# The application o monoterpene derived chiral ligands in Tsuji-Trost reaction

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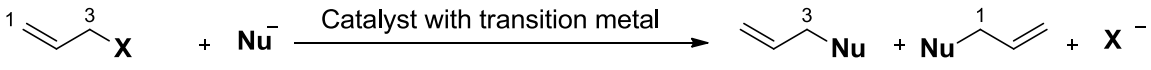
Allylic substitution catalyzed with transition metals is a widely used and universal reaction in modern organic synthesis. The new carbon-carbon and carbon-heteroatom bonds are created in this reaction (Scheme 1). The allylic substitution proceeds under mild conditions, milder than SN2. Moreover, this method is effective for a variety of functional groups and in many cases leads to obtain a product in high enantioselectivity, and therefore has a high potential for application in the synthesis of natural products and pharmaceuticals.[1,2] Acetates and carbonates are typical leaving groups in allylic nucleophilic substitution. More reactive halides or sulfonates are used less frequently, which is also an advantage with regard to the total synthesis of multifunctional compounds. Many transition metals such as palladium, nickel, rhodium, ruthenium, iridium, molybdenum, vanadium, iron, and platinum form complexes, which together with the corresponding ligands, successfully catalyze the reaction. The most widely used complexes in this reaction are palladium complexes. [3-7]




**Scheme 1**

In 1977, Trost and Streg provided the first example of transition metal catalyzed asymmetric allylic substitution. They used a catalyst prepared in the reaction of tetrakis(triphenylphosphin)palladium ($Pd(PPh_3)_4$) with a chiral bisphosphine ligand – 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP).[8] Although the reaction products were obtained in low enantiomeric excess, these studies provided a foundation for the discovery of many new effective ligands, which enantioselectively influenced the formation of C-C and C-heteroatom bonds.[9]

The first type of ligands used in catalytic asymmetric allylic substitution were bidentate bisphosphine ligands, which have already proved successful in enantioselective hydrogenation (Figure 1).

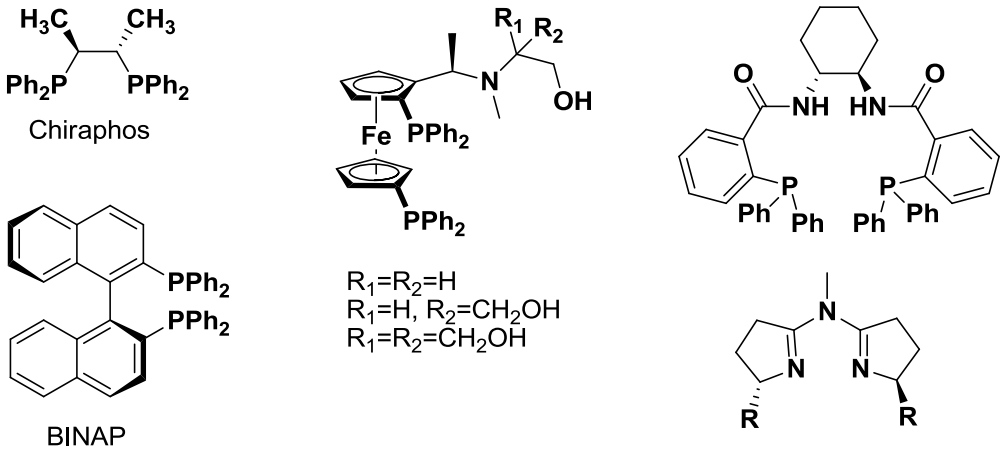
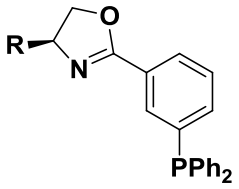



**Figure 1**

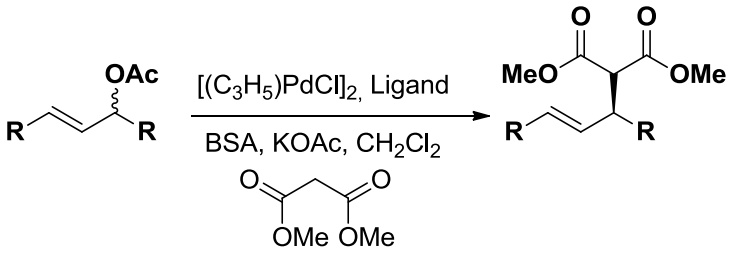
One of the first application of PHOX ligands was the allylic substitution with dimethyl malonate catalyzed by palladium complexes (**Błąd! Nie można odnaleźć źródła odwołania.**). [10,] **Błąd! Nie zdefiniowano zakładki.**[-] **Błąd! Nie zdefiniowano zakładki.** These ligands significantly improved reaction yields and the selectivity in relation to the previously used type of symmetric ligands BOX. Complexes of PHOX ligands with palladium have been applied successfully to large-scale allylic substitution reactions, therefore they are able to be a very good alternative to the diphosphine Trost's ligands (Table 1).



| Ligand | R |
|---|---|
| 1 | Me |
| 2 | Bn |
| 3 | *i*-Pr |
| 4 | Ph |
| 5 | *t*-Bu |

**Figure 2** PHOX ligands

**Table 1** Asymmetric allylic substitution catalyzed by Pd-PHOX (1-1,2% mol)

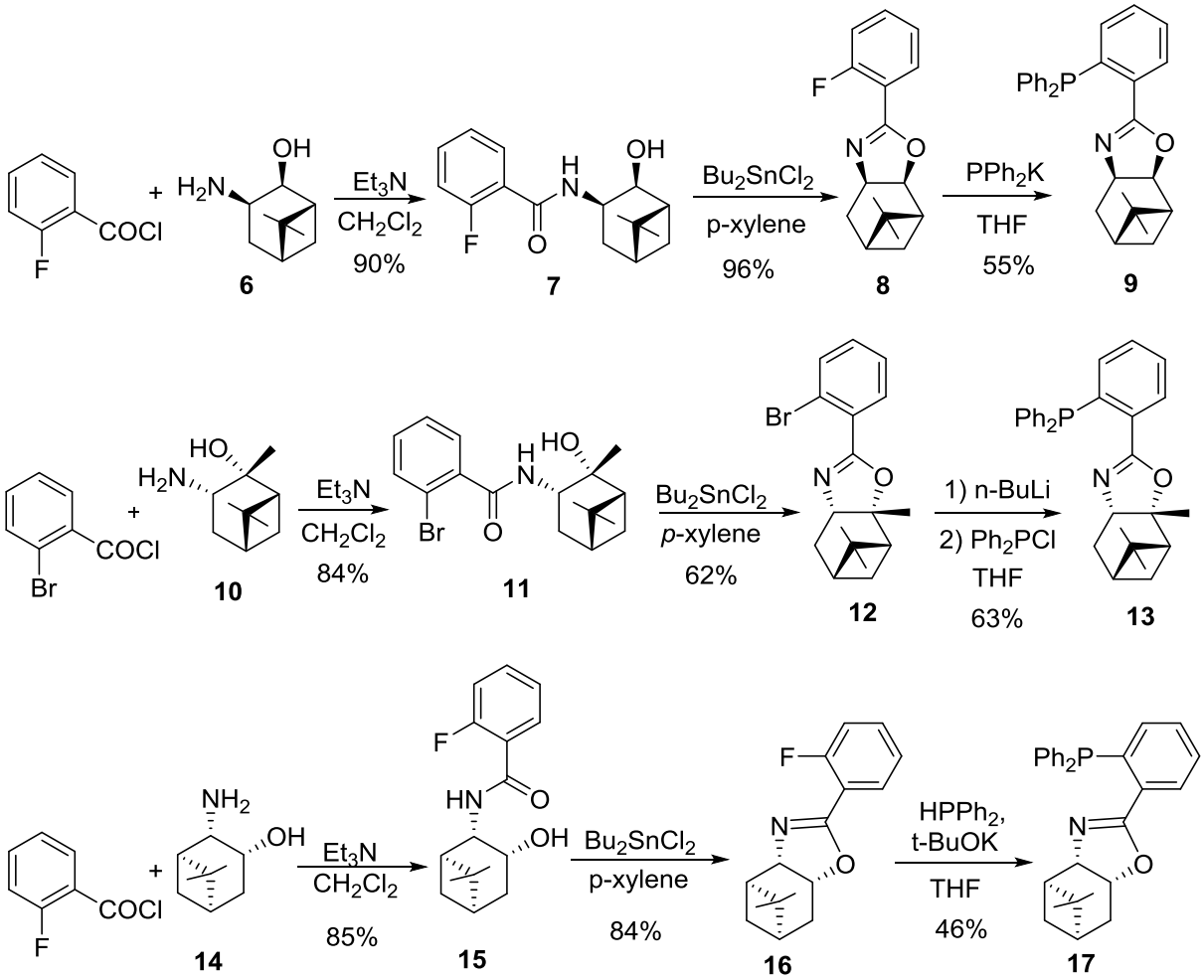



| Ligand | R | Yield [%] | Ee [%] |
|---|---|---|---|
| **1** | *i*-Pr | 91 | 93 |
| **2** | *i*-Pr | 92 | 92 |
| **3** | *i*-Pr | 88 | 94 |
| **4** | *i*-Pr | 93 | 89 |
| **5** | *i*-Pr | 88 | 96 |
| **1** | Me | 95 | 56 |
| **5** | Me | 96 | 69 |
| **1** | Ph | 98 | 89 |

| | | | |
|---|---|---|---|
| **4** | Ph | 98 | 98 |

## Synthesis of monoterpene derived PHOX ligands

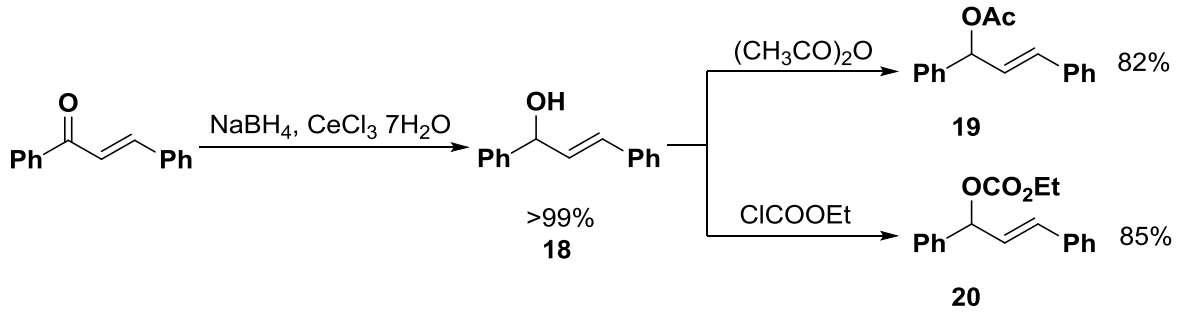
We commenced our new PHOX ligands syntheses from monoterpenes (α-pinene and β-pinene), which were transformed to the appropriate amino alcohols (**6**, **10**, **14**)[14, 15]. Then amino alcohols were converted into the amides (**7**, **11**, **15**) in reactions with 2-halogenobenzoyl chlorides in good yields. Cyclization utilizing Masamune protocol[16] in the presence of dibutyltin dichloride led to 2-halogenophenyloxazoline (**8**, **12**, **16**). Substitution of the halogen atom by diphenylophosphino group led to final products – PHOX ligands (**9**, **13**, **17**) (Scheme 2).




**Scheme 2** Synthesis of monoterpene derived PHOX ligands

Studies on the allylic nucleophilic substitution started with the synthesis of substrates (Scheme 3). (*E*)-1,3-Diphenyl-2-propen-1-ol (**18**) was selected as a model compound for the reaction. It was obtained from the commercially available (*E*)-chalcone by Luche's reduction with sodium borohydride in the presence of the cerium chloride heptahydrate (III) in methanol in quantitative yield (> 99%).[17] Then, **18** was converted into derivatives that are used in the allylic nucleophilic substitution reactions. Reaction with acetic anhydride gave

the acetate **19** in 82% yield. The second derivative was (*E*)-1,3-diphenylallyl ethyl carbonate (**20**) obtained in reaction of **18** with ethyl chloroformate in 85% yield.

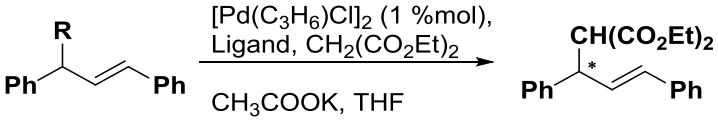



**Scheme 1** Synthesis of starting materials to the allylic nucleophilic substitution

All asymmetric Tsuji-Trost reactions were carried out applying the same procedure with 1 mol% of the catalyst generated in situ from allylpalladium (II) chloride dimer and the monoterpene derivative PHOX ligand. Reactions were carried out in dry tetrahydrofuran under nitrogen at room temperature for approx. 5 hours.

The results of asymmetric allylic substitution with ethyl malonate as a nucleophile are summarized in Table 2. All used PHOX ligands gave products with very good yields and enantiomeric excesses. For acetate, substitution proceeded almost quantitatively (> 99%), while substrate with the carbonate group gave lower yields (71-78%).

**Table 2** Nucleophilic allylic substitution with diethyl malonate catalyzed by Pd-PHOX

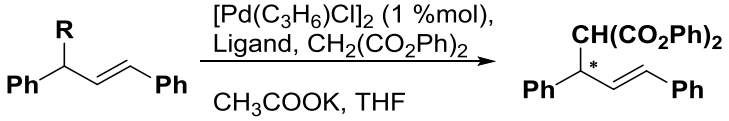



| Ligand | R = OAc + BSA | | R = $OCO_2Et$ | | Conf. |
|---|---|---|---|---|---|
| | W [%] | Ee [%] | W [%] | Ee [%] | |
| **9** | >99 | 95 | 78 | 96 | *R* |
| **13** | >99 | 93 | 71 | >99 | *S* |
| **17** | >99 | 97 | 77 | >99 | *S* |

The second nucleophile studied in Tsuji-Trost reaction was diphenyl malonate (Table 3). By changing the size of the ester groups, we wanted to examine whether the size of the nucleophile will influence the substitution. In the case of diphenyl malonate, we observed a decrease in both the yield (69-76%) and enantiomeric excess of the isolated products. For carbonate leaving group, the enantiomeric purity of the product was higher (80-85% ee) than for the acetate (72-78% ee). Comparing the Pd-PHOX catalyzed reactions carried out with malonic acid esters as nucleophiles, it can be concluded that increasing the size of

substituents in ester groups (from ethyl to phenyl) resulted in lower yields and enantiomeric excesses of substitution product.

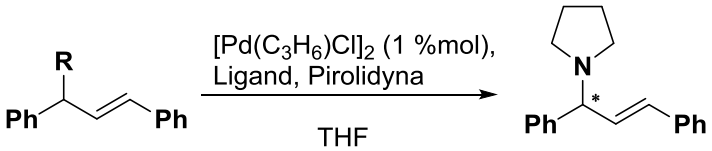
**Table 1** Nucleophilic allylic substitution with diphenyl malonate catalyzed by Pd-PHOX




| Ligand | R = OAc + BSA | | R = $OCO_2Et$ | | Conf. |
|---|---|---|---|---|---|
| | W [%] | Ee [%] | W [%] | Ee [%] | |
| **9** | 71 | 75 | 76 | 80 | *R* |
| **13** | 69 | 78 | 72 | 83 | *S* |
| **17** | 75 | 72 | 70 | 85 | *S* |

Next type of nucleophiles, which were tested in Tsuji-Trost reaction catalyzed with Pd-PHOX were nitrogen nuclephiles. We have choosen pyrrolidine, *para*-toluenesulfonamide, and $HN(Boc)_2$ as nucleophiles. Reactions were carried out under analogous conditions as for carbon nucleophiles. In the case of using pyrrolidine as the nucleophile for both substrates (acetate and carbonate), substitution products were isolated with similar good yields (77-89% for OAc 74-80% for $OCO_2Et$) (Table 4). Products with slightly higher optical purity were isolated from the reaction with acetate (60-70% ee) compared with the carbonate (58-66% ee).

**Table 4** Nucleophilic allylic substitution with pyrrolidine catalyzed by Pd-PHOX

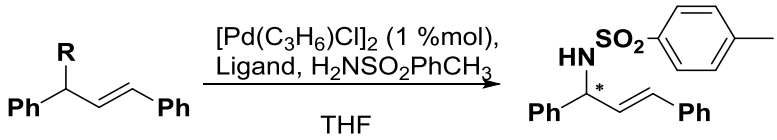



| Ligand | R = OAc +BSA | | R = $OCO_2Et$ | | Konfiguracja |
|---|---|---|---|---|---|
| | W [%] | Ee [%] | W [%] | Ee [%] | |
| **9** | 77 | 62 | 79 | 58 | *R* |
| **13** | 78 | 70 | 74 | 62 | *S* |
| **17** | 80 | 60 | 80 | 66 | *S* |

In the case of using *para*-toluenesulfonamide as a nucleophile, we observed higher influence of leaving group in substrate for yield and enantiomeric excess (Table 5.). Very high

yields (89-91%) and enantiomeric excesses (92%, 98%, >99% ee) were obtained for allylic carbonate.

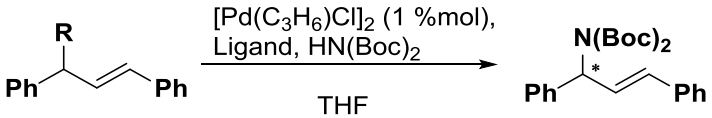
**Table 5** Nucleophilic allylic substitution with *p*-toluenesulfonamide catalyzed by Pd-PHOX




| Ligand | R = OAc +BSA | | R = $OCO_2Et$ | | Conf. |
|---|---|---|---|---|---|
| | W [%] | % ee | W [%] | % ee | |
| **9** | 70 | 60 | 90 | >99 | *R* |
| **13** | 72 | 58 | 89 | 92 | *S* |
| **17** | 74 | 66 | 91 | 98 | *S* |

The last nucleophile used for asymmetric allylic substitution was di-*tert*-butyl-iminodicarboxylate ($Boc_2NH$), which after substitution can be easily deprotected primary amine (Table 6). Unfortunately, these reactions compared to other nitrogen nucleophiles provided products in lower yields (64-70%) and enantiomeric excesses (48-65% ee).

**Table 6** Nucleophilic allylic substitution with di-*tert*-butyl-iminodicarboxylate catalyzed by Pd-PHOX




| Ligand | R = OAc +BSA | | R = $OCO_2Et$ | | Conf. |
|---|---|---|---|---|---|
| | W [%] | % ee | W [%] | % ee | |
| **9** | 70 | 60 | 69 | 48 | *R* |
| **13** | 68 | 65 | 64 | 52 | *S* |
| **17** | 65 | 63 | 70 | 56 | *S* |

## Conclusions

In this paper, we presented the synthesis of chiral monoterpene derived PHOX ligands and their application in asymmetric Tsuji-Trost reaction. All complexes of palladium and PHOX

ligands catalyzed allylic nucleophilic substitution with good yields and moderate to high enantioselectivities.

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