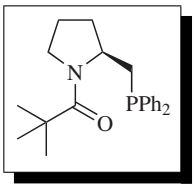
(*S*)-(−)-*N*-[(2,2′)-Dimethylpropionyl]-2-[(diphenylphosphino)methyl]pyrrolidine[1]



[145818-29-7] $C_{22}H_{28}NOP$ (353.44)

InChI = 1/C22H28NOP/c1-22(2,3)21(24)23-16-10-11-18(23)17-25(19-12-6-4-7-13-19)20-14-8-5-9-15-20/h4-9,12-15,18H,10-11,16-17H2,1-3H3/t18-/m0/s1

InChIKey = YUFICFYMFGQYMU-SFHVURJKBE

(enantioselective conjugate addition,[1] *N*-tosylimine addition[2])

Physical Data: mp 97–97.5 °C; $[\alpha]_D$ −67.3 (*c* 1.45, $CHCl_3$).

Solubility: soluble in most organic solvents (CH_2Cl_2, Et_2O, THF, and toluene).

Form Supplied in: colorless prisms, not commercially available.

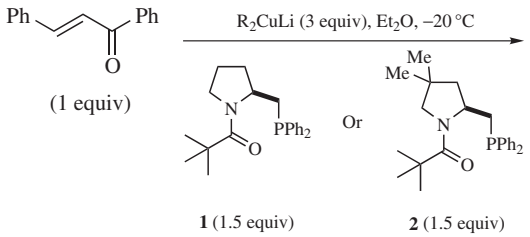
Analysis of Reagent Purity: NMR (^1H).

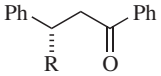
Preparative Methods: the ligand is prepared by the acylation of (*S*)-(−)-2-[(diphenylphosphino)methyl]pyrrolidine which is available from L-proline.[3]

Purity: the phosphine is oxygen-sensitive, however, the phosphine oxide by-product can be reduced back to the phosphine using Et_3SiH[4] or Cl_3SiH.[5]

Handling, Storage, and Precautions: the ligand is stable when stored under an inert atmosphere. The phosphine is air-sensitive and will oxidize to the phosphine oxide in the presence of oxygen or other oxidizing reagents.

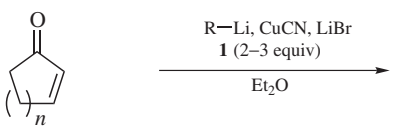
Stoichiometric and Catalytic Chiral Ligand for the Asymmetric Conjugate Addition of Organocopper Reagents to Enones. Phosphine ligand (**1**) is a very effective stoichiometric chiral ligand for the asymmetric conjugate addition of organocuprates generated from organolithium reagents and CuI to α,β-unsaturated carbonyl derivatives. The addition reactions of simple cuprates to chalcones in the presence of ligand **1** proceed with some level of enantiocontrol.[6,7] In some cases, the introduction of a *gem*-dimethyl group at the 4-position of the pyrrolidine ring generates a ligand **2** that induces slightly higher enantioselectivities (eq 1).[8] Ligand **1** is also quite an effective chiral controller in the asymmetric conjugate addition of organocopper reagents to cycloalkenones, but at least 2 equiv of **1** are required (eq 2).[9]





(1)

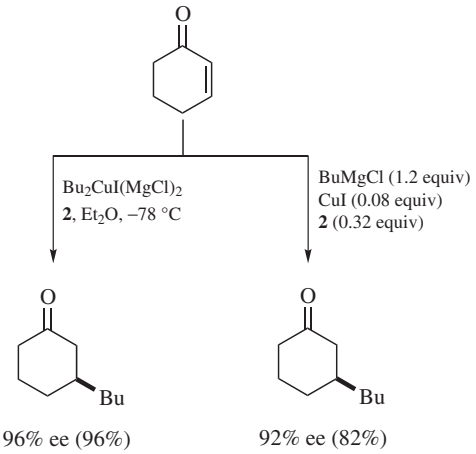
1; 84% ee (79%) (R = Me)
1; 24% ee (97%) (R = Bu)
2; 90% ee (99%) (R = Me)
2; 11% ee (95%) (R = Bu)



(2)

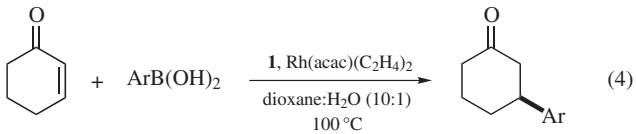
n = 2; R = Me	92% ee (66%)
n = 2; R = Et	91% ee (89%)
n = 2; R = Bu	90% ee (97%)
n = 1; R = Et	94% ee (90%)
n = 1; R = Bu	95% ee (99%)

It was later found that the amount of ligand **2** could be decreased to 0.32 equiv if the cuprate derived from a Grignard reagent and CuI was used (eq 3).[3,10]



(3)

Catalytic, Enantioselective Addition of Arylboronic Acids to Cycloalkenones. A complex between ligand **1** and a rhodium(I) salt was found to catalyze the asymmetric 1,4-addition reaction of arylboronic acids to cyclohexenone and cycloheptenone. The reaction proceeds with high enantiocontrol and excellent yields (eq 4).[11] Lower enantiomeric excesses were observed with cyclopentenone (83% ee), but a variety of substituted phenylboronic acids could be used.

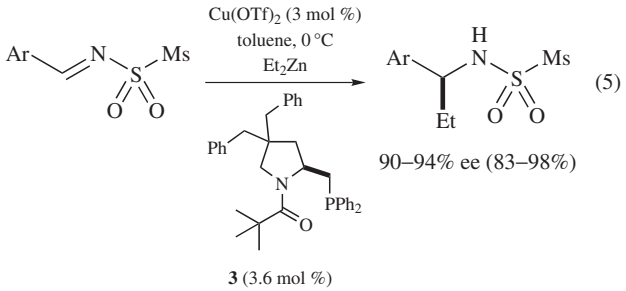


(4)

91–96% ee (90–99%)

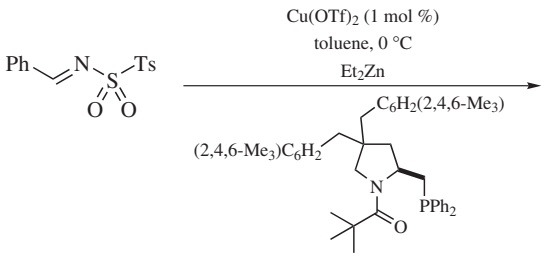
Catalytic Asymmetric Addition of Organozincs to Imines. This class of ligands is also very effective in the copper-catalyzed addition of diethylzinc to *N*-sulfonylimine derivatives derived from aromatic aldehydes (eq 5).[12] It was found that the ligand bearing a *gem*-dibenzyl substituent at the 4-position of the pyrrolidine heterocycle produced the highest enantiomeric excesses. Cleavage of the *N*-sulfonyl group upon treatment with Red-Al in

refluxing benzene for 12 h gave the secondary amine with slight racemization. The addition reaction proceeded almost equally well on the corresponding *N*-tosyl or *N*-trimethylsilylethylsulfonylimines. However, the advantage is significant in these latter two cases since the cleavage of the *N*-sulfonyl group to produce the secondary amine occurs without any racemization (SmI_2 in THF/HMPA or CsF in DMF, respectively). Replacement of the *gem*-dibenzyl substituent on the ligand by a *gem*-di(2,4,6-$Me_3C_6H_2CH_2$) group further increases the catalytic performance (eq 6).[13]

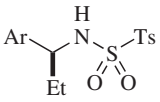


90–94% ee (83–98%) (5)

3 (3.6 mol %)



4 (1.3 mol %)



93 % ee (96 %) (6)

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