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# Palladium/BINAP(S)-Catalyzed Asymmetric Allylic Amination

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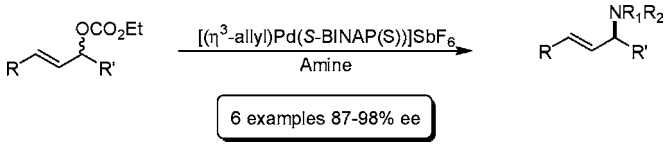
## ABSTRACT

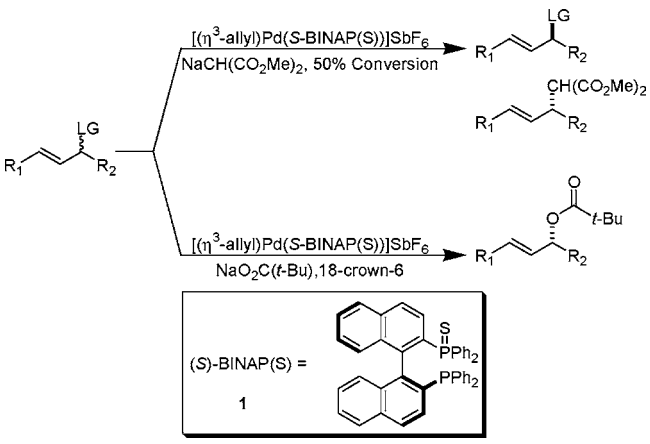



**The enantioselective allylic amination of acyclic allylic carbonates catalyzed by a palladium/(*S*)-BINAP(S) system was investigated. Amination of several substrates proceeded with high ee. Crotyl carbonates show an unusually high regioselectivity for the branched isomer. The use of (*S*)-TolBINAP(S) and (*S*)-3,5-xylyl-BINAP(S) as ligands was found to increase the enantioselectivity of the aminations. A *P,S* binding mode of the BINAP(S) ligand was found in an X-ray crystallographic study.**

The transition-metal-catalyzed allylic substitution reaction has developed into a powerful and versatile synthetic method in recent years.[1,2] In particular, the synthesis of secondary and tertiary allylic amines via this method has become an invaluable tool for synthetic chemists, as these types of amines are otherwise difficult to prepare.[3−14]

We have recently reported the highly selective Pd-catalyzed kinetic resolution of allylic esters[15] as well as a Pd-catalyzed asymmetric synthesis of allylic esters[16] utilizing the readily prepared heterobidentate BINAP(S) ligand **1** (Scheme 1). We were pleased to find that this system was also effective for the allylic amination of various classes of allylic substrates with several different classes of amine with high enantioselectivity.

**Scheme 1**

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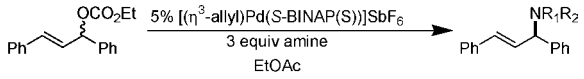
In addition, we wish to report the unambiguous identification of a $\kappa^2$-*P*,*S* binding mode of BINAP(S) on Pd based on an X-ray crystallographic study.

Our investigation into the Pd/(*S*)-BINAP(S)-catalyzed allylic amination was initiated using the ethyl carbonate of 1,3-diphenylallyl alcohol **2**. The results are summarized in Table 1. Primary amines benzylamine and allylamine (entries 1 and 2) reacted smoothly under our optimized conditions to produce allylic amines **3a** and **3b** with excellent enantioselectivity. Under the same conditions, the use of the secondary amines morpholine and piperidine (entries 3 and 5) led to diminished enantioselectivities.

**Table 1.** Allylic Amination of **2** with Various Amines[a]




**2** **3a-f**

Amines:
a = benzylamine d = piperidine
b = allylamine e = potassium phthalimide
c = morpholine f = sodium *p*-toluenesulfonamide

| entry | amine | *T* (°C) | *t* (h) | conversion[b] (%) | ee[c] (%) | abs config[d] |
|---|---|---|---|---|---|---|
| 1 | **a** | −25 | 24 | 99 | 95 | (−)-(*R*) |
| 2 | **b** | −25 | 24 | 99 | 94 | (−) |
| 3 | **c** | −25 | 0.5 | 99 | 55 | (−)-(*R*) |
| 4[e] | **c** | −25 | 16 | 99 | 89 | (−)-(*R*) |
| 5 | **d** | −25 | 0.5 | 99 | 75 | (−)-(*R*) |
| 6[e] | **d** | −25 | 16 | 99 | 90 | (−)-(*R*) |
| 7 | **e** | rt | 21 | 99 | 97 | (−)-(*R*) |
| 8 | **f** | rt | 48 | 0 | N/A | N/A |

[a] For general experimental procedure, see the Supporting Information. [b] Determined by $^1$H NMR spectroscopy of the quenched crude reaction mixture. [c] Determined by $^1$H NMR chiral shift experiments using (−)-MTPA as shift reagent. [d] Assigned by comparison of sign of optical rotation with published values. [e] Performed at 5× dilution.

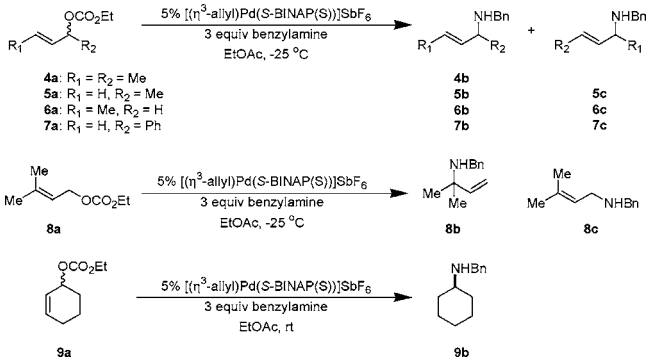
Interestingly, upon dilution of the overall reaction concentration by a factor of 5 (entries 4 and 6), products **3c** and **3d** were obtained in comparable enantiomeric excesses as their primary amine counterparts.

These results can be rationalized in terms of a memory effect,[3,17−20] i.e., an incomplete scrambling of stereochemical information of the initially formed Pd-$\pi$-allyl intermediate. Presumably, nucleophilic attack on the Pd-$\pi$-allyl intermediate is a second-order process, whereas the Pd-$\pi$-allyl diastereomeric equilibration is a first-order process. Therefore, by diluting the reaction mixture, nucleophilic attack should be slowed with respect to Pd-$\pi$-allyl diastereomeric equilibration. This allows for the establishment of the Curtin−Hammett conditions necessary to produce high ee's when using chiral racemic substrates in the Pd-catalyzed allylic substitution reaction.

Phthalimide derivative **3e** (a precursor to primary amines) was produced in high ee, but unfortunately the reaction with sodium *p*-toluenesulfonamide did not proceed even after prolonged reaction times.

Having established that this system allowed reaction with a range of amines, the reaction scope with respect to different allylic substrates (Table 2) was examined. We were pleased to find that sterically less demanding substrate **4a** was aminated in 87% ee; this represents a significant improvement over the previous best result (73%) for this substrate.[3]

**Table 2.** Allylic Amination of Various Substrates with Benzylamine[a]




| entry | substrate | *T* (°C) | *t* (h) | % conversion[b] | **b**/**c**[b,c] | ee (%) | abs config[f] |
|---|---|---|---|---|---|---|---|
| 1 | **4a** | −25 | 22 | 99 | N/A | 87[d] | (−)-(*S*) |
| 2 | **5a** | −25 | 22 | 99 | 93:7 | 44[d] | (+)-(*S*) |
| 3 | **6a** | −25 | 22 | 99 | 6:94 | 45[d] | (+)-(*S*) |
| 4 | **7a** | −25 | 18 | 99 | 0:100 | N/A | N/A |
| 5 | **8a** | −25 | 22 | 99 | 91:9 | N/A | N/A |
| 6 | **9a** | rt | 22 | 99 | N/A | 13[e] | (−)-(*S*) |

[a] For general experimental procedure, see the Supporting Information. [b] Determined by $^1$H NMR spectroscopy of the quenched crude reaction mixture. [c] Note that **5b** = **6c** which are the branched products. [d] Determined by $^1$H NMR chiral shift experiments using (−)-MTPA as shift reagent. [e] Determined by HPLC. [f] Assigned by comparison of sign of optical rotation with published values.

Unsymmetrically substituted substrates **5a**, **6a**, and **7a** allowed us to examine the regioselectivity of this catalytic system along with its enantioselectivity. In accordance with our previous studies, regioisomeric substrates **5a** and **6a** were preferentially substituted in the more-substituted position to yield branched products with moderate ee. Even the doubly substituted terminus of the 3-methylbut-2-en-1-yl ester **8a** was aminated with 91% regioselectivity. *This observed regioselectivity is the reverse of that found for most Pd systems*,[2] which give predominantly linear substitution products. This is in contrast to metals such as Ir,[7,10,11,21] Rh,[6,22] Mo,[23] and Ru,[24] which favor the branched substitution

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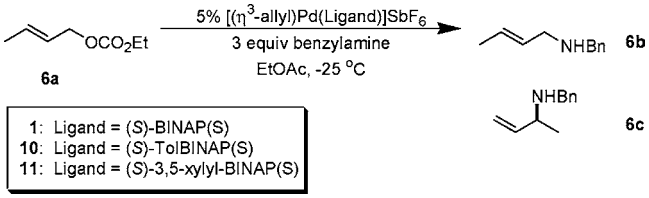
products. The cinnamyl substrate **7a**, however, was substituted exclusively in the less substituted position, giving rise to achiral **7b** under the conditions examined.

The cyclohexenylamine **9b**, however, was produced with low enantioselectivity for reactions carried out at ambient temperature. Low enantioselectivity for cyclic substrates is frequently encountered, but high enantioselectivity can occasionally be observed.[4,25]

In an attempt to increase the ee of the branched product **5b**/**6c**, allylpalladium complexes **10** and **11** derived from the monosulfides of (*S*)-TolBINAP[26] and (*S*)-3,5-xylyl-BINAP, respectively, were prepared and tested in the amination of **6a** with benzylamine (Table 3). Using **10** and **11** as catalysts,

**Table 3.** Ligand Effects on Amination of **6a** with Benzylamine




| entry | catalyst | **b/c** | ee | abs config |
|---|---|---|---|---|
| 1 | **1** | 6:94 | 45 | (+)-(*S*) |
| 2 | **10** | 5:95 | 58 | (+)-(*S*) |
| 3 | **11** | 5:95 | 65 | (+)-(*S*) |

**6c** was produced with similar regioselectivity, but with significantly enhanced enantioselectivity with respect to using the catalyst derived from **1**. The methyl substituents apparently enhance the chiral environment presented by the parent (*S*)-BINAP(S) ligand.[27]

To elucidate further the factors controlling the regio- and enantioselectivity observed in these reactions, X-ray crystallographic studies were performed on complexes **12** and **13** (Figures 1 and 2). Interestingly, the P2−S−Pd angle in both complexes is ∼105° as compared to a recently reported[28] analogous structure to **13** using (*S*)-BINAP(O) as a ligand in which the P−O−Pd angle is 130°. This can be attributed to the preference for sulfur to use pure *p*-orbitals relative to the greater hybridization observed with oxygen. The effect of this large difference in bond angles is to orient the naphthyl group attached to the phosphine sulfide underneath the allylic portion of the complex to a much greater extent than in the BINAP(O) complex. This modification of ligand backbone orientation resulting from the use of a sulfur donor rather than oxygen may have important consequences with

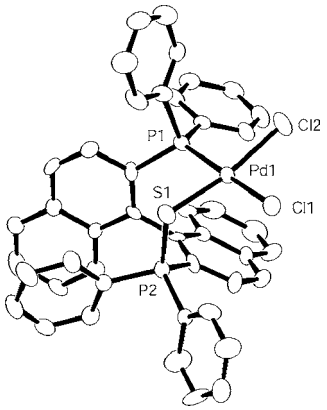



**Figure 1.** ORTEP diagram of (*S*)-BINAP(S)PdCl$_2$ (**12**): Pd1−Cl1 = 2.342(2); Pd1−Cl2 = 2.314(2); P2−S1−Pd1 = 105.5(1).

respect to the inverse regioselectivities that we observe relative to most Pd-catalyzed allylic substitutions. The greater trans influence of P versus S is also evident in the elongation of the bonds to atoms trans to P relative those trans to S.

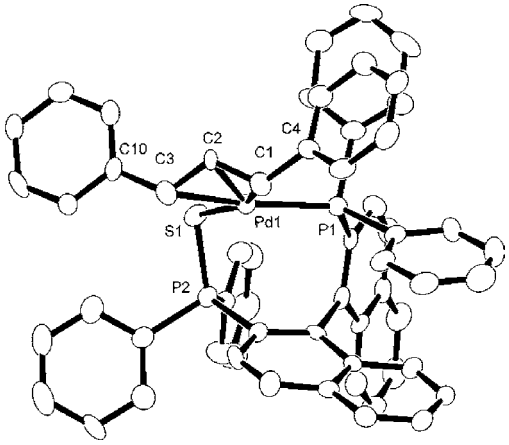



**Figure 2.** ORTEP diagram of [($\eta^3$-allyl)Pd(*S*-BINAP(S)]BF$_4$ (**13**): Pd1−C1 = 2.205(6); Pd1−C3 = 2.225(7); P2−S1−Pd1 = 104.6(1).

The crystal structures show that there is a Pd−S bond in the isolated allyl complex; however, it is possible that under the catalytic reaction conditions the sulfur could be displaced by ethyl carbonate and the BINAP(S) functions as a hemilabile monodentate ligand.[28] This could account for some of the memory effects observed.

In conclusion, the allylic amination of a structurally diverse set of allylic substrates was achieved with high regio- and enantioselectivity. This easily prepared system provides one of the few cases where >90% regioselectivity for the branched isomer is observed for crotyl substrates in pal-

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ladium-catalyzed reactions.[2,12,30] Modification of the parent bisphosphine monosulfide **1** led to an increase in enantioselectivity for the amination of the crotyl substrate while retaining high regiocontrol.

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**Supporting Information Available:** Synthetic procedures and characterization data for complexes **10**−**13**, preparation of (*S*)-3,5-xylyl-BINAP(S), general procedure for allylic aminations, as well as X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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