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(54) Titre : REACTIONS DE SUBSTITUTION D'UN COMPOSE ALLYLIQUE ENANTIOSELECTIF CATALYSE PAR LE CUIVRE

(54) Title: COPPER-CATALYZED ENANTIOSELECTIVE ALLYLIC SUBSTITUTION REACTIONS

(57) Abrégé/Abstract:
An allylic compound is reacted with an organozinc compound $Zn(R^6)_2$ to eliminate a group (the leaving group) from the allylic compound and to add a group from the organozinc compound to it in the presence of a copper salt catalyst and a chiral organic ligand for the copper.

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(54) Title: COPPER–CATALYZED ENANTIOSELECTIVE ALLYLIC SUBSTITUTION REACTIONS

(57) Abstract

An allylic compound is reacted with an organozinc compound $Zn(R^6)_2$ to eliminate a group (the leaving group) from the allylic compound and to add a group from the organozinc compound to it in the presence of a copper salt catalyst and a chiral organic ligand for the copper.

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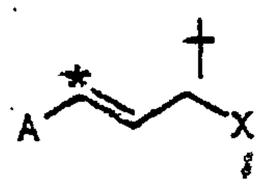
COPPER-CATALYZED ENANTIOSELECTIVE ALLYLIC SUBSTITUTION REACTIONS

This invention relates to selective synthesis and catalysts therefor.

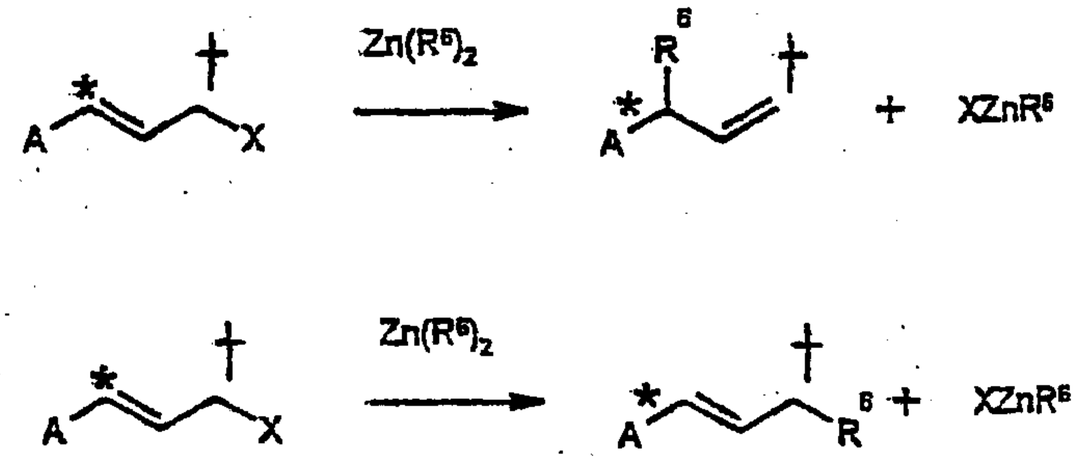
According to the invention an allylic compound is reacted with an organozinc compound $Zn(R^6)_2$ to eliminate a group (the leaving group) from the allylic compound and to add a group from the organozinc compound to it in the presence of a copper salt catalyst and a chiral organic ligand for the copper. Preferably the ligand is a primary or secondary amine in which the nitrogen atom is directly linked to the chiral centre.

The allylic compound is suitably of formula



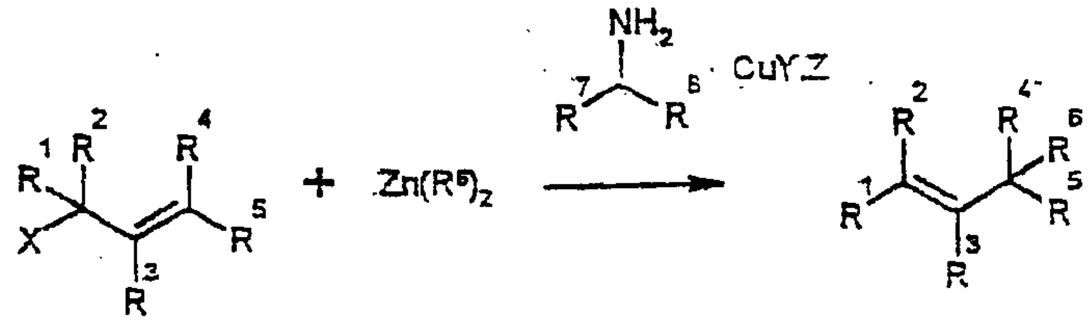
where X is the leaving group for example a chlorine atom and in which A is hydrogen or an alkyl or aryl group, preferably having 1-20 carbon atoms or 6-20 carbon atoms, respectively. If substitution occurs at the carbon atom marked * a chiral centre may be formed. This process is known as Sn2'substitution; an alternative substitution at the carbon atom marked † may occur in which case there may be no chiral centre, this process is known as Sn2 substitution.

The reactions are shown as follows:



where R^6 is a group from the organozinc compound. Surprisingly, in this process the former reaction is generally favoured and is influenced by the leaving group, ligands and solvents as shown below, tetrahydofuran being a particularly favourable solvent. The process is normally chemoselective for Sn2' substitution and/or stereoselective.

In a preferred form of the invention the reaction is as shown below:-



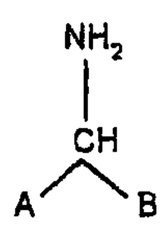
R^1 - R^6 are alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocyclyl groups optionally substituted by for example halogen, alkoxy, aryloxy, acyloxy, nitro, amide, acetamide, carboxylate, cyano, acetal, sulphide, sulphonate, sulfone, sulfoxide, phosphite, phosphonate, phosphine groups, each preferably having at most 20 and preferably less than 10 carbon atoms, or R^1 to R^5 may be H, R^7 is an aryl for example a phenyl or ferrocenyl or

substituted aryl or ferrocenyl group of which the substituents may be for example 1-aminobenzyl, 1-amino-2-naphthylmethyl, 1-amino-(4-tert-butylphenyl)methyl, trimethylsilyl, phosphite, phosphine, alkyl, alkoxy, thiophosphonate, amino and/or halogen (eg Cl or Br) atoms and R^8 is an alkyl or aryl, preferably a methyl, ethyl, propyl, tert-butyl, phenyl or naphthyl for example 2-naphthyl group which may be substituted for example by nitro, alkoxy, alkyl and/or haloalkyl group. X is halogen, OR^9, $OCOR^9$, OCO_2R^9, OSO_2R^9, OCS_2R^9 $CH(OR^{10})_2$, $OPO(OR^9)_2$, SOR^9, or SO_2R^9 where R^9 and R^{10} are optionally substituted C_1-C_{10} alkyl or aryl, of which the substituents may be halogen, nitro, methoxy, trifluoromethoxy, methyl, ethyl, tert butyl or sulphonate groups e.g. methyl, ethyl, trifluoromethyl, phenyl, tosyl, p-bromophenyl, p-nitrophenyl, p-methoxyphenyl, or R^7 and R^8 may together form a 5 or 6 membered carbocyclic or heterocyclic ring providing that a carbon atom to which the nitrogen is attached is chiral. For example R^7 and R^8 together may be 1-indane, bornylamine or 2-cyclohexylamine. Y is halogen, carboxylate for example, acetate, acetoacetate, cyanide, or thiocyanate and Z is an ether or thioether for example dimethylsulfide, tetrahydrofuran or diethylether. Preferably R^1 - R^2 and R^3 and one of R^4 or R^5 are H and the other one of R^4 or R^5 is aryl, for example phenyl, 4-chlorophenyl or 4-trifluoromethyl phenyl or is a trialkyl (e.g. tri-isopropyl) silyl oxymethyl groups R^6 is alkyl, tri-alkyl (e.g. trimethyl) silyl methyl, phenyl or 2,2-dimethylbut-3-enyl. R^7 is ferrocenyl, R^8 is naphthyl, X is chloride, Y is chloride or bromide and Z is dimethylsulfide. R^5 is preferably phenyl and R^6 is preferably neopentyl. The substituents of R^7 preferably have at most 10 carbon atoms in total and those of R^8 preferably at most 8 carbon atoms in total. Alkanes, cyclo alkanes and/or aromatic solvents for example toluene may be present.

Preferred solvents are ethers for example diethylether, 1,4-dioxane, tertbutylmethylether and especially tetrahydrofuran. Preferred temperatures are -120°C to 25°C more preferably -100°C to 20°C and especially -90°C to -50°C.

Preferred concentrations of catalyst are 0.1 atom% to 20 atom%, especially 0.5 atom% to 5 atom% expressed as copper atoms based on moles of the allylic compound.

The ratio of copper atoms to the amine ligand molecules is suitably 1:10 to 2:1.
Compounds for formula



in which A is a ferrocenyl or substituted ferrocenyl group and B is a group R^8 other than a methyl or phenyl group are believed to be novel. The groups A and B should be different in order to obtain stereospecificity. B is preferably a 2-naphthyl group.

Example 1

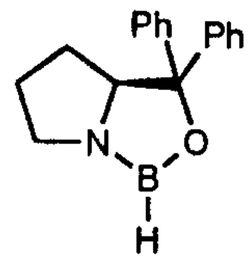
Preparation of (R)-(1-amino-2-naphthylmethyl) ferrocene

Step1

Ferrocene (4.5 g, 24 mmol) and aluminium trichloride (3.5 g, 26 mmol) were combined in dry dichloromethane (100 ml) at 0°C under argon. To the greenish suspension was added a solution of 2-naphthoyl chloride (5.0 g, 26 mmol) in dichloromethane (20 ml) at 0°C over a period of 20 min to obtain a dark purple solution. The reaction was stirred for 2h at room temperature and then quenched by careful addition of saturated aqueous ammonium chloride solution (100 ml). The organic layer was separated, washed with sat. aqueous sodium bicarbonate solution (2 x 30 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel using 1 : 1 pentane: diethyl ether by volume as eluent to give the ketone (5.6 g, 69%) as a red solid.

Step 2

The ferrocenyl ketone (4.5 g, 13.2 mmol) and borane dimethyl sulfide complex (1.4 ml, 14 mmol) were added simultaneously over a period of 30 minutes to a solution of the CBS catalyst (0.70 g, 2.5 mmol) in THF (80 ml) at 0°C under argon. CBS catalyst is



The catalyst is prepared from 1,1-diphenyl pyrrolidine methanol and borane (see Synlett 1993, 929)

After stirring for an additional 30 min the mixture was quenched with aq. ammonium chloride solution (70 ml). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using 1: 1 pentane : ether as eluent affording the desired alchohol (4.0 g, 89%) as an orange solid.

Step 3

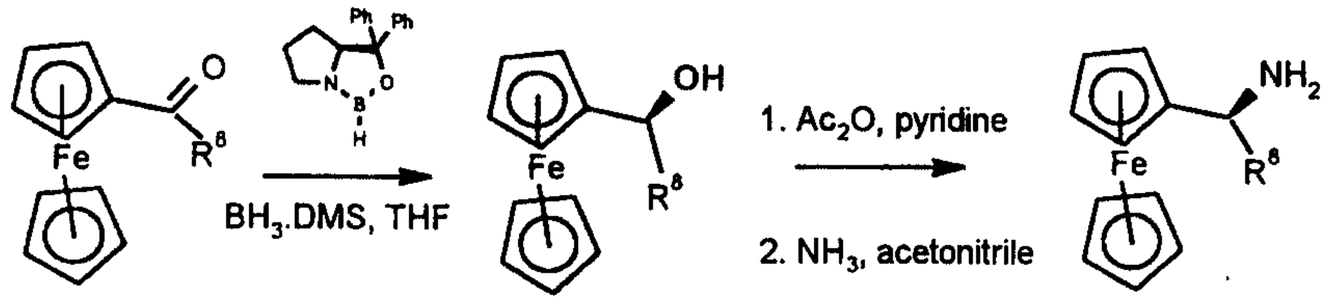
The ferrocenyl alcohol (4.0 g, 11.6 mmol) was dissolved in dry pyridine (30 ml) and acetic anhydride (20 ml) at room temperature. After stirring for 18h at room temperature all volatiles were removed under high vacuum at 50°C furnishing the pure acetylated alcohol (4.5 g, 100 %) as a red glue, that smoothly crystallised on standing to a red solid.

The acetylated alcohol (3.0 g, 8 mmol) was dissolved in acetonitrile (200 ml) and 37% aqueous ammonia solution (40 ml). After stirring for 24h at room temperature the mixture was poured into 10% aqueous hydrochloric acid (200 ml). The resulting precipitate was removed by filtration and washed with ether (4 x 20 ml). The residue was

dissolved in 20% aqueous sodium hydroxide solution (200 ml) and the desired product re-extracted with ether (5 x 50 ml). After drying ($MgSO_4$), the solvent was removed under reduced pressure and the pure (R)-(1-amino-2-naphthylmethyl) ferrocene (1.8 g, 66%) was obtained as an orange solid.

The corresponding compounds in which the naphthyl group is replaced by phenyl, o-tolyl, 1-naphthyl, 2-naphthyl, methyl, cyclohexyl, o-biphenyl, p-biphenyl, phenanthrenyl, o-bromophenyl and p-butylphenyl were prepared similarly. Compounds in which the ferrocenyl is symmetrically 1,1' disubstituted with 1-aminobenzyl, 1-amino-2-naphthylmethyl, 1-amino-(4-tert-butylphenyl)methyl, or 2-substituted with trimethylsilyl were prepared using the method given in example 1 except that two mole equivalents of aluminium chloride and acylchloride were used in step 1, two mole equivalents borane dimethylsulfide and 30 mol% CBS catalyst were used in step 2, and two mole equivalents acetic anhydride, pyridine and ammonia were used in step 3. The enantiomeric excess was in each case greater than 99%.

The reaction is illustrated below. The reaction was also carried out with the compounds indicated below, the % figures indicating the stated yields of pure material based on starting material,



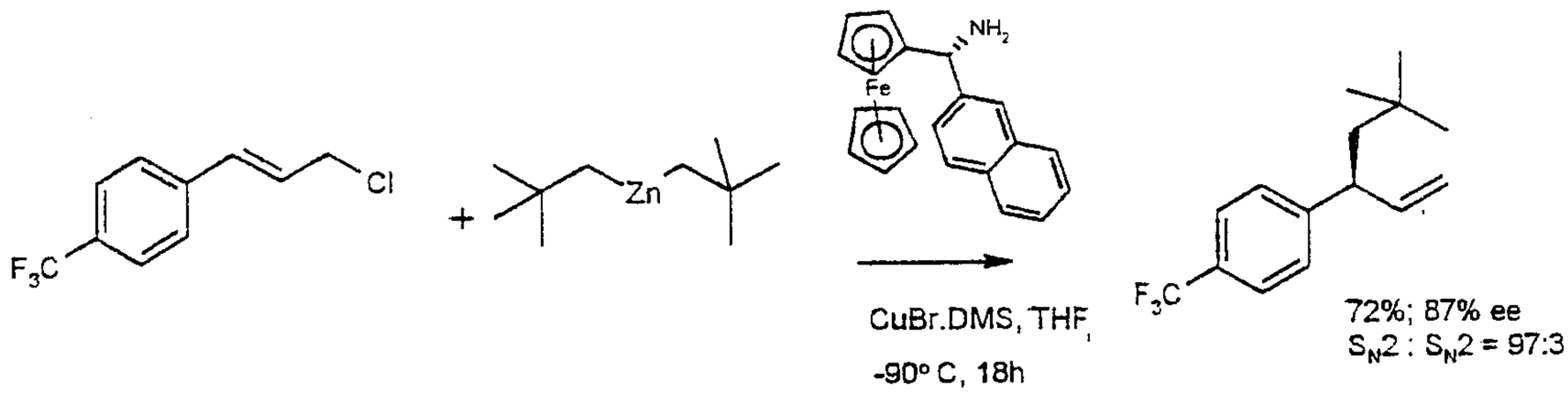
R^8 = Ph	R^8 = Ph; 88%	R^8 = Ph; 45%
R^8 = o-Tolyl	R^8 = o-Tolyl; 62%	R^8 = o-Tolyl; 48%
R^8 = 1-Naphth	R^8 = 1-Naphth;73%	R^8 = 1-Naphth;44%
R^8 = 2-Naphth	R^8 = 2-Naphth;81%	R^8 = 2-Naphth;66%
R^8 = Methyl	R^8 = Methyl	R^8 = Methyl
R^8 = Cyclohexyl	R^8 = Cyclohexyl;	R^8 = Cyclohexyl;
R^8 = 2-Biphenyl	R^8 = 2-Biphenyl	R^8 = 2-Biphenyl
R^8 = 4-Biphenyl	R^8 = 4-Biphenyl	R^8 = 4-Biphenyl
R^8 = phenanthrenyl	R^8 = phenanthrenyl	R^8 = phenanthrenyl
R^8 = 2-bromophenyl	R^8 = 2-bromophenyl	R^8 = 2-bromophenyl
R^8 = 4-bromophenyl	R^8 = 4-bromophenyl	R^8 = 4-bromophenyl

DMS is dimethyl sulphide and THF is tetrahydrofuran.

Example 2

Enantioselective allylation. Preparation of (+)-(S)-5,5-dimethyl-3(4-trifluoromethylphenyl)-1-hexene

This reaction is shown below



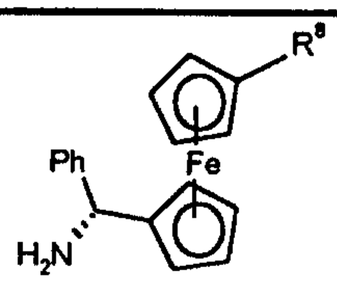
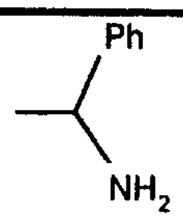
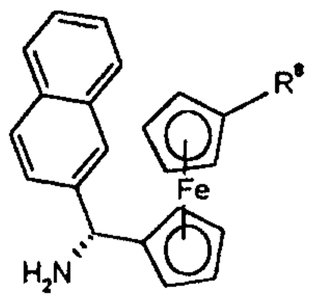
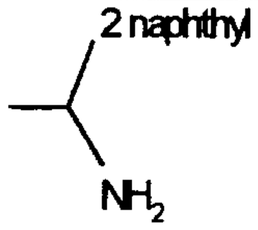
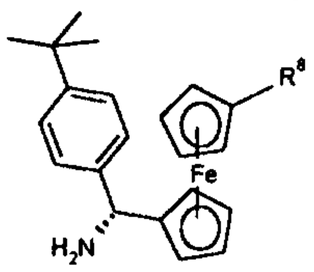
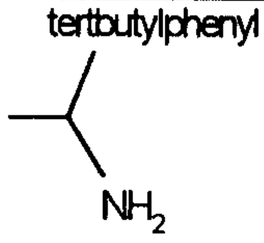
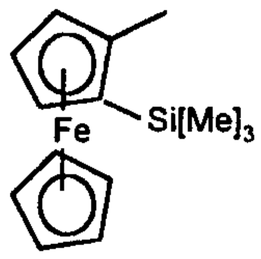
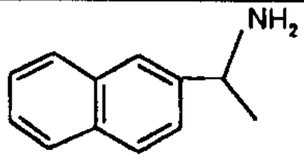
The chiral organic ligand R^7=ferrocenyl, R^8=2-naphthyl (70 mg, 0.2 mmol) and $CuBr.Me_2S$ (3 mg, 0.02 mmol) were dissolved in THF (5 ml) yielding a clear solution. After cooling to -90°C, neo-$Pent_2Zn$ (0.3 ml, 2.4 mmol) and 4-trifluoromethylcinnamyl chloride were added successively. The reaction mixture was stirred for 18h at -90°C and was worked up. The crude residue obtained after evaporation of the solvents was purified by flash-chromatography (ether : pentane 1 : 50) leading to the desired product (370 mg, 72% yield: S_N2'/S_N2 ratio : 97 : 3). The enantiomeric excess of the chiral product was determined by gas chromatography to be 87% using a Chiraldex™ capillary column.

Use of different substituents R^7 and R^8 in asymmetric allylation reaction

The following Table 1 shows the use of different chiral organic ligands (lig*) R^7 and R^8 as indicated in table 1, in the reaction of cinnamyl chloride with di-neopentyl zinc at -50°C. The chiral organic ligands were prepared according to the methods in example 1 and are of the (R) configuration. The experimental conditions are analogous to those in Example 2 above.

Table 1

Entry	R^7	R^8	Yield (%)	S_N2' : S_N2	ee
1	Ferrocenyl	Phenyl	73	95 : 5	32%
2	Ferrocenyl	o-Tolyl	79	96 : 4	16%
3	Ferrocenyl	1-Naphthyl	72	93 : 7	33%
4	Ferrocenyl	2-Naphthyl	77	95 : 5	42%
5	Ferrocenyl	Methyl	74	88 :12	7%
6	Ferrocenyl	Cyclohexyl	74	92 : 8	15%[1]
7	Ferrocenyl	o-Biphenyl	n.d.	92 : 8	4%
8	Ferrocenyl	p-Biphenyl	84	97 : 3	38%
9	Ferrocenyl	Phenanthrenyl	69	98 : 2	61%
10	Ferrocenyl	2-Naphthyl	75	97 : 3	67%
11	Ferrocenyl	o-Bromophenyl	67	96 : 4	38%
12	Ferrocenyl	p-'Butylphenyl	69	96 : 4	56%

Entry	R^7	R^8	Yield (%)	S_N2' : S_N2	ee
13			68	99 : 1	51%
14			68	97 : 3	52%
15			69	96 : 4	45%
16			66	98 : 2	11%
17	phenyl	methyl	>95	94 : 6	44%
18	2-naphthyl	methyl	>95	95 : 5	42%
19	1-naphthyl	methyl	>95	95 : 5	52%
20	R^7+R^8 = (R)-2-bornyl		80%	86 : 14	18%
21	R^7+R^8 = (R)1-indanyl		>95%	93 : 7	16%
22	R^7+R^8 = (S)-trans-2-cyclohexylamine		70%	>99 : 1	0%
23	(S)-2-aminobenzyl	phenyl	70%	>99 : 1	0%

Entry 1-8: Ratio CuBr Me_2S/Lig*/Substrate = 1/1/20. Entry 9 - 23:1/10/100

[1] Opposite stereoisomer in excess

Use of different substrates for the substitution

The following Tables 2 and 3 show the use of different allyl reagents R^1 and R^2 and (except in entry 13 of Table 3) R^3 = H, R^4 and R^5 as indicated in the tables, in the reaction with di-neopentyl zinc using the chiral ligand R^7=ferrocenyl, R^8=2-naphthyl of the (R) configuration. The experimental conditions are analogous to those in Example 2 above.

Reactions run at -50°C

Table 2

Entry	R^4	R^5	Yield (%)	S_N2' : S_N2	ee
1	H	phenyl	75	97 : 3	67%
2	phenyl	H	50	96 : 4	22%
3	H	2-trifluoromethyl phenyl	55	80 : 20	-[1]
4	H	4-trifluoromethyl phenyl)	70	98 : 2	74%
5	H	1-naphthyl	74	97 : 3	58%
6	H	cyclohexyl	70	(78 : 22)	59%
7	H	phenylmethyl	50	18 : 82	4%
8	CH_2OMe	H	67	>99 : 1	2%
9	CH_2OAc	H	74	> 99 : 1	14%
10	$CH_2OSitBuMe_2$	H	30	> 99 : 1	29%
11	$CH_2OSi(iPr)_3$	H	53	>99 : 1	47%
12	H	$CH_2Osi(iPr)_3$	55	>99 : 1	38%
13	CH_2OSiPh_2tBu	H	70	>99 : 1	12%

[1] Separation of enantiomers was not possible.

Reactions run at -90°C

Table 3

Entry	R^4	R^5	R^3	Yield (%)	S_N2' : S_N2	ee
1	H	phenyl	H	68	95 : 5	82%
2	H	4-trifluoromethyl phenyl	H	72	97 : 3	87%
3	H	1-naphthyl	H	65	94 : 6	71%
4	H	2-naphthyl	H	60	91 : 9	70%
5	H	cyclohexyl	H	67	98 : 2	76%
6	H	3-thienyl	H	70	94 : 6	63%
7	$CH_2OSi(iPr)_3$	H	H	45	>99 : 1	64%
8	H	4-isopropylphenyl	H	70	90 : 10	76%
9	H	4-chlorophenyl	H	71	96 : 4	79%
10	H	3-chlorophenyl	H	72	97 : 3	70%
11	H	3,4-dichlorophenyl	H	68	96 : 4	22%
12	H	1-cyclopentenyl	H	63	64 : 36	60%
13	phenyl	H	$-CO_2Et$	71	87 : 13	12%

Use of different diorganozincs at - 50°C

The following Table 4 shows the use of different organozinc reagents $Zn(R^6)_2$, in the reaction with trans-cinnamyl chloride using the chiral ligand R^7=ferrocenyl, R^8=2-naphthyl of the (R) configuration. The experimental conditions are analogous to those in Example 2 above.

Table 4

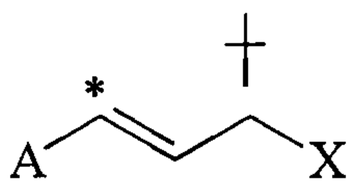
Entry	R^6	Yield (%)	S_N2' : S_N2	ee
1	Methyl	90	98 : 2	10%
2	Ethyl	88	98 : 2	10%
3	*iso*Propyl	87	98 : 2	29%
4	*iso*Butyl	69	98 : 2	45%
5	Pentyl	88	98 : 2	26%
6	*neo*Pentyl	75	97 : 3	67%
7	1R-(+)-Pinane	65	97 : 3	41%
8	1S-(-)-Pinane	60	98 : 2	37%
9	$PhMe_2SiCH_2$	50	90 : 10	42%
10	Me_3SiCH_2	52	94 : 6	67%
11	Me_2PhCCH_2	--[1]	68 : 32	25%
12	$Me_2PhSi(CH_2)_2$	78	98 : 2	15%
13	$H_2C{=}CH_2C(CH_3)_2CH_2$	65	95 : 5	79%[2]

[1] Reaction worked up before completion. [2] Reaction done at -85°C

CLAIMS:

1. A process in which an allylic compound is reacted stereospecifically with an organozinc compound to eliminate a leaving group from the allylic compound and to add a group from the organozinc compound to it in the presence of a copper salt catalyst and a chiral organic ligand for the copper.

2. A process according to claim 1, wherein the allylic compound is of formula



wherein

X is the leaving group,

A is hydrogen, a C_1-C_{20} alkyl group or a C_6-C_{20} aryl group,

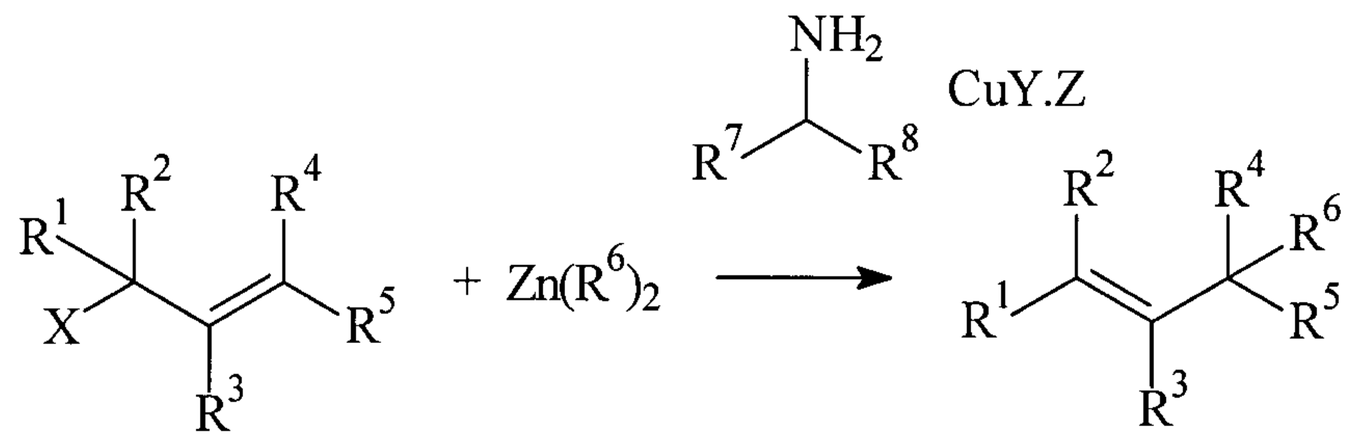
* identifies a carbon atom at which a chiral center may be formed, and

† identifies a carbon atom at which alternative substitution may occur which does not lead to the formation of a chiral center.

3. A process as claimed in claim 2, wherein X is a chlorine atom.

4. A process according to claim 1, 2 or 3, wherein S_N2' substitution giving a chiral centre occurs.

5. A process according to claim 1, wherein the reaction is as follows:



R^1 - R^6 are optionally substituted alkyl, alkenyl, alkynyl, aryl, aralkyl or heterocyclyl groups, or R^1 to R^5 may be H,

R^7 is an optionally substituted aryl or ferrocenyl group,

R^8 is an optionally substituted alkyl or aryl group,

X is halogen, OR^9, $OCOR^9$, OCO_2R^9, OSO_2R^9, OCS_2R^9 $CH(OR^{10})_2$, $OPO(OR^9)_2$, SOR^9, or SO_2R^9 in which R^9 and R^{10} are optionally substituted C_1-C_{10} alkyl or aryl,

Y is halogen, carboxylate, cyanide, or thiocyanate, and

Z is an ether or thioether.

6. A process according to claim 5, wherein the optional substituents in R^1 - R^6 are halogen, alkoxy, aryloxy, acyloxy, nitro, amide, acetamide, carboxylate, cyano, acetal, sulphide, sulphonate, sulfone, sulfoxide, phosphite, phosphonate, and phosphine groups.

7. A process according to claim 6, wherein each of the alkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclyl, alkoxy, aryloxy, acyloxy, amide, acetal, sulfone, sulfoxide,

phosphite and phosphonate groups of R^1 - R^6 have at most 20 carbon atoms.

8. A process according to claim 6, wherein each of the alkyl, alkenyl, alkynyl, aryl, aralkyl, heterocyclyl, alkoxy, aryloxy, acyloxy, amide, acetal, sulfone, sulfoxide, phosphite and phosphonate groups of R^1 - R^6 have at most 10 carbon atoms.

9. A process according to any one of claims 5 to 8, wherein R^1, R^2, R^3 and one of R^4 and R^5 are hydrogen, and in which the other of R^4 and R^5 is a phenyl, 4-chlorophenyl, 4-trifluoromethylphenyl, or trialkylsilyloxymethyl group.

10. A process according to any one of claims 5 to 9 in which R^5 is a phenyl group and R^6 is a neopentyl group.

11. A process according to any one of claims 5 to 8, wherein R^1, R^2, R^3 and one of R^4 and R^5 are hydrogen the other of R^4 and R^5 is an aryl or trialkylsilyloxymethyl group, R^6 is an alkyl group, R^7 is a ferrocenyl group, and R^8 is an aryl group.

12. A process according to any one of claims 5 to 10, wherein R^7 is phenyl.

13. A process according to any one of claims 5 to 10, wherein R^8 is an aryl group substituted by a halogen or haloalkyl group.

14. A process according to any one of claims 5 to 10, wherein R^8 is a phenyl group.

15. A process according to any one of claims 5 to 10, wherein R^8 is a naphthyl or substituted naphthyl group.

16. A process according to any one of claims 5 to 10, wherein R^7 is a ferrocenyl or substituted ferrocenyl group and R^8 is a naphthyl or substituted naphthyl group.

17. A process according to any one of claims 5 to 16, wherein X is chloride and Y is chloride or bromide.

18. A process according to any one of claims 1 to 17, wherein an alkane, cycloalkane and/or aromatic solvent is present.

19. A process according to any one of claims 1 to 17, wherein an ether is present as a solvent.

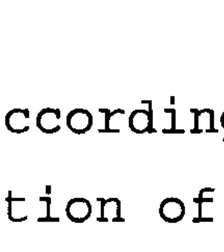
20. A process according to claim 19, wherein the ether is diethylether, 1,4-dioxane, tertbutylmethylether, or tetrahydrofuran.

21. A process according to any one of claims 1 to 20, which is carried out at a temperature of -90°C to -50°C.

22. A process according to any one of claims 1 to 21, wherein the concentration of the catalyst is in the range 0.5 to 5 atom%, expressed as copper atoms based on moles of the allylic compound.

23. A process according to any one of claims 1 to 22, wherein the ratio of copper atoms to the chiral organic ligand molecules is 1:10 to 2:1.

24. A compound of formula



in which A is a ferrocenyl group and B is C_6-C_{20} aryl group other than a phenyl group.

25. A compound according to claim 19, wherein B is a 2-naphthyl group.

26. A complex which comprises a compound as claimed in claim 24 or 25 and copper.

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