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A new chiral iminophosphine ligand derived from (1*S*,4*S*)-fenchone in palladium-catalyzed asymmetric allylic alkylations

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Abstract

A new chiral iminophosphine ligand derived from (1*S*,4*S*)-fenchone has been developed, and its usefulness as a chiral ligand in asymmetric synthesis was demonstrated in palladium-catalyzed allylic alkylations.

In recent years, asymmetric synthetic reactions have received much attention for the creation of new stereogenic centers, especially in the pharmaceutical field.[1] Among the known asymmetric synthetic methods, a catalytic asymmetric reaction with a chiral ligand is the most important and challenging method from the point of efficient enantioselectivity,[2] and various kinds of chiral ligands, involving heteroatoms such as phosphorus,[3] nitrogen,[4,5] oxygen,[6] and sulfur[7] groups as coordinating elements, have been developed so far.

An *o*-phosphinophenyl imine functionality[8] has planarity over a rather long range of distance with five atoms (P–C–C–N–C). Therefore, if one can introduce a chiral auxiliary with efficient face enantioselectivity in the imino function, and can control the *syn* or *anti* geometry relative to the imino group with high selectivity, such an iminophosphine system should be expected to have a high potential as a chiral ligand in transition metal-catalyzed reactions. We wish to communicate herein a new efficient chiral iminophosphine ligand derived from readily available (1*S*,4*S*)-fenchone, the usefulness as a chiral ligand being demonstrated in palladium-catalyzed allylic alkylations.

Chiral iminophosphines (1*S*,4*S*)-**3a** and (1*R*,4*R*)-**3b** were obtainable from the readily available terpenes, (1*S*,4*S*)-fenchone **1a** and (1*R*,4*R*)-camphor **1b** (Scheme 1). *N*-(2-Bromophenyl)imines **2a**,**b** were prepared in 45 and 67% yield, respectively, by condensation of 2-bromoaniline with (1*S*,4*S*)-**1a** and (1*R*,4*R*)-**1b** in refluxing toluene in the presence of $TiCl_4$ (0.6 equiv.).[9] Lithiation of *N*-(2-

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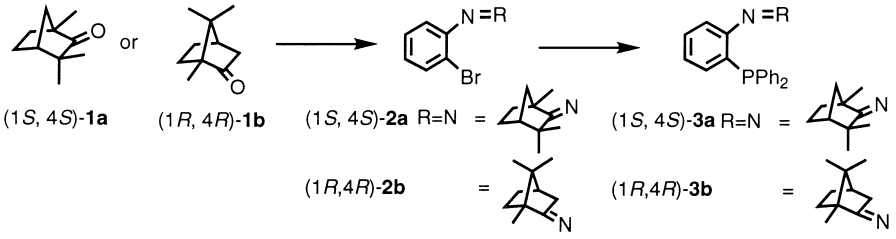
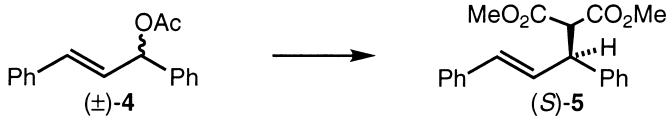
bromophenyl)imines **2a**,**b** with *n*-butyllithium followed by phosphinylation with chlorodiphenylphosphine gave imines (1*S*,4*S*)-**3a** and (1*R*,4*R*)-**3b** in 57 and 45% yield, respectively.



Scheme 1.

Stereochemical studies of palladium-catalyzed asymmetric alkylations of (±)-**4** with dimethyl malonate using iminophosphines (1*S*,4*S*)-**3a** and (1*R*,4*R*)-**3b** as chiral ligands were undertaken under various reaction conditions. The reactions of (±)-**4** with dimethyl malonate (3.0 equiv.) were carried out in dichloromethane at 0°C in the presence of a palladium catalyst (0.03 equiv.), (1*S*,4*S*)-**3a** (0.06 equiv.), *N*,*O*-bis(trimethylsilyl) acetamide (BSA)[10] (3.0 equiv.), and a catalytic amount of sodium, potassium, or cesium acetate (Scheme 2). The results are summarized in Table 1. The marked effects of the palladium species and the acetate counter ions in this allylic alkylation were observed as listed in Table 1; among the species of palladium catalysts examined (entries 1–5), the highest chemical yield (87%) and enantiomeric excess (84%) were obtained with $Pd_2(dba)_3 \cdot CHCl_3$ and $[PdCl(\pi\text{-allyl})]_2$, respectively. The use of the smaller counter ion (Na) unequivocally resulted in an enhanced enantiocontrol of the asymmetric induction (84%) in contrast to that with the larger counter ions (K and Cs) (entries 5–7).



Scheme 2.

Solvent effects in this asymmetric induction are demonstrated in Table 1; high enantioselectivity was obtained in each case except for DMSO (66%), toluene (65%), and 1,2-dichloroethane (69%), and the highest enantioselectivity (90%) was achieved with DME at −20°C.

The chiral iminophosphine (1*R*,4*R*)-**3b**, derived from (1*R*,4*R*)-camphor, provided a slightly lower enantioselectivity for (*R*)-**5**, compared with that of (1*S*,4*S*)-**3a**, in the palladium-catalyzed allylic alkylations of (±)-**4**. The effects of species of palladium catalysts were studied by employing palladium catalysts (0.03 equiv.) such as $Pd(OAc)_2$, $Pd(dba)_2$, $Pd_2(dba)_3 \cdot CHCl_3$, or $[PdCl(\pi\text{-allyl})]_2$ in the allylation of (±)-**4** with dimethyl malonate (3.0 equiv.), using the chiral ligand (1*R*,4*R*)-**3b** (0.06 equiv.), BSA (3.0 equiv.), and a catalytic amount of NaOAc in dichloromethane at 0°C for 10–86 h, affording (*R*)-**5** in 17, 60, 63, 80% yield with low *ee*s (27–33%), respectively. The solvent effects were studied under the same reaction conditions using dichloromethane, THF, DME, or CH_3CN as solvents at −20°C for 40–130 h, resulting in the formation of (*R*)-**5** in 74, 10, 12, or 17% yield with increasing *ee*s (34–51%), respectively.

A plausible mechanism for asymmetric induction by these bicyclic iminophosphine ligands is presented to rationalize the stereochemical results observed. With regard to the geometrical isomer of the carbon–nitrogen double bond in the imine derived from (1*S*,4*S*)-fenchone, presumably the *anti*-imine would be exclusively formed in preference to the *syn*-isomer, because of the severe steric interference between the 3,3-dimethyl group in the fenchone part and the 2-(diphenylphosphino) phenyl ring in the *syn*-imine. The geometry of the *anti*-imine was confirmed by the observation of the NOE between the

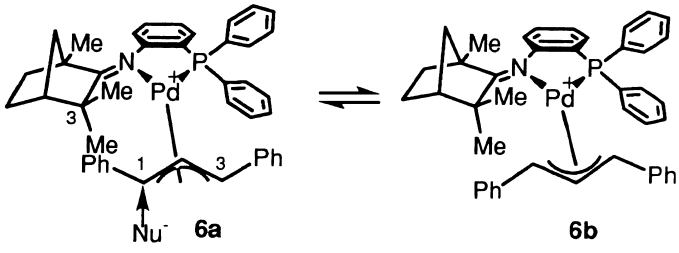
Table 1

Entry	Ligand	Catalyst	Solvent	Acetate Salt	Reaction temp. (°C)	Reaction time (h)	Yield (%) of **5**	e.e. (%) of **5**[b] (Abs. confign.)
1	(1*S*,4*S*)-**3a**	$Pd_2(dba)_3 \cdot CHCl_3$	CH_2Cl_2	NaOAc	0	24	87	76 (*S*)
2		$Pd(dba)_2$	CH_2Cl_2	NaOAc	0	24	68	73 (*S*)
3		$PdCl_2(CH_3CN)_2$	CH_2Cl_2	NaOAc	0	120	11	79 (*S*)
4		$Pd(OAc)_2$	CH_2Cl_2	NaOAc	0	72	77	69 (*S*)
5		$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	NaOAc	0	15	71	84 (*S*)
6		$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	KOAc	0	24	88	57 (*S*)
7		$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	CsOAc	0	9	83	53 (*S*)
8		$[PdCl(\pi\text{-allyl})]_2$	DMF	NaOAc	-20	110	56	86 (*S*)
9		$[PdCl(\pi\text{-allyl})]_2$	CH_3CN	NaOAc	-20	75	57	84 (*S*)
10		$[PdCl(\pi\text{-allyl})]_2$	THF	NaOAc	0	30	65	86 (*S*)
11		$[PdCl(\pi\text{-allyl})]_2$	DME	NaOAc	-20	160	47	90 (*S*)
12		$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	NaOAc	-20	40	76	85 (*S*)
13	(1*R*,4*R*)-**3b**	$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	NaOAc	0	10	80	27 (*R*)
14		$[PdCl(\pi\text{-allyl})]_2$	CH_2Cl_2	NaOAc	-20	40	74	51 (*R*)
15		$[PdCl(\pi\text{-allyl})]_2$	THF	NaOAc	0	116	75	35 (*R*)

a) The reactions of (±)-**4** with dimethyl malonate (3.0 equiv.) were carried out in dichloromethane at 0°C in the presence of a catalyst (0.03 equiv.) and chiral ligands (1*S*,4*S*)-**3a** or (1*R*,4*R*)-**3b** (0.06 equiv.), BSA (3.0 equiv.), and a catalytic amount of acetate salt.

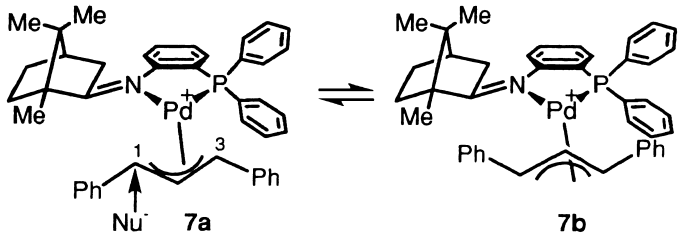
b) The enantiomeric excess (e.e.) of (*S*)-**5** was determined by the HPLC analysis with Chiralpak AD.[11]

methyl group at C1 and the aromatic hydrogen at C6 in the NMR spectral analysis. In the equilibrium of the stereoisomeric π-allyl systems **6a**,**b** derived from the *anti*-imine, a W-type isomer **6a** is preferable to an M-type one **6b** due to the steric hindrance between the phenyl group at the allyl terminus and the methyl substituent (*endo*) at C3 of the fenchone part in the iminophosphine **6b** (Scheme 3). Thus, the preferential alkylation via **6a** occurs from the back side of the palladium catalyst at the allyl terminus C1 *trans* to the better π-acceptor,[12] which is the phosphine group in the present case,[5e,8c] affording (*S*)-**5** with high enantioselectivity.



Scheme 3.

A similar discussion is applicable to the reactions with (1*R*,4*R*)-**3b** derived from (1*R*,4*R*)-camphor. The geometric isomer with the *anti* configuration relative to the imino function is preferred due to the steric hindrance arising from the methyl group at C1 of the camphor part in (1*R*,4*R*)-**3b**.[9] In the conformational equilibrium of the π-allylpalladium complexes **7a**,**b** derived from this preferable *anti* isomer of (1*R*,4*R*)-**3b**, an M-type π-allylpalladium complex **7a** is preferred to a W-type one **7b** because of the steric interference between the methyl substituent at C1 of the camphor part and the phenyl group at the C1 allyl terminus in **7b** (Scheme 4). The preferential alkylation proceeds from the back side of the palladium catalyst at the allyl terminus C1 in **7a** *trans* to the better π-acceptor,[12] which is the phosphine group in this case,[5e,8c] providing (*R*)-**5** with rather moderate enantioselectivity.



Scheme 4.

The chiral vicinal phosphino imino function derived from readily available (1*S*,4*S*)-fenchone has been shown to serve as an efficient chiral ligand in a palladium-catalyzed allylic alkylation, providing good asymmetric induction.

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