Scheme 2 for simplicity as the timing of its formation or breakdown with respect to the proton transfer step does not impact this analysis. (*R*)-**3**-H$^+$ is then reversibly deprotonated by either the excess benzylamine, another product molecule, or the ethyl carbonate leaving group acting as a base (A$^-$) to give (*R*)-**3**. As the reaction proceeds, more protons are generated and eventually the palladium-catalyzed back reactions (dashed arrows) to reform **2** become favorable. Because (*R*)-**3** is present in higher concentrations due to the catalyst's high enantioselectivity, its back reaction is favored over the back reaction of (*S*)-**3**. Effectively (*R*)-**3** and (*S*)-**3** are in equilibrium because (*S*)-**3** can also reform **2**, albeit at a slower rate initially. If the reaction is allowed to proceed long enough and the palladium-catalyst remains active, an equal mixture of (*R*)-**3** and (*S*)-**3** will result regardless of the initial ligand enantioselectivity as an ultimate consequence of thermodynamics.

We next investigated the scope of reversible product formation and the generality of DBU and Cs_2CO_3 in preventing it. We selected a variety of commercially available chiral ligands (**5**–**15**) having both C_1 and C_2 symmetry across a range of scaffolding types including many of the so called 'privileged' chiral ligands[13] (Fig. 2). We carried out the same test reaction for each one, but

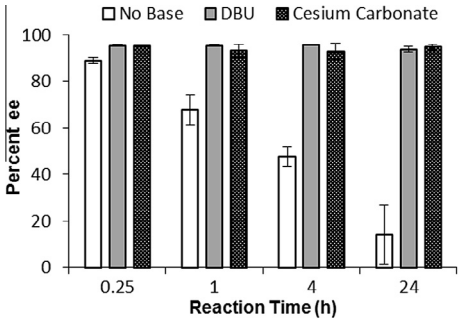
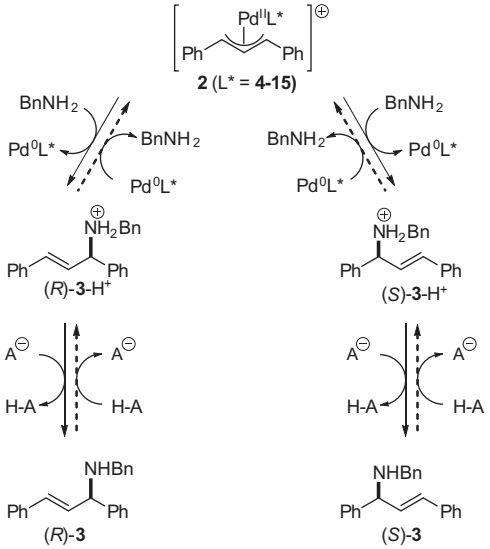


Figure 1. Effect of reaction time and added base on the observed ee of (*R*)-**3** with ligand **4** (PHOX). Each time point is the average of **4**–**7** individual reaction trials with error bars showing ±1 standard deviation.



Scheme 2. Mechanism for equilibration of (*R*)-**3** and (*S*)-**3**.

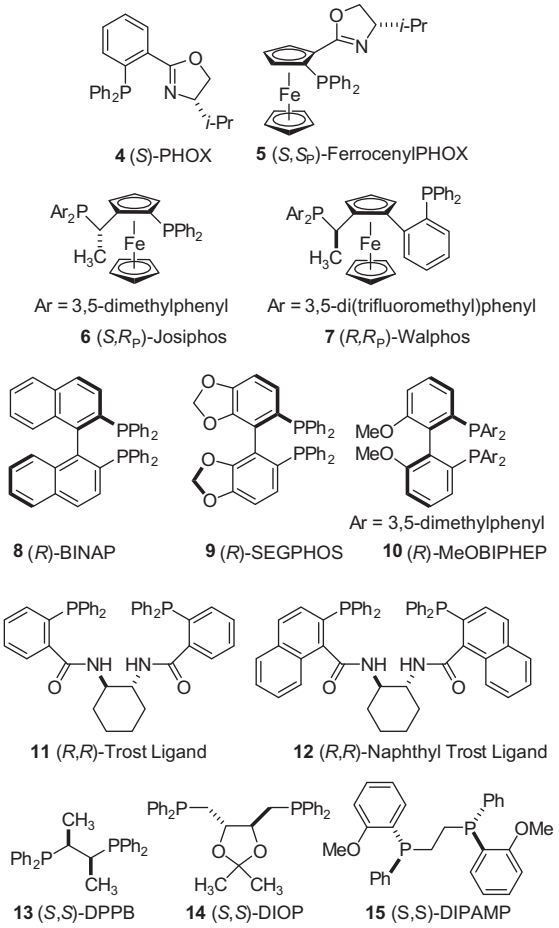


Figure 2. Structures of chiral ligands **4**–**15**.

did not attempt to optimize the reaction conditions (time, temperature, or solvent) to obtain the best enantioselectivity for each chiral ligand. Rather, we kept the reaction conditions standard (Scheme 1) and looked for differences in the ee when DBU or Cs_2CO_3 were added (Table 1). We used 4 h as the initial reaction time for each ligand. If the reaction was not complete in 4 h, we used 24 h for that ligand.