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Synthesis and exploration of electronically modified (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX in palladium-catalyzed enantio- and diastereoselective allylic alkylation: a practical alternative to (*R*)-(*p*-CF_3)$_3$-*t*-BuPHOX

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ABSTRACT

The synthesis of the novel electronically modified phosphinooxazoline (PHOX) ligand, (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX, is described. The utility of this PHOX ligand is explored in both enantio- and diastereoselective palladium-catalyzed allylic alkylations. These investigations prove (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX to be an effective and cost-efficient alternative to electronically modified PHOX ligands derived from the prohibitively expensive (*R*)-*t*-leucine.

Introduction

Phosphinooxazoline (PHOX) ligands, developed by Helmchen,[1] Williams,[2] and Pfaltz,[3] have proven to be a privileged ligand scaffold in transition metal catalysis.[4] PHOX ligands have found application in a variety of asymmetric transition metal-catalyzed transformations including asymmetric hydrogenation,[5] azomethine ylide cycloadditions,[6] intermolecular Heck couplings,[7] and hydrosilylation[8] as well as transition metal-catalyzed allylic substitution[4,9] and protonation[10] reactions. Our lab has extensively explored the utility of the PHOX ligand scaffold in the palladium-catalyzed enantioselective allylic alkylation of carbocyclic[11] and heterocyclic[12] substrates. These investigations have revealed electronically modified PHOX ligands (i.e. (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***S*****)-L1**), Fig. 1)[13] can profoundly enhance the rate of reaction as well as yield, enantiomeric excess (*ee*) and/or diastereomeric ratio of a product containing an all-carbon quaternary center (e.g. use of (***S*****)-L1** vs (***S*****)-L2** to construct lactam **2**,[12e] cyclohexanone **4**,[13c] cyclohexenone **6**,[13b] and cyclohexanone diastereomers **9** and **10**,[14] Schemes 1A–C and 2, respectively).

Most commonly, transition metal complexes employing *tert*-leucinol-derived PHOX ligands (e.g. (***S*****)-L1** and (***S*****)-L2**, Fig. 1) enable the formation of the corresponding products with the best enantiomeric and diastereomeric ratios. Although (*R*)-*t*-BuPHOX has been employed in natural product synthesis[15] and explored in transition-metal catalyzed allylic alkylations,[10a,16] these examples are quite rare considering the nearly prohibitive cost of the requisite starting material for ligand synthesis, (*R*)-*t*-leucine.[17] Previously, 5,5-geminally disubstituted (*R*)-valine-derived PHOX ligands (e.g. (***R*****)-L3** and (***R*****)-L4**, Fig. 2) have been constructed as cost-effective alternatives to (*R*)-*t*-BuPHOX ((***R*****)-L2**).[18] We sought to extend this precedent to the synthesis of electronically modified congener (*R*)-5,5-dimethyl-(*p*-CF_3)$_3$-*i*-PrPHOX ((*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2}, (***R*****)-L5**, Fig. 2) and explore its efficacy as a ligand in palladium-catalyzed enantio- and diastereoselective allylic alkylation reactions.

Results and discussion

Synthesis of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((*R*)-L5)

Synthesis of (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R*****)-L5**) was initiated with acid chloride **11**[19] and the hydrogen chloride salt of (*R*)-valine derivative **12**[18] (Scheme 3). Intermolecular coupling of acid chloride **11** and amino alcohol **12** in the presence of excess Et_3N provides amide **13** in 79% yield. Intramolecular cyclization of amide **13** under acidic conditions furnishes oxazoline **14** in 87% yield.

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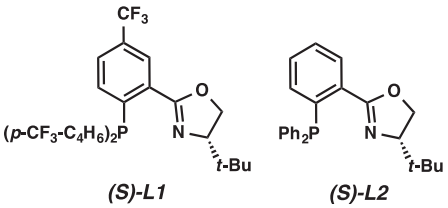
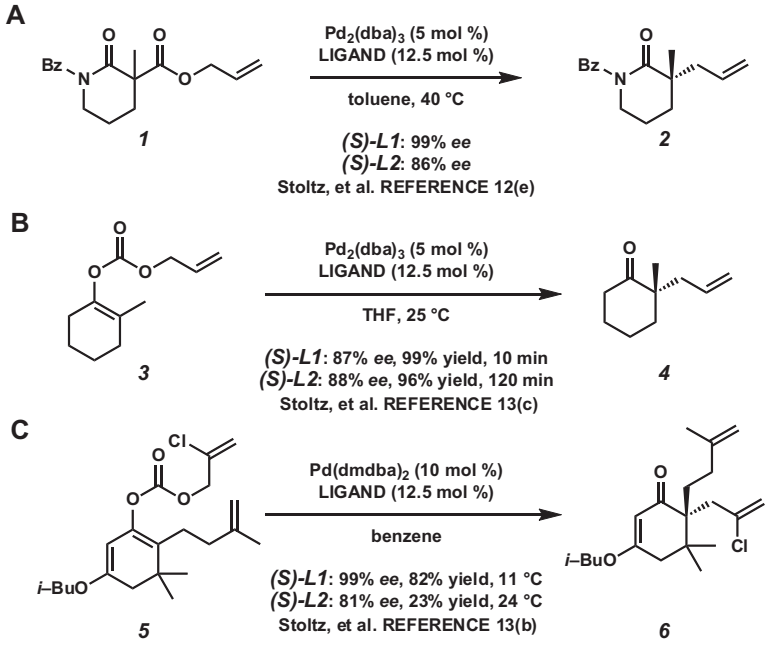


Figure 1. Electronically modified and unmodified (*S*)-*t*-BuPHOX ligands.

Completion of desired ligand (***R***)-**L5** was accomplished over two steps, beginning with the copper-mediated coupling of phosphine oxide **15** with bromide **14** at elevated temperature.[20] This procedure produces phosphine oxide **16** in 63% yield. Reduction of phosphine oxide **16** was subsequently accomplished in neat Ph_2SiH_2 at 140 °C over 48 hours, providing the desired ligand (*R*)-(*p*-CF_3)$_3$-*i*-PrPHOX^{Me2} ((***R***)-**L5**) in 81% yield in the final step of the synthetic sequence.



Scheme 1. Comparison of electronically modified (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***S***)-**L1**) and unmodified (*S*)-*t*-BuPHOX ((***S***)-**L2**) in intramolecular palladium-catalyzed enantioselective allylic alkylation.

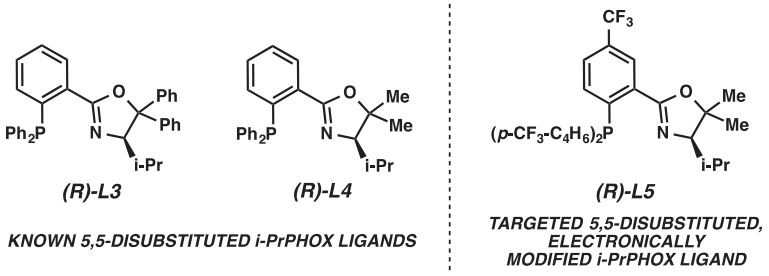
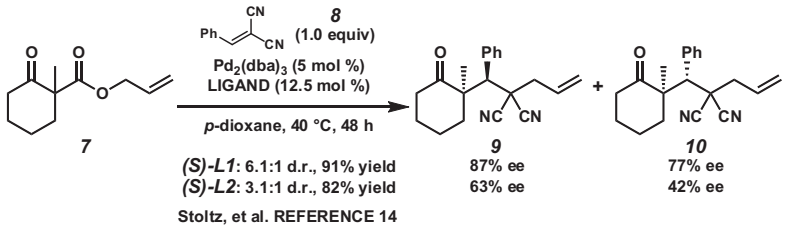


Figure 2. 5,5-Geminally disubstituted (*R*)-valine-derived PHOX ligands.



Scheme 2. Comparison of electronically modified (*S*)-(*p*-CF_3)$_3$-*t*-BuPHOX ((***S***)-**L1**) and unmodified (*S*)-t-BuPHOX ((***S***)-**L2**) in diastereoselective decarboxylative alkylation cascade.