A superior P-H phosphonite: Asymmetric allylic substitutions with fenchol-based palladium catalysts
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Abstract
The fenchol-based P-H phosphonite BIFOP-H exceeds with 65% ee other monodentate ligands in the Pd-catalyzed substitution of 1-phenyl-2-propenyl acetate with dimethylmalonate.

Introduction
Palladium catalyzed allylic substitutions provide valuable tools for stereoselective C-C- and C-heteroatom connections.[1,2] The control of regio- and enantioselectivity is challenging, especially with unsymmetrical substrates, e.g. with monoaryl allyl units. According to computational analyses of electronic effects,[3,4] regioselectivity in favor of the branched product is supported at strong donor-substituted (e.g. alkyl, O-alkyl) allylic positions. Frequently employed Pd-catalysts most often favor linear, nonchiral products (Scheme 1).

Scheme 1: Pd-catalyzed allylic substitution with unsymmetrical substrates (Nu = dimethylmalonate, Nf = OAc).

Pfaltz et al. improved the yield of the chiral, branched product by employing electron withdrawing substituents on the P-donor atoms in P, N-oxazoline ligands[5] (Scheme 2) [6]. Such phosphites were thought to favor a more SN1-like addition at the substituted, allylic C-atom. High regio- and enantioselectivities were also achieved with biphenylphosphites by Pamies et al. (Scheme 2) [7].

Scheme 2: Bidentate P, N-ligands and a monodentate phosphoramidite for Pd-catalyzed allylic substitutions with unsymmetric substrates, cf. Scheme 1.

Besides bidentate P, N-ligands, monodentate ligands are useful, as was demonstrated successfully by Hayashi et al. with the MeO-MOP ligand, yielding 90% branched product with 87% ee for a C-methylated malonate nucleophile and the 4-methoxymethylene allyl substrate [8]. Van Leeuwen’s bulky, monodentate TADDOL based phosphoramidite gave rise to intriguing memory effects [28b] and yielded 6% branched product with 25% ee (Scheme 2) [9].

We have recently employed modular, chelating fencholates,[10-14] in enantioselective organozinc catalysts,[15-
19] and in chiral n-butyllithium aggregates [20-24]. In Pd-catalyzed allylic substitutions of diphenylallyl acetate, fenchyl diphenylphosphinites (FENOPs) with phenyl or anisyl groups favor the S-enantiomer, but with a 2-pyridyl unit the R-enantiomer was preferred (Scheme 3) [25].

According to computational transition structure analyses, these phenyl and anisyl phosphinites are not "monoden-tate" but form chelate complexes via π-coordination. Biphenyl-2,2'-bisfenchol (BIFOL) [13] was developed as combination of a flexible biaryl axis (as in BINOL) and sterically crowded hydroxy groups (as in TADDOLs). BIFOL based phosphines (BIFOPs) are sterically highly hindered and were employed in copper-catalyzed 1,4-additions of diethylzinc to 2-cyclohexenone [26].

Scheme 3: Fenchole-based phosphorus ligands (i.e. FENOPs and BIFOPs) for Pd-catalyzed allylic substitutions. Pd-p arene or Pd-N coordinations give rise to different enantioselectivities.

Here we use a selection of fenchol-based bidentate pyridine FENOP- and monodentate BIFOP-ligands in Pd-catalysts to study allylic substitutions of the challenging 1-phenyl-2-propenyl acetate (Scheme 1, R=Ph) [27].

Results and discussion

Fenchylphosphinites (FENOPs) and biphenylbisfenchol based phosphorus ligands are all suitable for Pd-catalyzed allylic alkylations of 1-phenyl-2-propenyl acetate (Scheme 4, Table 1, see additional file 1 for full experimental data).

All three P, N-bidentate FENOP ligands, FENOP, FENOP-Me and FENOP-NMe2, favor branched alkylation products (Table 1). This tendency towards formation of chiral, branched products is even apparent from X-ray crystal structure analyses of corresponding Pd-phenylallyl intermediates. All three Pd-allyl complexes, Pd-FENOP, Pd-FENOP-Me and Pd-FENOP-NMe2 (Figures 1, 2 and 3) exhibit the allylic phenyl group trans situated relative to phosphorus. Rather long C3-Pd distances (2.30 Å, 2.30 Å and 2.25 Å) are apparent for these trans position in comparison to the shorter C1-Pd bond distances (2.13 Å, 2.08 Å and 2.13 Å, cf. Figures 1, 2 and 3). This differentiation agrees with the "trans to phosphorus" rule, [1,28,29] which predicts the attack of the nucleophile

Table 1: FENOP- and BIFOP-Pd-catalysts in enantioselective allylic substitutions of phenylallylacetate by dimethylmalonate.a)

| Ligand          | Linear / branched b) | % ee (major enantiomer) c) | % yield b) |
|-----------------|----------------------|---------------------------|------------|
| FENOP           | 42 / 58              | 19 (R)                    | 54         |
| FENOP-Me        | 39 / 61              | 31 (R)                    | 43         |
| FENOP-NMe2      | 44 / 56              | 37 (R)                    | 50         |
| BIFOP-Cl        | 89 / 11              | 39 (S)                    | 60         |
| BIFOP-Br        | 85 / 15              | 37 (S)                    | 56         |
| BIFOP-H         | 80 / 20              | 65 (S)                    | 68         |
| BIFOP-Et        | 85 / 15              | 8 (S)                     | 70         |
| BIFOP-nBu       | 65 / 35              | 5 (S)                     | 75         |
| BIFOP-Oph       | 68 / 32              | 29 (S)                    | 58         |
| BIFOP-NEt2      | 52 / 48              | 10 (S)                    | 52         |

a) All catalyses were performed in THF, 12 h at -78°C then 24 h at RT with 0.0055 mmol of the ligand, 0.0055 mmol of [Pd(allyl)Cl]2 (1 mol% catalyst) and 0.57 mol of 1-phenylallylacetate substrate.

b) Linear / branched ratios as well as yields were determined by integration of 1H-NMR spectra.

c) Enantiomeric excesses (%ee) of the branched products were determined by HPLC (Daicel-OD-H, hexanes / i-PrOH = 99/1, 0.55 mi /min., l= 220 nm, tR = 16.7 min. (R), 17.7 min. (S).

Figure 1

X-ray crystal structure of the cationic complex Pd-FENOP (CCDC 299944), the perchlorate counterion and hydrogen atoms are omitted. The allylic phenyl groups is positioned trans to phosphorus. In agreement with the the "trans rule", C3-Pd is longer than C1-Pd. The nucleophile (i.e. malonate) is expected to attack at C3 yielding the branched product. Distances are given in Angstroms.

![Scheme 3: Fenchole-based phosphorus ligands (i.e. FENOPs and BIFOPs) for Pd-catalyzed allylic substitutions. Pd-p arene or Pd-N coordinations give rise to different enantioselectivities.](image1)

![Scheme 4: Allylic alkylation of 1-phenyl-2-propenyl acetate by sodium dimethylmalonate (BSA-method) with Pd-FENOP- or Pd-BIFOP- catalysts.](image2)
(i.e. malonate) at the weakest (longest) C3-Pd bond, yielding preferably the chiral, branched product.

Monodentate BIFOP ligands yield more of the linear alkylation product (Table 1), despite their huge steric demand. Surprisingly, the chloro- and bromophosphites, BIFOP-Cl and BIFOP-Br, are stable ligands under these reaction conditions: no conversion with nucleophiles (e.g. malonate), as was observed previously with diethylzinc, [26] was found. The ligands were recovered after catalysis. Apparently, the absence of strongly Lewis-acidic electrophiles (Na+ vs. Zn2+) and the huge steric shielding prevents halide substitutions and BIFOP-Cl(Br) decompositions.

With regard to enantioselectivities, some monodentate BIFOPs are even superior to the pyridine-phosphinites (FENOPs). While FENOPs favor the R-enantiomeric product, the S-enantiomer is preferred by all BIFOP ligands. Enantioselectivities increase from FENOP with 19% ee to FENOP-Me with 31% ee and to FENOP-NMe2 with 37% ee, reflecting the effect of steric demanding and electron donating pyridine groups on enantioselectivity.

The surprisingly stable halogen phosphites BIFOP-Cl and BIFOP-Br yield even higher enantioselectivities (39% and 37% ee) than the corresponding phosphate BIFOP-OPh or the phosphoramidite BIFOP-NEt2 (10% and 29% ee, Table 1). To our knowledge, this is the first successful application of halogen phosphites as ligands in enantioselective catalysis [26]. The highest enantioselectivity however is achieved with the P-H phosphonite BIFOP-H (65% ee, Table 1). As in copper-catalyzed 1,4-additions of diethylzinc to cyclohexenone, [26] the small steric hindrance of the hydrido-substituent and the shielding by the chiral bis-fenchane cavity provide the best combination among the tested BIFOPs for the P-H phosphonite BIFOP-H.

Computational transition structure analyses of allylic substitutions with ammonia mimicking the malonate nucleophile help to understand origins of enantioselectivities, [30-33] as we have shown recently for Pd-FENOP catalysts with the diphenyl allyl substrate [25]. For the P, N-bidentate pyridyl FENOP system, an exo allyl arrangement and a trans to phosphorus addition of the nucleophile is slightly preferred (cf. the two most stable transition state in Figure 4). This favored Si-addition of the nucleophile explains the experimentally observed formation of the R-alkylation product (Table 1). Systematic conformational analyses of transition structures with BIFOP-H in allylic substitutions yields BIFOP-H-Re as the most stable transition structure. Its Re-addition of the NH3-nucleophile is slightly more favored than the Si-addition in the competing transition structure BIFOP-H-Si (Figure 5). This agrees with the experimentally observed formation of the S-alkylation product with BIFOP-ligands (Table 1).

![Figure 2](image-url)  
**Figure 2**  
X-ray crystal structure of the cationic complex Pd-FENOP-Me (CCDC 600369), the perchlorate counterion and hydrogen atoms are omitted. The allylic phenyl groups is positioned trans to phosphorus. In agreement with the "trans rule", C3-Pd is longer than C1-Pd. The nucleophile (i.e. malonate) is expected to attack at C3 yielding the branched product. Distances are given in Angstroms.

![Figure 3](image-url)  
**Figure 3**  
X-ray crystal structure of the cationic complex Pd-FENOP-NMe2 (CCDC 600370), the perchlorate counterion and hydrogen atoms are omitted. The allylic phenyl groups is positioned trans to phosphorus. In agreement with the "trans rule", C3-Pd is longer than C1-Pd. The nucleophile (i.e. malonate) is expected to attack at C3 yielding the branched product. Distances are given in Angstroms.
Conclusion

Besides P, N-bidentate FENOP ligands, monodentate BIFOP ligands can be employed successfully in Pd-catalyzed allylic substitution of 1-phenyl-2-propenyl acetate with dimethylmalonate. Surprisingly, the halogen phosphites BIFOP-Cl and BIFOP-Br are stable towards nucleophiles under catalysis conditions, apparently due to absence of strongly Lewis-acidic cations and the large steric shielding of the phosphorus-halogen functions. With respect to enantioselectivities, the P-H phosphonite BIFOP-H is clearly superior and reaches 65% ee, a rather high selectivity for a monodentate ligand.

Additional material

Additional File 1 contains all experimental data
Click here for file
[http://www.biomedcentral.com/content/supplementary/1860-5397-2-7-S1.pdf]
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