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Palladium-Catalyzed Asymmetric Amination and Imidation of 2,3-Allenyl Phosphates

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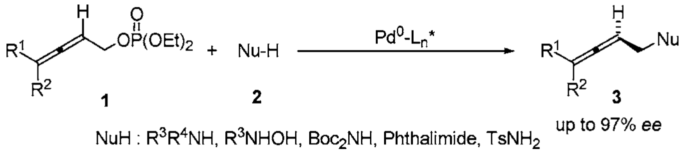
ABSTRACT



Asymmetric amination of 2,3-allenyl phosphates with nitrogen nucleophiles such as amines, hydroxylamines, and imides can be performed efficiently using a combination of zerovalent palladium complexes and SEGPHOS or MeOBIPHEP ligand, affording the corresponding optically active 1-aminated derivatives with enantiomeric excess of up to 97% ee.

Due to specific axial chirality, optically active allenes have been used as useful synthetic intermediates for various reactions such as cycloaddition, oxidation, and coupling reactions.[1] In general, they are prepared by conventional methods, including optical resolution from allenyl carboxylic acids and chirality transfer of optically active propargyl alcohols.[2] An attractive strategy for preparing these compounds is direct conversion of racemic or achiral compounds; however, previous methods along this line are limited to reactions resulting in low enantioselectivities of 20−60% ee.[3] During the course of our systematic studies on catalytic transformations of allyl phosphates via π-allylpalladium intermediates, various useful molecular transformations have been developed utilizing the excellent leaving ability of the phosphate group.[4] To extend this principle, we succeeded in developing a catalytic, enantioselective method for alkylation of 2,3-allenyl phosphates by controlling the axial chirality of the products through α-methylene π-allylpalladium intermediates.[5−7] The reaction provides a practical method for direct asymmetric functionalization of 2,3-allenyl substrates. In this paper, we describe the application of this method to catalytic asymmetric aminations using a variety of nitrogen nucleophiles, affording optically active 2,3-allenylamine derivatives, which are a synthetically and biologically important class of compounds (Scheme 1).[8]

Various parameters for asymmetric induction were examined for the reaction of diethyl 5,5-dimethyl-2,3-hexadienyl

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(6) Synthesis of optically active allenes by palladium-catalyzed asymmetric alkylation of 2-bromo-1,3-alkadienes with malonate esters: Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089.

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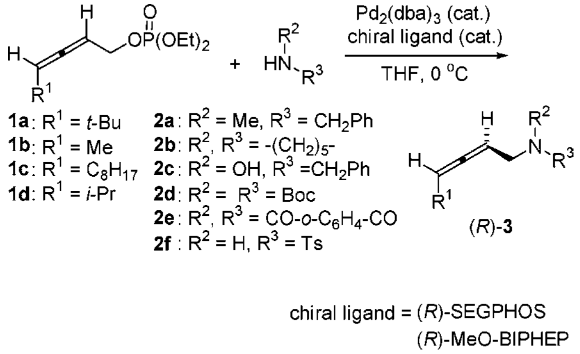
Scheme 1



phosphate (**1a**) with *N*-methylbenzylamine (**2a**). High enantioselectivity of the product (*R*)-**3aa** (84% ee)[9] was obtained with the catalyst prepared in situ from $Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*)-SEGPHOS[10] at room temperature. The use of (*R*)-MeO-BIPHEP[11] as a ligand gave 84% ee of **3aa** under similar conditions, while other chiral ligands, such as BINAP and H^8-BINAP, yielded low product enantioselectivity. Greater asymmetric induction can be achieved at 25 °C or below, and similar treatment with (*R*)-SEGPHOS at 40 °C gave lower selectivity (72% ee). THF was the best solvent; other solvents such as toluene, Et_2O, CH_3CN, and EtOH gave unsatisfactory results.

Asymmetric amination of 2,3-allenyl phosphates can be performed with a variety of amine nucleophiles as shown in Table 1. Typically, the reaction of **1a** with piperidine (**2b**) in the presence of $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and (*R*)-SEGPHOS (5.0 mol %) in THF at 0 °C gave (*R*)-1-(5,5-dimethyl-2,3-hexadienyl)piperidine (**3ab**) with 91% ee (entry 3). It is noteworthy that the method can be applied to the synthesis of optically active *N*-2,3-allenylhydroxylamines (entry 4), which can be readily converted to nitrones, important synthetic intermediates, via catalytic oxidation.[4b] The present method can be applied to a variety of imide nucleophiles, using nearly 1 equiv of 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) as an organic base. Thus, similar treatment of **1a**−**d** with iminodicarboxylic acid di-*tert*-butyl ester (**2d**) gave the protected 2,3-allenylamines with 82−97% ee (entries 5−8). Other imide nucleophiles, such as phthalimide (**2e**) and *p*-toluenesulfonamide (**2f**), also gave the corresponding products with high enantioselectivity (entries 9 and 10).

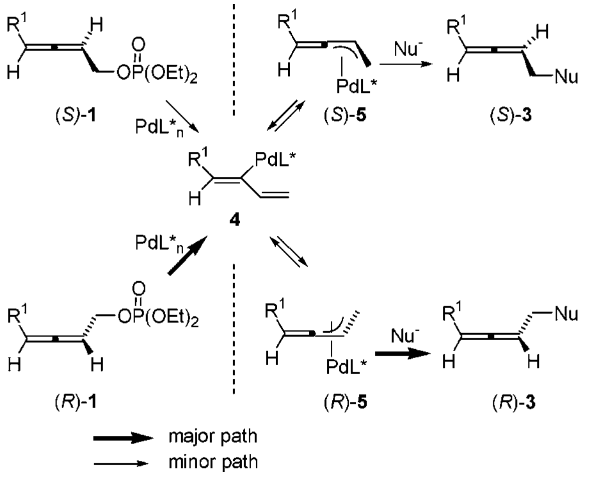
Table 1. Asymmetric Amination and Imidation of 2,3-Allenyl Phosphates[a]

entry	phosphate	nucleophile	product	yield of **3**, %[b]	ee of **3**, %[c]
1[d]	**1a**	**2a**	**3aa**	72	84
2[d,e]	**1a**	**2a**	**3aa**	90	84
3	**1a**	**2b**	**3ab**	56	91
4	**1a**	**2c**	**3ac**	59	76
5[f]	**1a**	**2d**	**3ad**	77	97
6[f]	**1b**	**2d**	**3bd**	60	85
7[f]	**1c**	**2d**	**3cd**	85	82
8[f]	**1d**	**2d**	**3dd**	51	87
9[f]	**1a**	**2e**	**3ae**	64	83
10[f]	**1a**	**2f**	**3af**	26	80

[a] All reactions were conducted in THF (0.075 M) at 0 °C for 16−25 h. The ratio of **1**/**2**/$Pd_2(dba)_3{\cdot}CHCl_3$/(*R*)-SEGPHOS was 100/110/2.5/5.0. [b] Isolated yield. [c] Determined by HPLC or GLC analysis using a chiral stationary phase column. [d] The reaction was performed at 25 °C. [e] (*R*)-MeO-BIPHEP was used instead of (*R*)-SEGPHOS. [f] DBU (1.3 equiv) was added.

To gain insight into the mechanism for the asymmetric induction, time dependencies of the optical activities of the phosphate and the product were determined by HPLC analysis of the reaction of **1a** with **2d** under standard conditions using *N*,*O*-bis(trimethylsilyl)acetamide as a base at 25 °C. The enantiomeric excess value of the product (*R*)-**3ad** was consistently 86−89% ee at all stages of the reaction, and that of the remaining (*S*)-**1a** increased, even after 50% conversion of **1a**, eventually reaching 84% ee at 77% conversion. Calculated *E* values[12] were consistently in the range of 4.1−4.2. These results can be ascribed to inclusion of two independent asymmetric inductions[13] in the catalytic process, as shown in Scheme 2. The first static kinetic resolution occurs via enantiomer-differentiating oxidative addition of a chiral palladium species to **1** to afford σ-1,3-

Scheme 2



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[13] Asymmetric synthesis of allylic sulfides, allylic sulfones, and allylic alcohols: Gais, H.-J.; Hagusch, T.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem.−Eur. J.* **2003**, *9*, 4202.

alkadien-3-yl palladium intermediate **4**, which is in equilibrium with (*S*)- and (*R*)-forms of α-methylene π-allylpalladium intermediates **5**.[5,6] The second asymmetric induction occurs during nucleophilic attack of nitrogen nucleophiles to **5** with assistance of the chiral ligand on the palladium, affording the corresponding optically active 2,3-allenylamine derivatives.

Efforts are currently underway to investigate the full scope of the reaction and to provide definitive mechanistic information.

Supporting Information Available: Experimental results and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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