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A novel direct catalytic asymmetric synthesis of cyclic indole derivatives by intramolecular carbopalladation of allenes and subsequent intramolecular amination

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Abstract—A novel asymmetric synthetic method allowing a facile entry to chiral cyclic indole compounds has been developed by means of asymmetric carbopalladation–amination of allenes using a palladium catalyst with chiral phosphine ligands: intramolecular carbopalladation of allenes, which bear *o*-iodophenyl amino groups, was followed by intramolecular amination of the resultant π-allylpalladium intermediates. The enantioselectivity of the asymmetric reactions were found to be dependant on the chiral phosphine ligands and the solvent used; *N*-methylpyridone was the most effective solvent for achieving efficient enantioselectivity with high chemical yields, and (*S*)-(−)-BINAP or (*S*)-Tol-BINAP were revealed to be the most useful of the chiral phosphine ligands examined, depending on the substrate employed.

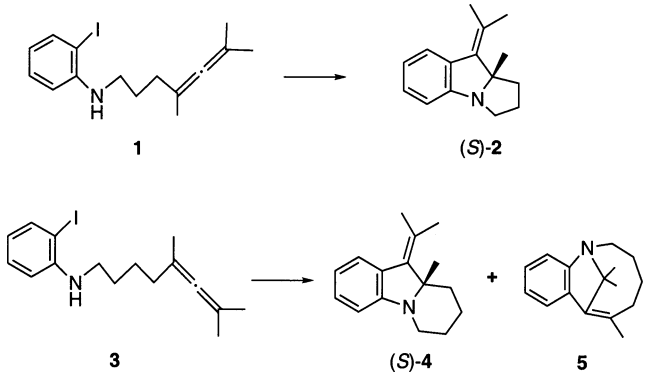
In recent years, allenes have received much attention as three-carbon units in organic synthesis, particularly in transition metal-catalyzed reactions.[1] Furthermore, quite recently, increasing interest has been placed on the chemistry of allenes with axial chirality and asymmetric synthesis with allenes.[2]

We wish to communicate a novel, direct catalytic asymmetric synthesis of cyclic indole derivatives by palladium-catalyzed reactions of allenes, which involve *o*-iodoaryl groups and amino components as nucleophiles in the molecules.

In general, upon treatment with aryl iodides or allylic halides under palladium catalysis, allenic compounds provide β-aryl or -allylic π-allylpalladium complexes which can be reacted with nucleophiles to give α,β-functionalized olefinic compounds in one-pot reactions.[3] Previously, we reported the stereospecificity of the above reactions of chiral allenes,[4] and the palladium-catalyzed asymmetric α,β-functionalization of allenes by intermolecular carbopalladation and nucleophilic substitution of the allene using a palladium catalyst with chiral phosphine ligands.[5]

Evidently, it should be of great importance and interest for the construction of polycyclic compounds that upon treatment with a palladium catalyst, allenes bearing *o*-iodoaryl groups and nucleophilic functionalities undergo intramolecular carbopalladation at the allene function, followed by intramolecular nucleophilic substitution reactions, providing a facile and direct entry to heterocycles or carbocycles in one-pot reactions.[6] Herein, we report our recent results on the palladium-catalyzed asymmetric reactions of allenes involving the above-mentioned two functional groups at the appropriate sites in the molecules (Scheme 1).

The carbopalladation–amination of allene **1** using K_2CO_3 or Et_3N as base gave a cyclized product, 7a,8-



Scheme 1.

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dihydro - 8 - *i* - propylidene - 7a - methylpyrrolido[1.2 - *a*]-indole **2** in good yields but with almost no asymmetric induction. Therefore, we investigated the reactions using silver salts (which are well known as readily counterion-exchangable reagents) instead of K_2CO_3 or Et_3N.[6,7] The reactions were carried out in MeCN, DME, DMSO, benzene, or *N*-methylpyridone (NMP) at 50–60°C in the presence of $Pd(dba)_2$ (0.1 equiv.), a chiral ligand (0.2 equiv.), and Ag_3PO_4 (1.5 equiv.), to give the chiral cyclized product **2**, in moderate yields. Of the chiral phosphine ligands examined: {(*S*)-(−)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), (*S*)-(+)-2,2′-bis-(di-*p*-tolylphosphino)-1,1-binaphthyl (Tol-BINAP), (4*R*)-*trans*-[(2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)]bis(diphenylphosphine) ((−)-DIOP), (4*R*,5*R*) - (+) - 4,5 - bis[bis(4′ - methoxy - 3′,5′ - dimethylphenyl)phosphinomethyl] - 2,2 - dimethyl - 1,3 - dioxolane ((+)-MOD-DIOP), (*S*)-*N*,*N*-dimethyl-1-[(*R*)-2-(diphenylphosphino)ferrocenyl]ethylamine (PPFA), (*S*)-*N*,*N*-dimethyl-1-[(*R*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine (BPPFA), (*S*) - 1 - [(*R*) - 1′,2 - bis-(diphenylphosphino)ferrocenyl]ethanol (BPPFOH), and (*S*) - 1 - [(*R*) - 1′,2 - bis(diphenylphosphino)ferrocenyl]ethyl acetate (BPPFOAc)}, (*S*)-(−)-BINAP was found to induce high enantioselectivity (82%) under the reaction conditions in NMP at 50°C with Ag_3PO_4. The use of NMP as solvent resulted in the highest chemical yields and good enantiomeric purities of (*S*)-**2**. The highest enantioselectivity of (*S*)-**2** (e.e. = 88%) was obtained using (*S*)-Tol-BINAP as a chiral ligand in NMP at 50°C. The enantiomeric excess (e.e.) of the product **2** was determined by HPLC analysis with a Chiralcel OJ column. The results obtained are summarized in Table 1.

Other chiral phosphine ligands provided **2** with much lower enantioselectivity: (−)-DIOP (17% e.e. (*S*)) and (+)-MOD-DIOP (12% e.e. (*S*)) and the use of ferrocenyl ligands such as (*S*)-(*R*)-PPFA, (*S*)-(*R*)-BPPFA, (*S*)-(*R*)-PPFOH, and (*S*)-(*R*)-BPPFOAc also resulted in the formation of **2** with poor enantioselectivities (1% (*S*), 2% (*R*), 5% (*R*), and 12% e.e. (*S*), respectively).

Similarly, the carbopalladation–amination reaction of another allene, **3**, was investigated. The reactions were carried out at 60°C with $Pd(dba)_2$ (0.1 equiv.), a chiral phosphine ligand (0.2 equiv.), and Ag_3PO_4 (1.5 equiv.), providing 8a,9-dihydro-9-*i*-propylidene-8a-methylpiperido[1.2-*a*]indole **4**, as the main product. Unexpectedly, in this model, a small amount of 1,4-(dimethylmethano)-5-methyl-1-azabenzo[2.3]cyclonon-4-ene **5** was detected as a by-product (the ratio of **4** to **5** was determined to be over 99% by the ^1H NMR analysis).[6]

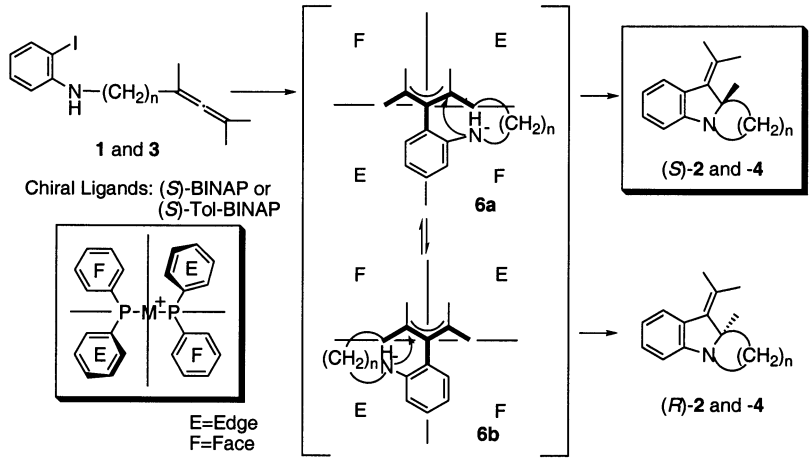
Surprisingly, unlike the aforementioned model **1**, in the reactions of **3** (*S*)-(−)-BINAP was ineffective, but a ferrocenyl ligand, (*S*)-(*R*)-BPPFOAc, was demonstrated to be rather useful in achieving high asymmetric induction (58%) for (*S*)-**4**, as listed in Table 1. The highest asymmetric induction (87%) for (*S*)-**4** was obtained in the palladium-catalyzed reaction of **3** using (*S*)-Tol-BINAP as a chiral ligand in NMP at 60°C. Other phosphine ligands ((+)-MOD-DIOP, (*S*)-(*R*)-PPFA and (*S*)-(*R*)-BPPFA) provided **4** with low enantioselectivities (8% (*R*), 10% (*S*), and 4% (*R*) e.e., respectively).

The aforementioned absolute configurations of the products **2** and **4** obtained with chiral phosphine lig-

Table 1. Asymmetric synthesis of indoles by palladium-catalyzed reactions of allenes[a]

Substrate	Ligand	Solvent	Reaction temp. (°C)	Reaction time (h)	Product yield (%)[b]	E.e. (%) of the products (*S*)[c,d]
1	(*S*)-(−)-BINAP	MeCN	60	18	8 (35) (3)	21
1	(*S*)-(−)-BINAP	DME	60	18	19 (47) (3)	8
1	(*S*)-(−)-BINAP	DMSO	60	18	3 (13) (3)	54
1	(*S*)-(−)-BINAP	Benzene	60	18	31 (100) (3)	20
1	(*S*)-(−)-BINAP	NMP	60	18	72 (98) (3)	65
1	(*S*)-(−)-BINAP	NMP	50	48	67 (88) (3)	82
1	(*S*)-Tol-BINAP	NMP	50	48	58 (90) (3)	88
3	(*S*)-(−)-BINAP	MeCN	60	24	21 (57) (4)	28
3	(*S*)-(−)-BINAP	DMSO	60	36	47 (60) (4)	28
3	(*S*)-(−)-BINAP	NMP	60	12	63 (68) (4)	37
3	(*S*)-Tol-BINAP	NMP	60	20	73 (96) (4)	71
3	(*S*)-Tol-BINAP	NMP	50	48	68 (90) (4)	87
3	(*S*)-(*R*)-BPPFOH	NMP	60	20	26 (52) (4)	39
3	(*S*)-(*R*)-BPPFOAc	NMP	60	20	53 (77) (4)	58

[a] The reactions of **1** or **3** were carried out in the presence of $Pd(dba)_2$ (0.1 equiv.), ligands (0.2 equiv.), and Ag_3PO_4 (1.5 equiv.).
[b] Yields based on recovered starting material are described in parentheses.
[c] The enantiomeric excess (e.e.) of **2** and **4** was calculated by HPLC analysis using a Chiralcel OJ column.
[d] The absolute configuration of the newly created stereogenic carbons in the products is predicted by the plausible mechanism proposed.



Scheme 2.

ands were deduced on the basis of the steric environment of the intermediate π-allylpalladium complex formed by carbopalladation of the allene with chiral ligands. With (*S*)-BINAP or (*S*)-Tol-BINAP as the chiral controller, as shown in Scheme 2, the formation of two transition states **6a**,**b** including π-allylpalladium complexes coordinated with (*S*)-BINAP or (*S*)-Tol-BINAP would be possible. However, the formation of **6a** is more favorable owing to the existence of steric interference between the nucleophilic (amine) part and the edge group of (*S*)-BINAP and (*S*)-Tol-BINAP in **6b**. Therefore, the intramolecular nucleophilic reaction (amination) occurs through **6a** from the less crowded side opposite the palladium catalyst to afford (*S*)-**2** and -**4**.

Thus, it should be noted that a novel asymmetric cyclization reaction is realized by the intramolecular α,β-functionalization of an allene under palladium catalysis with chiral phosphine ligands. We are now in the process of further investigation of asymmetric synthesis along this line, by applying other heteroatoms and carbanions as intramolecular nucleophiles for direct construction of chiral polycyclic heterocycles and carbocycles.

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