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Preparation Of Axially Chiral Amines And Its Attention In Asymmetric Catalysis: A Review

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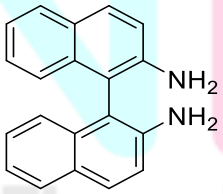
Abstract : The axially chiral compounds/atropisomers with functional group such as phosphine (BINAP) and phenol (BINOL) have found remarkable applications in chiral resolving agents, asymmetric catalysis, chiral auxiliary and in supramolecular chemistry. Likewise, axial chiral compounds with amine as the functional group have comparable potential in chiral applications. Nonetheless, further research is needed to understand the chemistry of axially chiral compounds in terms of both its synthesis and applications. The various synthetic approaches for obtaining axially chiral compounds and amines are illustrated in this review article. Moreover, it explains how axially chiral amines are used for various chiral organic transformations.

IndexTerms **– Atropisomerism, Binaps, Binols, Axially chiral amines, Stereoselective synthesis.**

INTRODUCTION

Chirality is a fascinating aspect of nature; chirality is found in many naturally occurring which are physiologically active substances. These extremely selective therapeutic activities are due to particular interactions with enzyme active sites with the distinct three-dimensional structure of chiral molecules. [1-3]. It is evidenced by an examination of 1900 small-molecule medicines in the USD FDA Drug Bank (FDA: Food and Drug Administration); 15% of scaffolds approved by the FDA had one or more atropisomeric axes, and 10% of molecules are "proatropisomeric." More significantly, since 2011, the frequency of atropisomeric substances has increased significantly. Almost one in three FDA-approved small molecules now have an atropisomeric ingredient, and 16% more are proatropisomeric.

Moreover, axially chiral biaryls possess significant potential as preferred ligands in asymmetric catalysis, as evidenced by the well-known phosphoric acids produced using BINAP (phosphine), BINOL (phenol), and their combinations [7-8]. Despite possessing similar potential, the second axially chiral biaryl with an amine functional group is less developed. 1,1′ -Binaphthyl-2,2′ -diamine serves as the most widely utilized example of an axially chiral amine (BINAM). The axially chiral amines are certainly useful in asymmetric catalysis, chiral auxiliaries, chiral resolving agents, supramolecular chemistry, and drug development.



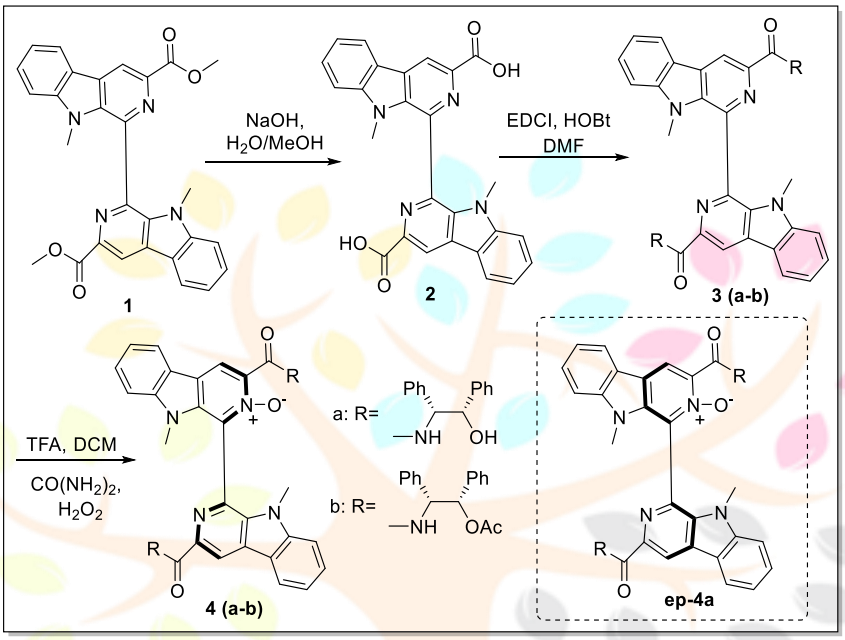
BINAM

The objective in this study is to provide a concise synopsis of the synthesis and uses of axially chiral amines as a possible resource for the scientific community. In here common reactions such as enantioselective hydrogenation, allylic substitution, Asymmetric Mannich reaction, kinetic resolution, conjugate addition, transamination reaction, and coupling reaction are used to broadly classify the application of axially chiral amines. The synthesis of axially chiral amines and its specific chiral organic transformation application are coupled with each general class presentation.

Enantioselective hydrogenation reaction

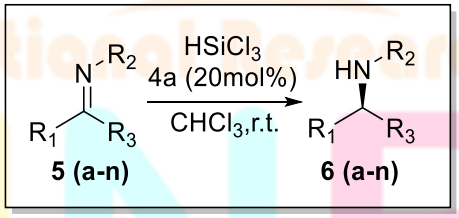
Enantioselective hydrogenation is a chemical process wherein an unsaturated substrate molecule, such as an alkene, ketone, or imine, has two hydrogen atoms added to one of its two faces preferentially. The way the substrate attaches to the chiral catalysts determines the selectivity.

Hua-Jie Zhu et.al [9] have fabricated a innovative asymmetric-axle-supported chiral N-O amide by hydrolysis of 1 to its corresponding diacid 2, which on acid amine coupling with chiral amino alcohols gave compound 3 (a-b) in a yield of 95%. It is followed by oxidation to N-oxide derivatives 4 (a-b) (scheme 1). One major epimer product was obtained with a single step yield of 48% after column chromatography. The 4a was found to be a highly efficient Lewis basic organocatalyst for the hydrosilylation of N-aryl ketimines 5 (a-n) with HSiCl3. High conversion yield and high enantioselectivity up to 96% were assesed as illustrated from Table 1. N-oxide pyridine compounds has been used in this model reaction for the first time. The effect of different moiety of the catalyst on the hydrosilylation was investigated. The loss of the free eOH (e.g., ligand 4b) led to a decrease in ee% from 93% to 30%. Once the -O on N was removed, as in 3a, the ee% decreased to 7%.



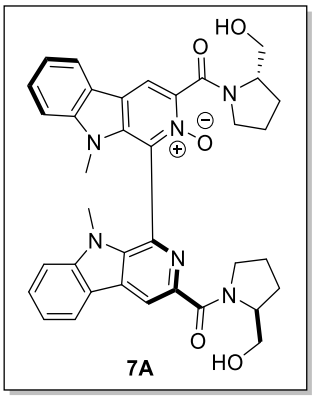
Scheme 1. Preparation of catalyst, 4 (a-b)

Table 1. **4a** catalyzes the asymmetric hydrosilylation of different ketimines.



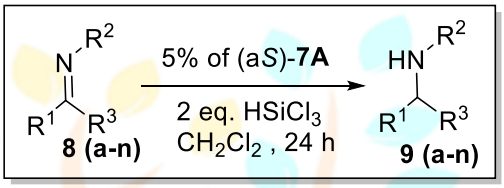
Entry	$R^1R^2R^3$	Yield %	Ee%	OR
1(a)	Ph, Ph, Me	95	93	-13.5
2(b)	4-F-ph, Ph, Me	98	95	-17.1
3(c)	4-Cl-ph, Ph, Me	97	94	-12.1
4(d)	4-Br-ph, Ph, Me	96	93	-17.1
5(e)	4-F_3C-ph, Ph, Me	95	84	-40.0
6(f)	4-NO_2-ph, Ph, Me	95	78	+16.5
7(g)	4-Br-- Ph, Ph, Me	98	76	+11.7
8(h)	4MeO-ph, Ph, Me	94	67	-13.9
9(i)	Ph, PMP, Me	97	96	-2.0
10(j)	Ph, 4-EtO-ph, Me	95	94	-18.2
11(k)	Ph, 4-Me-Ph, Me	95	93	+5.7
12(l)	Ph, 4-Et-Ph, Me	95	89	-1.74
13(m)	Ph-4-Br-Ph, Me	98	75	+26.6
14(n)	Ph, Ph, Et	95	94	+40

In extension of work on axial chiral compounds and its use for hydrogenation reaction Huajie Zhu and his colleagues [10] developed methodology of chiral axial-biscarboline based alcohol 7A catalyzed enantioselective 1,2-transfer hydrogenations of ketimines 8 (a-n) using HSiCl3 (Table 2) The substrate scope study demonstrated highest enantioselectivity of up to 99%. The minimum of the enantioselectivity values is 91% with more than 90% of conversions (Table 2).



7A

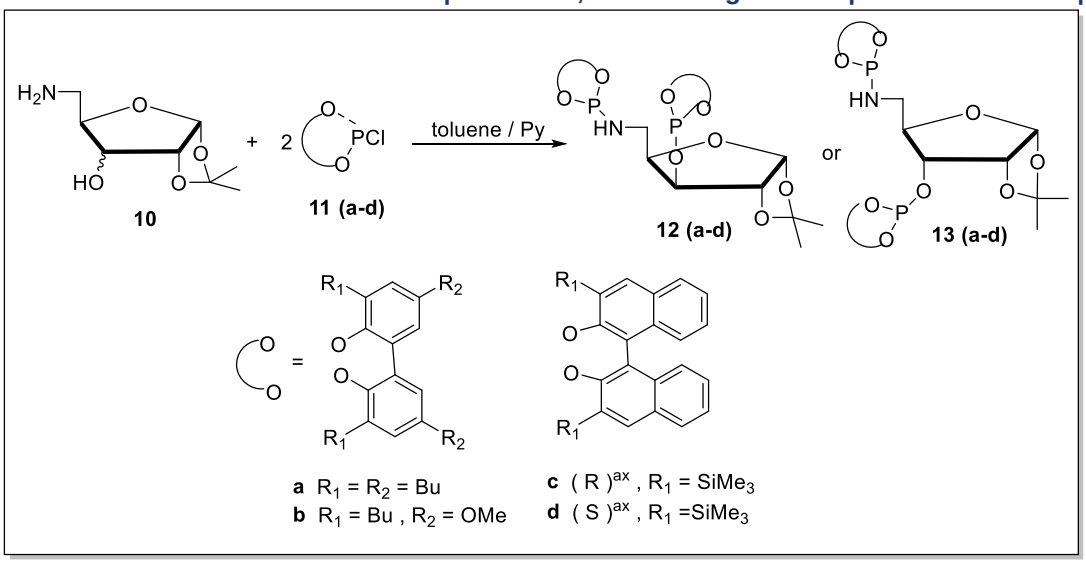
Table 2. The enantioselectivities in 1,2-transfer hydrogenations of fourteen ketimines, 8 (a-n) catalyzed by (aS)-7A



Entry	$R^{1,}R^{2,}R^{3}$	Yield%	Ee%
1	4-Br-C_6h_4, Ph, Me (**8a**)	91	97(S)
2	4-F-C_6h_4, Ph, Me (**8b**)	90	95(S)
3	4-Cl-C_6h_4, Ph, Me (**8c**)	89	96(S)
4	4-Br-C_6h_4, Ph, Me (**8d**)	92	96(S)
5	4-NO_2-C_6h_4, Ph, Me (**8e**)	90	92(R)
6	4-Me-C_6h_4, Ph, Me (**8f**)	90	94(R)
7	Ph,4-Me-C_6h_4, Ph, Me (**8g**)	92	98(S)
8	Ph,4-EtOC_6h_4, Ph, Me (**8h**)	94	98(S)
9	Ph-4Me-C_6h_4, Ph, Me (**8i**)	90	93(R)
10	Ph-4-Et-C_6h_4, Ph, Me (**8j**)	90	95(S)
11	Ph-4-Br-C_6h_4, Ph, Me (**8k**)	92	96(R)
12	4-Br-C_6h_4, Ph, Me (**8l**)	93	92(S)
13	Ph, Ph, Me (**8m**)	90	95(S)
14	Ph, Ph, Et (**8n**)	90	93(S)

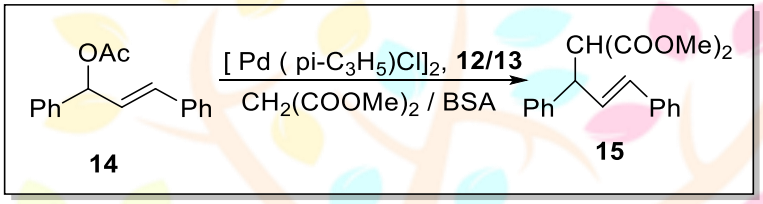
Allylic Substitution reaction

Allylic substitution is substitution reactions involving substrates that contain a leaving group in an allylic position. Oscar Pamies, Montserrat Dieguez and coworkers [11] have synthesized the series of phosphite-phosphoroamidite ligands **12 (a-d)** and **13 (a-d)** derived from reacting readily available D-xylose and axially chiral derivatives **11 (a-b)/11(c-d)**. Authors have first tested the series of eight phosphite-phosphoroamidite ligands **12 (a-d)** and **13 (a-d)** in the Pd-catalyzed allylic substitution of *rac*-1, 3-diphenyl-3-acetoxy-1-ene **14** with dimethyl malonate (Table 3). In general, ligands **12 (a-d)**, with an *S* configuration on C-3, produced better performances and enantioselectivies than ligands **13 (a-d)** (entries 1-4 vs 5-8). The best enantioselectivity (ee's up to 98%) was obtained with ligand **12d**, with an *S* configuration at carbon C-3 of the furanoside backbone and two enantiopure binaphthyl moieties with *S* configuration and bulky trimethylsilyl groups in the *ortho* positions.



Scheme 2. Synthesis of Phosphite-phosphoroamidite Ligands 12 (a-d) and 13 (a-d).

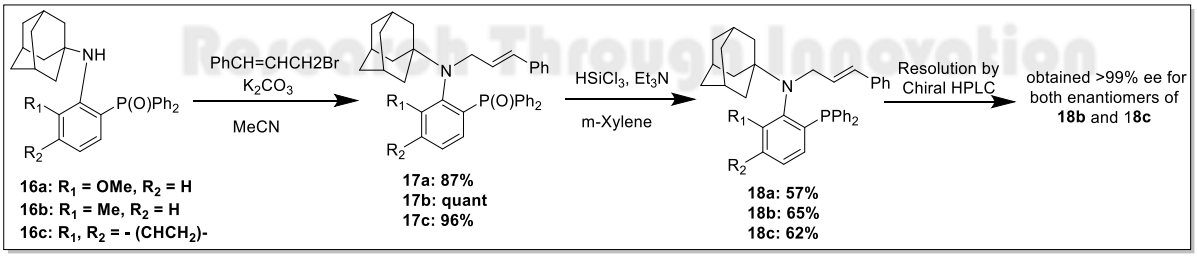
Table 3. Pd-Catalyzed Allylic Alkylation of Substrate S1 using Ligands 3 and 4a



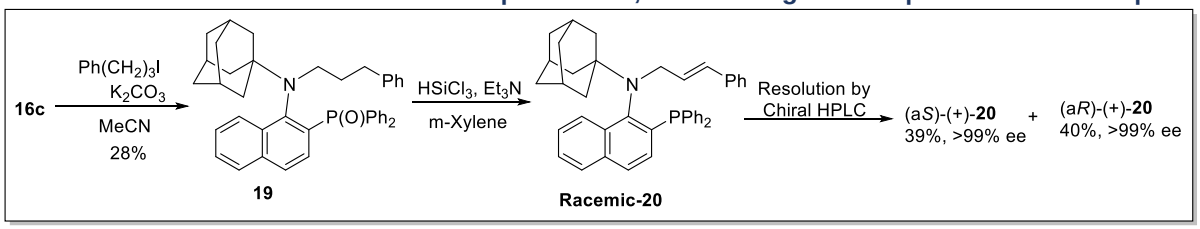
Entry	ligand	% conv (min)	% ee
1	**12a**	88	62
2	**12b**	100	59
3	**12c**	71	6
4	**12d**	96	98
5	**13a**	64	55
6	**13b**	83	52
7	**13c**	12	80
8	**13d**	15	12

Takashi Mino and collaborators [12] synthesized P/N-type ligands with C(aryl)–N(amine) bond axial chirality **18 (a-c)** and **20**. The synthesis of **18 (a-c)** consist of N-alkylation of 16 (a-c) with cinnamyl bromide occurred in the presence of K_2CO_3 to afford aminophosphine oxide 17 (a-c) which was converted into the desired racemic aminophosphine (±)-18 (a-c) using trichlorosilane–triethylamine in good yields (Scheme 3). Further, enantiopure compounds were obtained by resolution using chiral HPLC of racemic aminophosphine (±)-**18b** and (±)-**18c** to separate the both enantiomers of each racemic compound. The synthesis of enantiopure **20** followed similar synthetic strategy of N-alkylation of **16c** with 1-iodo-3-phenylpropane and subsequent reduction followed by resolution of racemic **20** by chiral HPLC (scheme 4).

Authors have discovered the palladium-catalyzed asymmetric allylic alkylation of indoles with 1,3-diaryl-2-propenyl acetate using N-1-adamantyl-N-cinnamylaniline derivative **18c** with C(aryl)–N(amine) bond axial chirality as a ligand in MeCN gave the desired products **22** in good yields with moderate to high enantioselectivities (up to 98% ee) (Table 4).

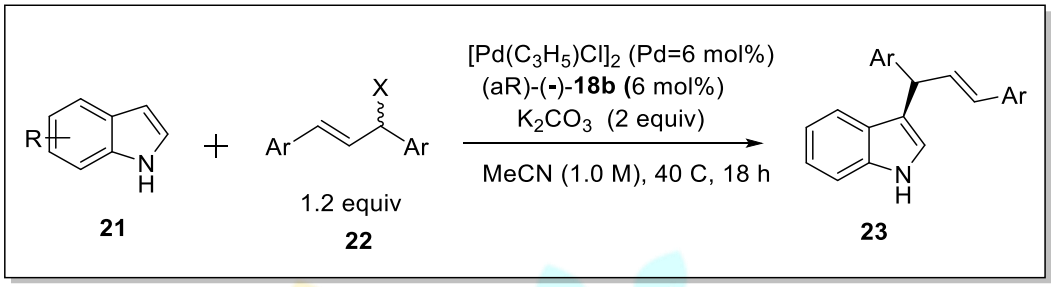


Scheme 3. Preparation of racemic aminophosphines (±)-**18 (a-c)** and enantiopure **18 (b-c)**.



Scheme 4. Preparation of racemic aminophosphines (±)-**20** and enantiopure **20**.

Table 4. Palladium-catalyzed asymmetric allylic alkylation of indoles **21** using (a*R*)-(-)-**18c**



In extension of work on synthesis of P/N-type of chiral ligands Takashi Mino and collaborators [13] have synthesized series of *N*,*N*-disubstituted allylic amine type aminophosphine **24-26** (chart 1) which are derivatives of **18 (a-c)** by following same synthetic strategy.

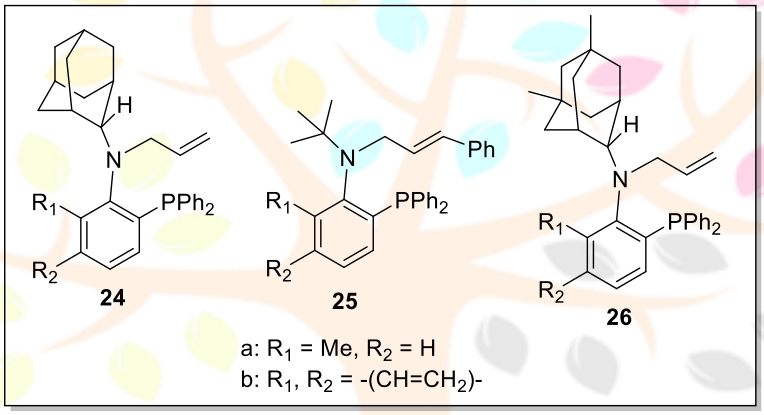
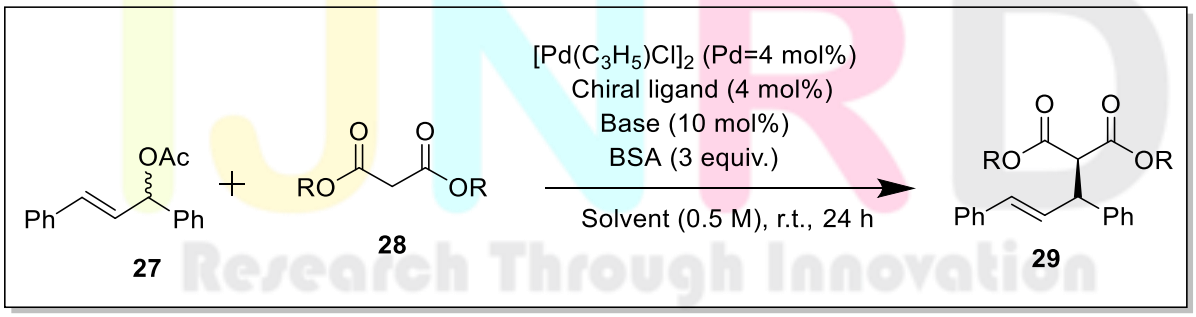


Chart 1. P-N type of axially chiral ligands **24-26**.

Aminophosphines **24**–**26** exist in C(aryl)– N(amine) bond axial chirality by chiral High performance liquid chromatography analysis. Both enantiomeric isomers of **26b** were successfully acheived in an enantiomerically pure form. Authors demonstrated that **18a**, **18b**, and **26b** can be used as effective chiral ligands for the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate **27** with malonates in high enantioselectivities (up to 90% ee) (Table 5).

Table 5. Palladium-catalyzed asymmetric allylic alkylation with malonate using chiral ligands.



Entry	Chiral ligand	R	Solvent	Base	Yield (%)[b]	Ee (%)[c]
1	(–)-**4b**	Me	PhMe	LiOAc	86(**12a**)	62
2	(a*R*)-(–)-**1a**	Me	PhMe	LiOAc	94(**12a**)	79
3	(a*R*)-(–)-**1b**	Me	PhMe	LiOAc	95(**12a**)	48
4	(a*R*)-(–)-**1a**	Me	THF	LiOAc	91(**12a**)	33
5	(a*R*)-(–)-**1a**	Me	Et2O	LiOAc	98(**12a**)	38
6	(a*R*)-(–)-**1a**	Me	DCM	LiOAc	86(**12a**)	58
7	(a*R*)-(–)-**1a**	Me	Hexane	LiOAc	76(**12a**)	58
8	(a*R*)-(–)-**1a**	Me	$PhCF_3$	LiOAc	87(**12a**)	53
9	(a*R*)-(–)-**1a**	Me	PhMe	KOAc	95(**12a**)	73
10	(a*R*)-(–)-**1a**	Me	PhMe	NaOAc	86(**12a**)	83
11[d]	(a*R*)-(–)-**1a**	Me	PhMe	NaOAc	99(**12a**)	90
12[d,e]	(a*R*)-(–)-**1a**	Me	PhMe	NaOAc	91(**12a**)	86
13[d]	(a*R*)-(–)-**1a**	Et	PhMe	NaOAc	94(**12b**)	90
14[d]	(a*R*)-(–)-**1a**	*t*-Bu	PhMe	NaOAc	86(**12c**)	87

Furthermore, Masami Sakamoto and group [14] synthesized few more N-trans-cinnamyl-N-cyclohexylaniline type aminophosphine **30** and a series of N-2-adamantyl-N-trans-cinnamylaniline type aminophosphines **31**. Although aminophosphine **30** was unsuccessful to find the existence of axial chirality, aminophosphines **31**, which exist in the axial chirality in a C(aryl)–N(amine) bond by chiral HPLC analysis as 1-adamantyl type chiral ligands **18 (a-c)** (chart 2). Enantiomeric isomers of **31b**, **31c**, and **31d** were obtained in an enantiomerically pure form by resolution by chiral HPLC.

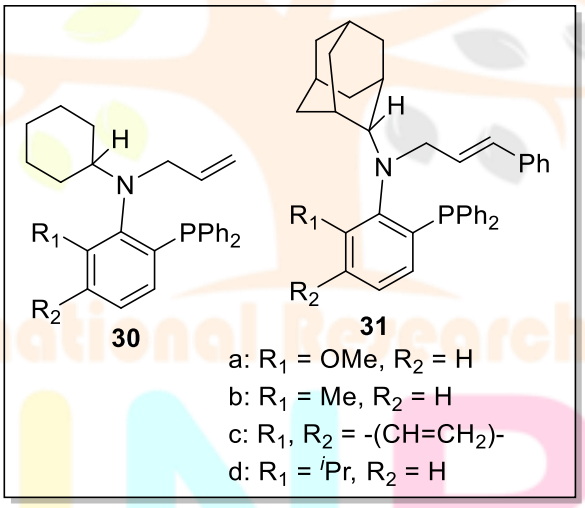
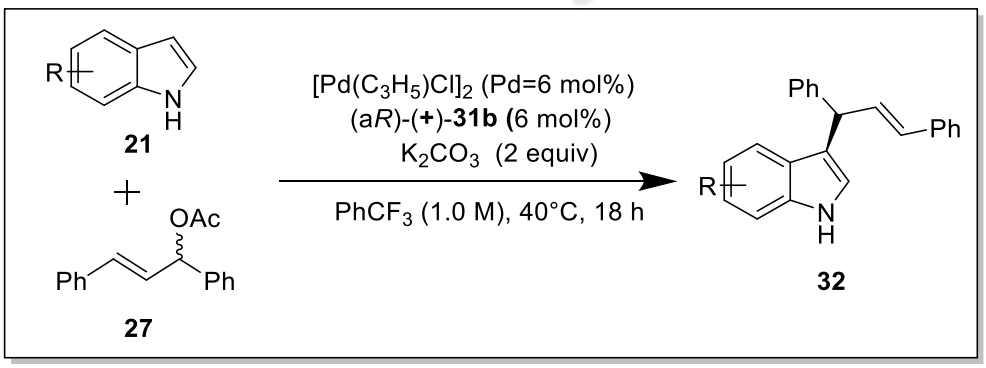


Chart 2. P/N ligands **30** and **31**

Authors also tested the palladium-catalysed asymmetric allylic substitution of 1,3-diphenyl-2-propenyl acetate **27** with indoles **21** using aminophosphines **31b** as valuable chiral ligands in high enantioselectivities (up to 96% ee) (Table 6).

Table 6. Palladium-catalyzed asymmetric allylic substitution of indoles using (a*R*)-(+)-**31b**

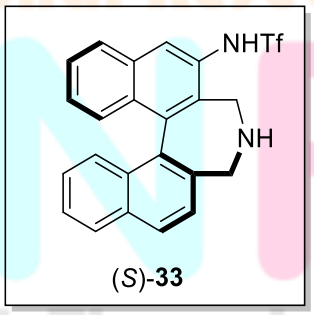


Entry	R	Yield[a] (%)	ee[b] (%)
1	H	69 (9a)	93
2	6-Me	66 (9b)	95
3	6-MeO	77 (9c)	77
4	6-BnO	70 (9d)	85
5	6-NO_2	68 (9e)	96
6	6-F	58 (9f)	95
7	6-Cl	77 (9g)	89
8	6-Br	78 (9h)	96
9	5-Br	72 (9i)	96
10	4-Br	70 (9j)	71
11	4-Me	69 (9k)	90
12	7-Br	45 (9l)	59
13	2-Ph	60 (9m)	92

Asymmetric Mannich reaction

The Mannich reaction is a multicomponent reaction resulting in amino alkylation of an acidic proton placed next to a carbonyl functional group. It involves an appropriate carbonyl compound, such as formaldehyde and a primary or secondary amine or ammonia. The final product is a β-amino-carbonyl compound known as a Mannich base. Reactions between aldimines and α-methylene carbonyls are also considered as Mannich reaction since these imines are generated from the reaction of amines and aldehydes. It includes the reaction of primary or secondary amines or ammonia, formaldehyde and appropriate α-CH-acidic compounds (nucleophiles) such as carbonyl compounds having α-CH-acidic, nitriles, acetylenes, aliphatic nitro compounds, α-alkyl-pyridines or imines. The asymmetric Mannich reaction ranks among the most potent enantioselective and diastereoselective C–C-bond forming reactions. In current years, organo catalyzed versions of asymmetric Mannich processes have been increasingly reported and used in a rapidly growing number of applications.

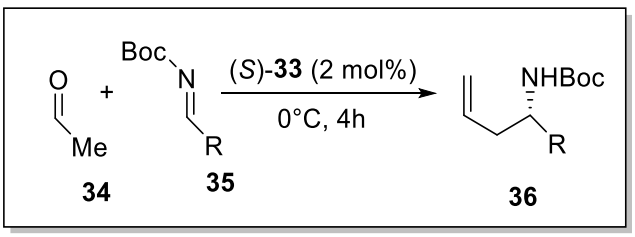
Keiji Maruoka et.al. [15] have developed a highly stereoselective direct asymmetric Mannich reaction between acetaldehyde **34** and N-Boc-protected imines **35** catalyzed by (*S*)-**33** (Table 7). In general, these direct asymmetric Mannich reactions proceeded smoothly, and the desired products were obtained in good yields and excellent enantioselectivity in all the cases examined.
Authors also accomplished the direct asymmetric Mannich reaction between various aldehydes, **37** and N-Boc-protected imines, **38**. As depicted in Table 8, the corresponding anti-Mannich adducts were obtained with good anti selectivity and superb enantioselectivity in all the cases examined under the optimized conditions. When a solution of the N-Boc-protected imine was added gradually to the reaction mixture by syringe pump, the catalyst loading could be reduced to 1 mol% without loss of stereoselectivity (Table 8, entries 3 and 4). Moreover, N-Boc-protected heteroaromatic imines as well as an N-Boc-protected aliphatic imine were found to be applicable to the present reaction system (Table 8, entries 8–10).



(*S*)-**33**

Chart 3. The structure of axially chiral amino sulfonamide, (*S*)-**33**

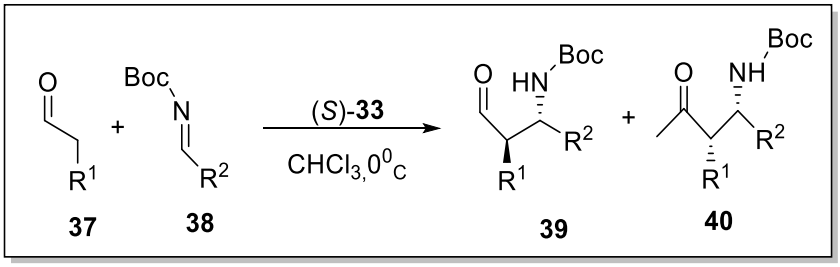
Table 7. Direct Mannich reactions between acetaldehyde **34** and various N Boc-protected imines **35** catalyzed by (*S*)-**33**.



34 **35** **36**

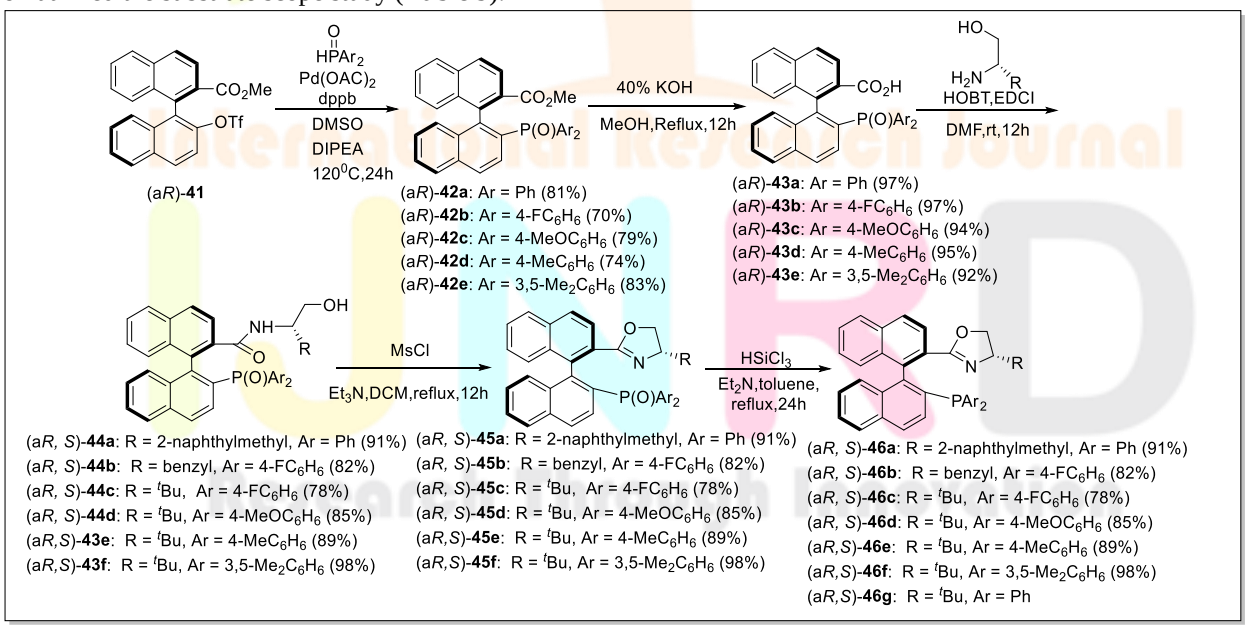
Entry	R	Yield (%)	ee (%)
1	Ph	87	99
2	2-naph	82	99
3	4-$MeOC_6H_4$	92	99
4	4-ClC_6H_4	73	99
5	2-furyl	70	98
6	Cyclohexyl	70	99

Table 8. anti-Selective Mannich reactions between various aldehydes and N-Boc-protected imines catalyzed by (*S*)-**36**.



Entry	R^1	R^2	Cat. (mol%)	Yield (%)	*Anti/sin*	ee (%)
1	Me	Ph	5	92	7.7:1	99
2	^{i}Pr	Ph	5	97	8.8:1	99
3	Bu	Ph	5	93	16:1	99
4	Bu	Ph	1	88	15:1	99
5	Bu	Ph	5	80	15:1	99
6	Bu	4-$MeOC_6H_4$	5	91	8.2:1	99
7	Bu	4-ClC_6H_4	5	78	11:1	99
8	Bu	2-furyl	5	88	7.5:1	99
9	Bu	3-pyridyl	5	92	16:1	99
10	Me	cyclohexyl	10	66	>20:1	99

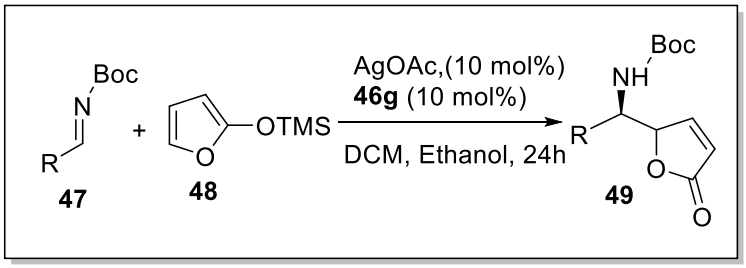
Min Shi et.al.[16] have synthesized axially chiral phosphine oxazoline ligands **46a-46g**. The synthesis of ligands followed the synthetic pathway shown in scheme 5. Axially chiral phosphine oxazoline ligand **46g** was found to be a fairly effective chiral ligand in silver (I) catalyzed asymmetric Mannich reaction of N-Boc aldimines **47** with trimethylsiloxy furan, **48**. The optimized reaction condition utilized the substrate scope study (**Table 9**).



Scheme 5. Reaction procedure for the preparation of ligands **46a-46g**.

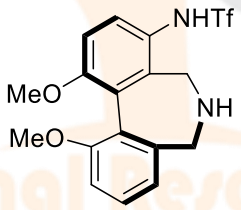
It was found that the N-Boc-protected imines **47(b-i)** bearing an aromatic ring (R group = aromatic ring) could react with **48** smoothly to give the corresponding asymmetric vinylogous Mannich-type products **49(b-i)** in good to high yields (79%-97%) and good diastereoselectivities (4:1e7:1 dr) as well as moderate to good enantiomeric excesses (63%-83% ee) for the major diastereoisomers whether they have electron-rich or electron-poor aromatic groups (Table 9, entries 2-9). When R is a heteroaryl group, such as 2-furyl group, similar outcome was obtained, affording the desired adduct **49j** in 79% yield, 80% ee and 7:1 dr (Table 9, entry 10). As for alkyl N-Boc-protected imine **47k**, the reactions also proceeded smoothly to give the corresponding N-Boc-protected g-butenolides **49k** in 75 yield and 75% ee along with 6:1 dr value (Table 9, entry 11).

Table 9. Scope and limitations of AVM reaction of N-Boc aldimines, **47** and siloxyfuran, **48**



Entry	R	Yield (%)	Anti:sin	Anti,ee(%)
		49	**49**	**49**
1	*p*-MeOC$_6$H$_4$, **47a**	**49a**, 97	6:1	86
2	*m*-MeOC$_6$H$_4$, **47b**	**49b**, 95	7:1	78
3	*p*-MeC$_6$H$_4$, **47c**	**49c**, 90	4:1	83
4	*m*-MeC$_6$H$_4$, **47d**	**49d**, 92	6:1	71
5	3,4,5-(MeO)$_3$C$_6$H$_2$, **47e**	**49e**, 94	5:1	76
6	Ph, **47f**	**49f**, 82	6:1	77
7	p-FC$_6$H$_4$, **47g**	**49g**, 93	6:1	63
8	p-BrC$_6$H$_4$, **47h**	**49h**, 88	6:1	67
9	m-BrC$_6$H$_4$, **47i**	**49i**, 79	7:1	73
10	2-Furyl, **47j**	**49j**, 79	7:1	80
11	Cydohexyl, **47k**	**49k**, 88	6:1	75

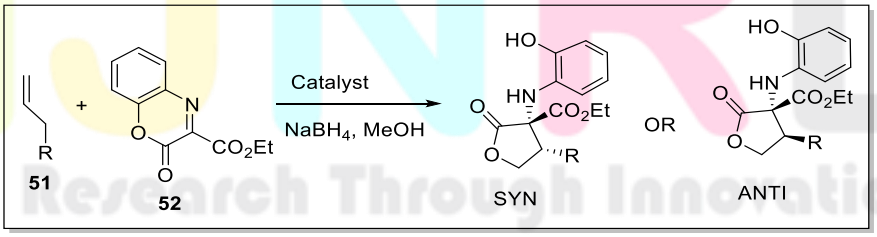
Keiji Maruoka et.al.[17] have exploited a highly diastereoselective and enantioselective direct Mannich reaction of ketamine **51** with aldehydes **52** which was catalyzed by the axially chiral amino sulfonamide (*S*)-**50** (Table 10). The diastereo - and enantioselective direct Mannich reaction of 1 with several other donor aldehydes was studied under the optimal reaction conditions (Table 3). All of the reactions with sterically less congested aldehydes resulted to give either syn- or anti-g-lactones with almost perfect diastereo- and enantioselectivity, respectively. However, the reactions with bulky aldehydes, such as 3-methylbutanal, has evidenced trace amount of the desired products.



(*S*)-**50**

Chart 3. The structure of axially chiral amino sulfonamide, (*S*)-**50**

Table 10. Mannich reactions between ketimine 1 and various aldehydes catalyzed by L-proline or (*S*)-**50**.

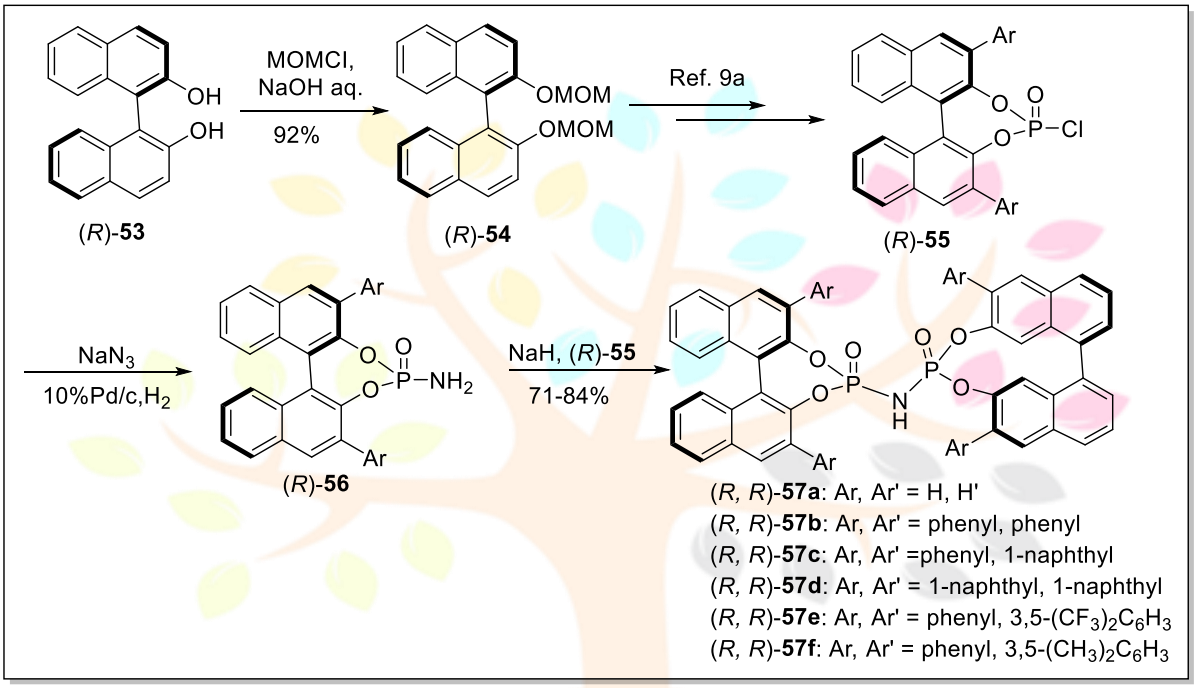


Entry	R	Conditions	Yield(%)	*Syn/Anti*	ee (%)
1	Et	A	62	>20:1	99
2	Bu	A	72	>20:1	99
3	Hex	A	62	>20:1	99
4	Bn	A	72	>20:1	99
5	CH_2Cy	A	71	>20:1	99
6	Et	B	60	1:>20	99
7	Bu	B	60	1:>20	99
8	Hex	B	79	1:>20	99
9	Bn	B	59	1:>20	99
10	$CH_{2C}y$	B	60	1:>20	99

Conditions A: The reaction of the aldehyde **51** (0.5 mmol) with **52** (0.1 mmol) was conducted in the presence of l-proline (0.02 mmol) and benzoic acid (0.01 mmol) in MeCN (50 mL) for 5 h at 0°C

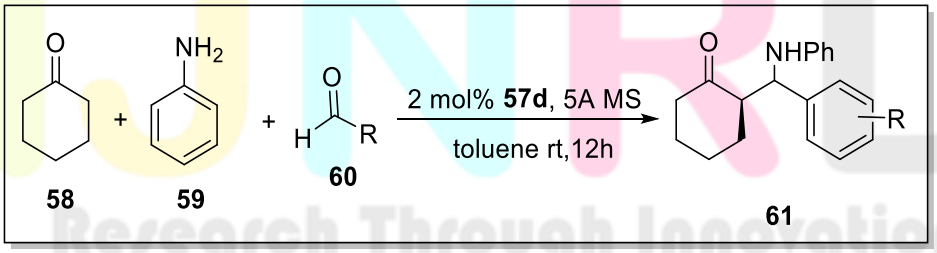
Conditions B: The reaction of the aldehyde **51** (0.3 mmol) with **52** (0.1 mmol) was conducted in the presence of (*S*)-**50** (0.005 mmol) in DMAc (50 mL) for 5 h at 45°C.

Liangyu Zheng and Suoqin Zhang group [18] have synthesized bisphosphorylimides **57 (a-f)** and its synthesis was started from (*R*)-BINOL **53**. The scheme 6 illustrates the protection of BINOL with a MOM group in saturated NaOH aq with 92% yield. Phosphoryl chlorides **55** were prepared as per given in the previous research paper [19]. Compounds **55** were converted into phosphoryl azides and then treated with catalytic hydrogenation to form phosphorylamides **56**. The final bisphosphorylimides **57 (a–f)** with good yields (71–84%) was produced by condensation of 4 and 5 in DMF. Under optimized condition studied the scope of the three-component asymmetric Mannich reactions using bisphosphorylimide catalyst, **57d** (Table 11). In entries 1–9, benzaldehyde and its derivatives containing electron withdrawing groups at the ortho-, meta-, and para-positions were assessed and *syn*-selective. The high yields of Mannich adducts were obtained entirely and with excellent enantioselectivity. Generally, benzaldehydes bearing nucleophilic groups offer their corresponding products with relatively low stereoselectivity in three-component Mannich reactions. Conversely, by using bisphosphorylimide **57d**, benzaldehydes **60 (j-m)** with nucleophilic groups were converted into the corresponding syn- amino carbonyl ketones with tremendous diastereoselectivity and enantioselectivity (Table 11, entries 10–13).



Scheme 6. Synthesis of BINOL-derived bisphosphorylimides **57 (a-f).**

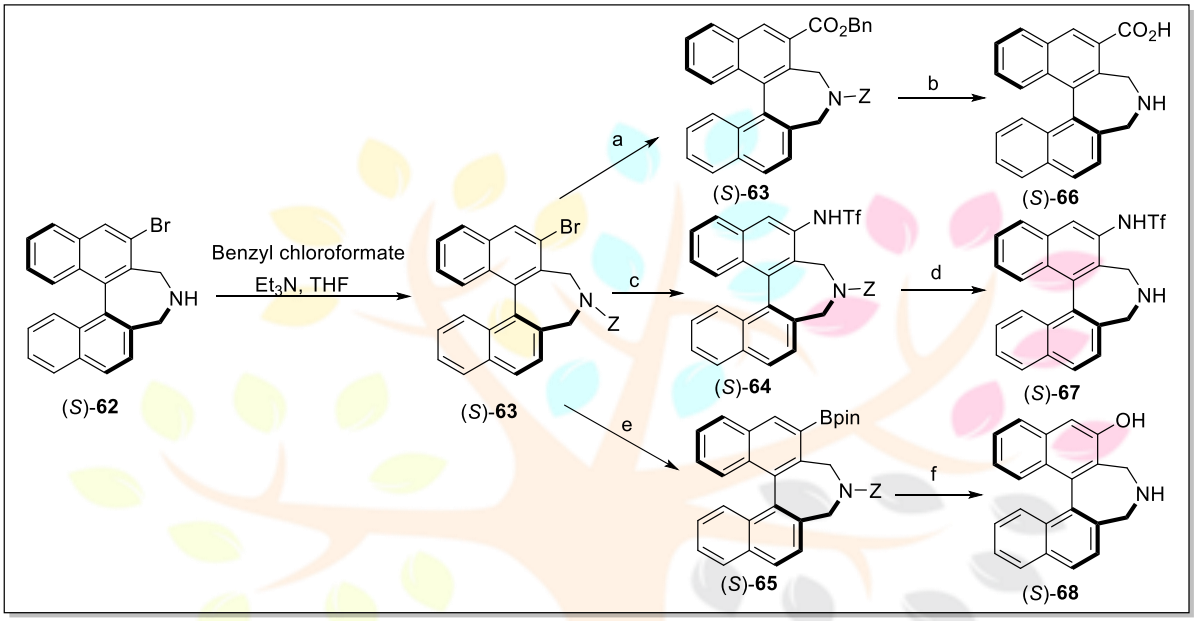
Table 11. Bisphosphorylimide **57d** catalyzed syn-selective three-component Mannich reactions



Entry	R	Product	Yield%	Dr(syn/anti)	ee%
1	4-$NO_2C_6H_4$	**61a**	>99	>99/1	99
2	C_6H_5	**61b**	>99	>99/1	98
3	2-FC_6H_4	**61c**	87	>99/1	99
4	3-FC_6H_4	**61d**	90	>99/1	99
5	4-FC_6H_4	**61e**	98	>99/1	96
6	4-ClC_6H_4	**61f**	92	>99/1	97
7	4-BrC_6H_4	**61g**	92	>99/1	97
8	4-CNC_6H_4	**61h**	>99	>99/1	99
9	4-CF_3C6H_4	**61i**	90	>99/1	98
10	3-MeC_6H_4	**61j**	96	>99/1	99
11	4-MeC_6H_4	**61k**	83	>99/1	95
12	4-$(CH3)_2CHC_6H_4$	**61l**	84	>99/1	90
13	3-$MeOC_6H_4$	**61m**	>99	>99/1	96

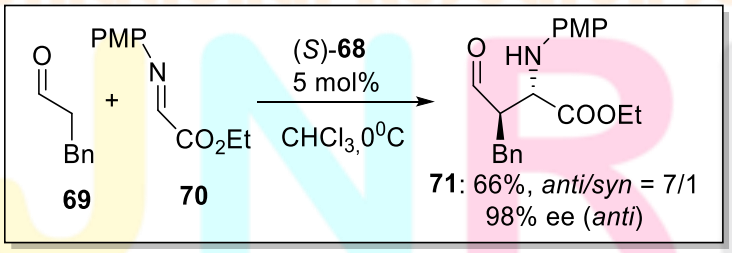
Qing Gu et.al.[20] have fabricated binaphthyl-based secondary amines, **66-68**. The synthesis of same is shown in scheme 7. With the key intermediate (*S*)-**62**, various substituents could be established at the 3-position of the binaphthyl moiety by coupling reactions after the protection of the amino group by the benzyloxycarbonyl (Z) group, (*S*)-**63** (Scheme 7). Example: benzyloxy carbonylation of (*S*)-**63** with CO in benzyl alcohol offered the benzyl ester (*S*)-**63** in 87% yield. Then, hydrogenation of (*S*)-**63** gave the amino acid (*S*)-**66**. In other way, the palladium-catalyzed amination of (S)-**63** with benzophenone imine, hydrolysis, and subsequent treatment with Tf_2O offered trifluoromethane sulfonamide (S)-**64** in 88%. Subsequent hydrogenation of (*S*)-**64** gave the amino trifluoromethane sulfonamide (*S*)-**67**.

Finally, a new type of amine organocatalyst called amino alcohol (*S*)-68 was successfully synthesized. The palladium catalyzed borylation of (*S*)-**63** with bis(pinacolato) diboron (B_2(pin)2) furnished the boronic pinacol ester (S)-**65** in 90% yield. Following introduction of a hydroxyl group at the 3-position of (*S*)-**65** by oxidation with mCPBA, deprotection of the Z group efficaciously afforded (*S*)-**68**. The obtained (*S*)-**68**was found to successfully catalyze the anti-selective Mannich reaction between 3-phenylpropanal, **69** and an α-imino ester, **70** to give the corresponding anti-Mannich adduct **71** with excellent enantioselectivity (Scheme 8)



Scheme 7. Synthesis of a series of binaphthyl-based secondary amine catalysts

Reagents and conditions for scheme 7: (a) CO, $Pd(OAc)_2$, dppp, $EtNiPr_2$, DMSO/BnOH (87%); (b) H_2, Pd/C, MeOH, 40 °C (80%); (c) (i) benzophenone imine, $Pd_2(dba)_3$, BINAP, NaOtBu, toluene, reflux, then 1 N HCl, THF, reflux; (ii) Tf_2O, N,N-dimethylaniline, CH_2Cl_2, room temperature (88% for three steps); (d) H_2, Pd/C, MeOH, 40 °C (93%); (e) $B_2(pin)_2$, $Pd(OAc)_2$, KOAc, DMF, 85 °C (90%); (f) (i) mCPBA, H_2O/EtOH, 0 °C; (ii) H_2, Pd/C, MeOH, 40 °C (45% for two steps).



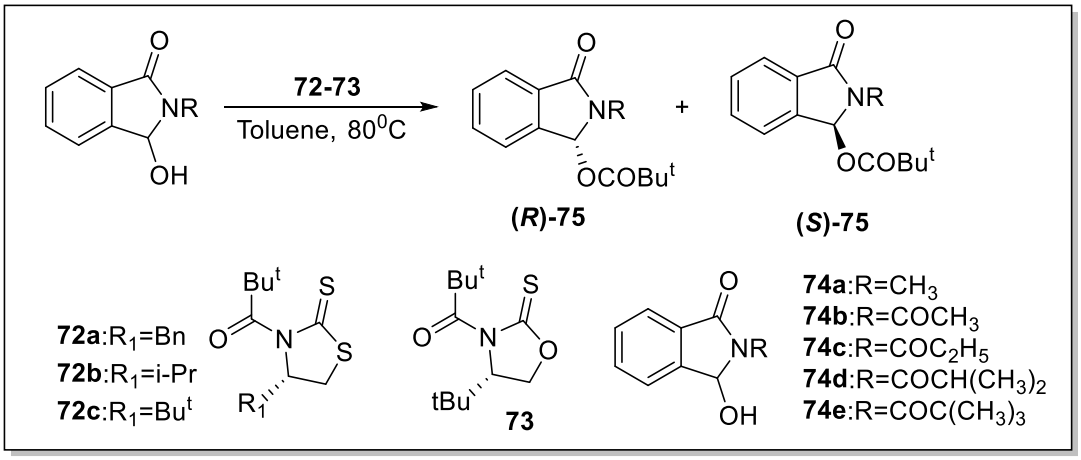
Scheme 8. Anti-selective Mannich reaction catalyzed by (*S*)-68

3.4 Kinetic resolution

Kinetic resolution is dealing with differentiating two enantiomers in a racemic mixture. In kinetic resolution, two enantiomers react with different reaction rates in a chemical reaction with a chiral catalyst or reagent, resulting formation of one of the enantiomer predominantly. It is an imperative tool in the production of optically active compounds, including drugs. As the chiral compounds are obtained from racemic ones in more than 50% yields the importance of dynamic kinetic resolution in asymmetric synthesis has been well known.

Shinji Yamada *et.al*. [21] reported dynamic kinetic resolution of hemiaminals was executed by the acyl-transfer reaction using chiral twisted amides as acylating reagents. Acylation of hemiaminals, **74(a-e)** with amides **72 (a-c)** and **73** was performed in toluene at 80°C for 2–10 days under neutral conditions. (**Scheme 9**) The HPLC analysis was used to determine enantiomer ratio using a chiral stationary phase. Various hemiaminals, **74(a-e)** were subjected to acylation transfer and corresponding obtained parameters summarized in **table 12**. Amide **73** was found to be more competant in acyl transfer reaction with good enantiomeric excess. Acylation of hemiaminal **74e** with **73** under similar reaction condition gives **75** with 68% ee of R isomer with composition 84:16 (75*R*: 75*S*). The success of the resolution would be due to the following two typical features of the twisted amides: (1) the moderate reactivity arising from the amide bond twisting toward the hydroxy groups, (2) the adjacent chiral center induced the axial chirality in the amide linkage. Thus, the moderate reactivity satisfied the criteria of the dynamic kinetic resolution, viz. the rate of acylation step must be much gentler than that of interconversion between the (*R*)- and (*S*)-isomers, and the induced axial chirality

enabled discrimination of the two enantiomeric hydroxyl groups. Further, reverse trend of ee of 75*R* and 75*S* i.e.16:84 was achieved in reaction of **74e** with strong base **4-DMAP**, its strong coordination with hydroxyl group confirmed by Nuclear magnetic resonance experiments leading to formation of predominantly, ***S*** isomer.



Scheme 9. Dynamic kinetic resolution of hemiaminals using chiral twisted amides

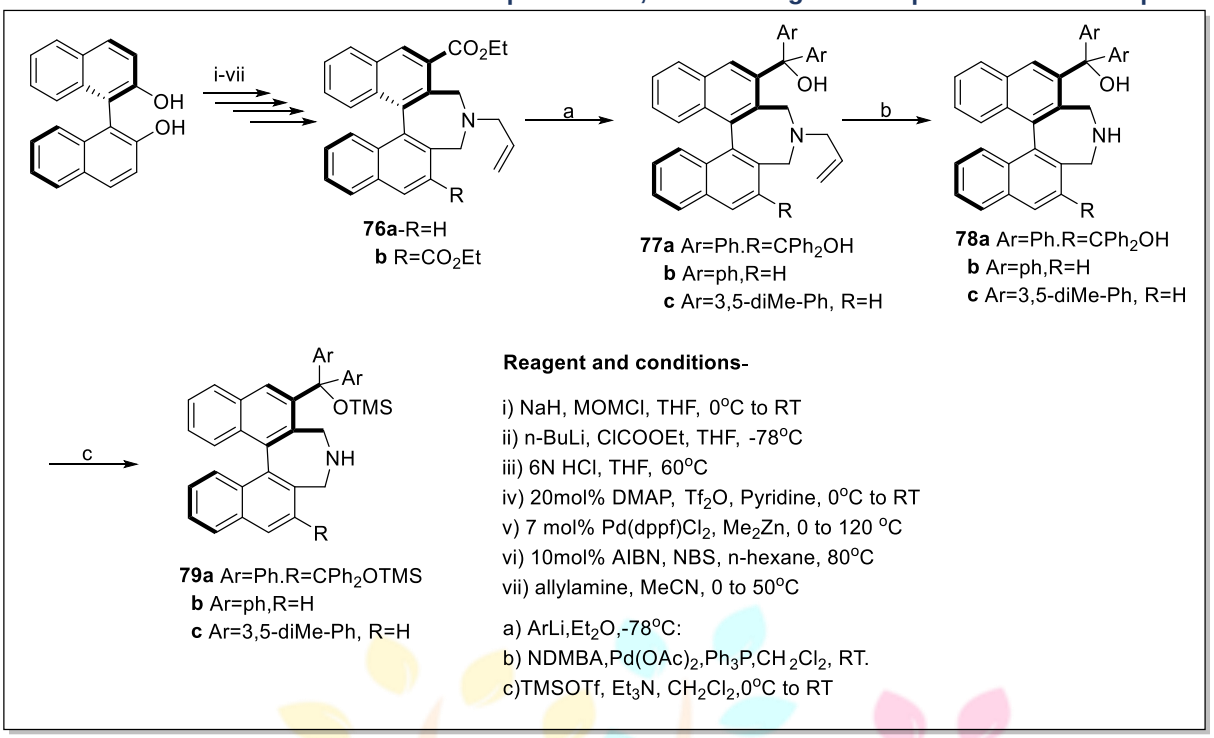
Table 12. Dynamic kinetic resolution of hemiaminals using chiral twisted amides.

Entry	Aminal	Amide	Time(days)	Yield %	e.r (R:S)
1	**5**	4(1.4)	2	65	50:50
2	**6**	4(1.2)	3	62	81:19
3	**7**	4(1.8)	7	70	81:19
4	**8**	4(1.5)	7	74	83:17
5	**9**	4(2.0)	7	76	**84:16**
6	**9**	3(1.8)	3	94	82:18
7	**9**	2(1.6)	9	91	75:25
8	**9**	1(1.3)	10	19	68:32

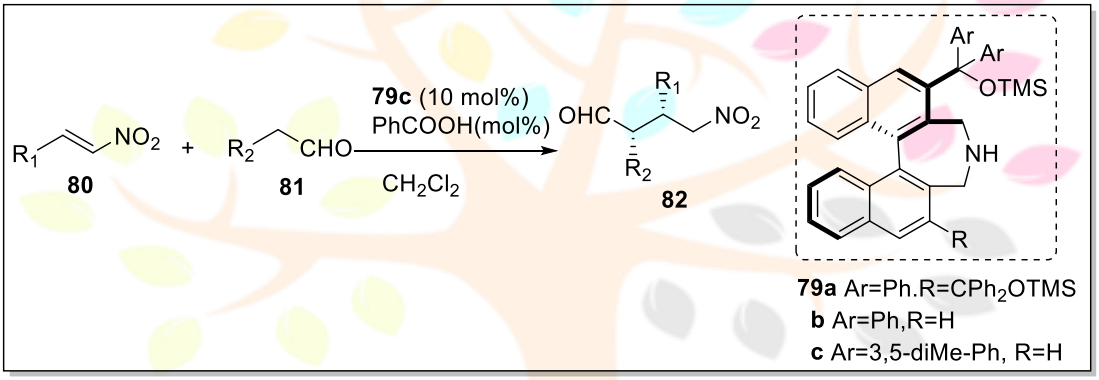
3.5 Conjugate Addition

Nucleophilic conjugate addition is a type of organic reaction. Ordinary nucleophilic additions or 1,2-nucleophilic additions deal mostly with additions to carbonyl compounds. Recent years hav shown tremendous development in the uses of chiral secondary amines as asymmetric catalysts in many carbon–carbon bond-forming reactions.

Gui Lu *et.al*. [22] developed new synthetic route for binaphthyl-based secondary amines, **79 (a-c)**. The vital features of this route include the selective direct esterification of the binaphthyl structure at the 3- or 3,3′-position and the methylation by a Negishi cross-coupling reaction. A series of 3- mono substituted and 3,3′-disubstituted chiral secondary amines with a binaphthyl backbone were prepared (**scheme 10**) and partitioned in the Michael reaction of aldehydes **81** to various nitroalkenes **80**. 3-Monosubstituted secondary amine **79c** was evidenced to be the best catalyst, affording yields of up to 95%, good to excellent enantioselectivities (up to 99%) and diastereoselectivities (syn/anti up to 99: 1) under the optimized reaction conditions (**scheme 11**).



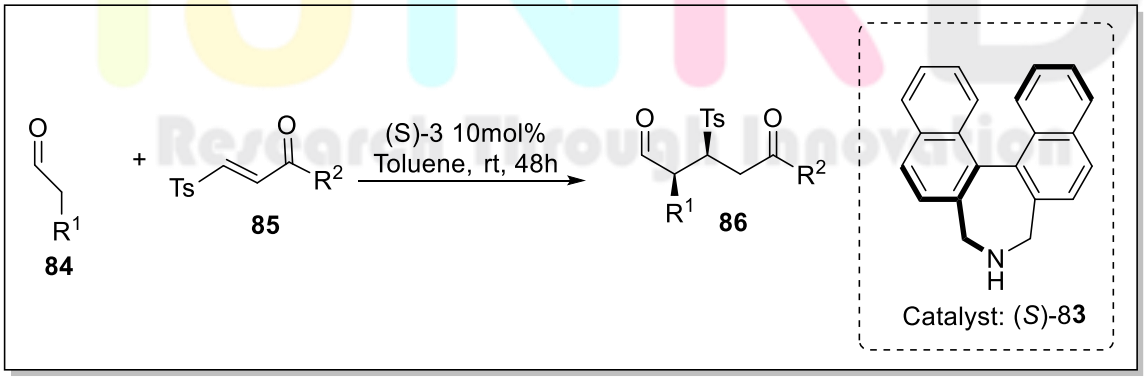
Scheme 10: Synthesis of binaphthyl-based secondary amine catalysts.



Scheme 11: Catalytic asymmetric Michael reaction of aldehydes and nitroalkenes.

Taichi Kano et.al. [23] inspected the possibility of conjugate addition of aldehydes **84** to beta-tosyl enones **85** in presence of a binaphthyl-modified chiralamine, (*S*)-**83**. Various aldehydes and beta- tosyl enones were screened in conjugate addition reaction. In the presence of (*S*)-**83** (10 mol%), conjugate adducts **86** in moderate to good yields with high stereoselectivity (**Table 13**) were proved for the corresponding reactions of various aldehydes with **1a** (R2=Me). In the reaction of propanal, elimination of tosyl group from the conjugate adduct **86** (R1=Me, R2=Me) was demonstrated (**Table 13**, entry 1), which explains the low yield of **86**. Since the reaction of 3-phenylpropanal with 1b (R2=Et) was slower than that with 1a (R2=Me), 20 mol% of (*S*)-**83** was used to obtain **86** (R1=Bn, R2=Et) in high yield (**Table 13**, entry 9). In all cases examined, conjugate addition occurred at the b position of **85** exclusively, and only syn isomers were obtained.

Table 13: Conjugate addition of aldehydes **84** to **85**

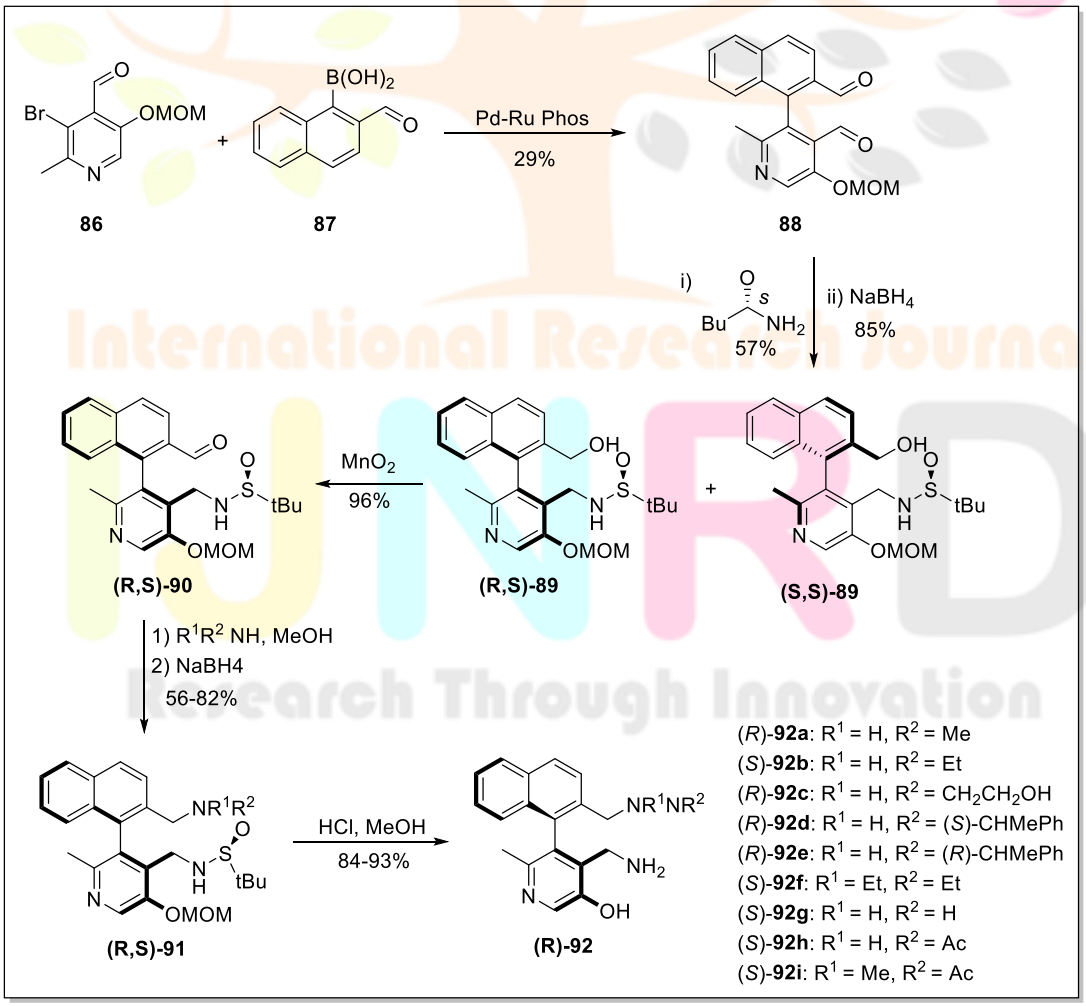


Entry	R^1	R^2	Yield (%)	Syn/anti	ee%
1	Me	Me	36	>20:1	94
2	Et	Me	68	>20:1	93
3	Bu	Me	74	>20:1	93
4	CH_2Cy	Me	81	>20:1	92
5	CH2CH2OBn	Me	77	>20:1	87
6	Allyl	Me	82	>20:1	91
7	Bn	Me	92	>20:1	91
8	iPr	Me	87	>20:1	92
9	Bn	Et	80	>20:1	92
10	Bn	Ph	0	-	-

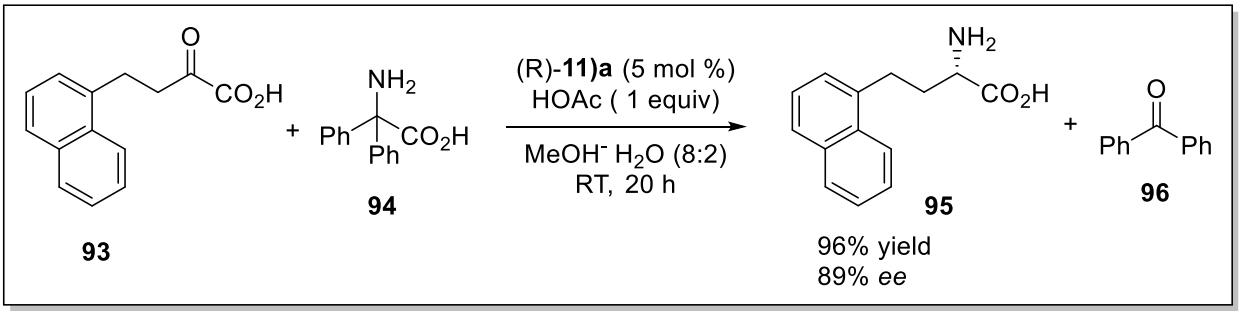
3.6 Transamination reaction

Transamination is a chemical reaction that transfers an amino group to a keto acid to form new amino acids. The deamination of most amino acids is done by this pathway. Transamination in biochemistry is accomplished by enzymes called transaminase or aminotransferases enzymatic transamination of α-keto acids is the most important process to access optically active α-amino acids in biological systems. The process uses pyridoxal/ pyridoxamine phosphates as catalyst and proceeds via a two-half-transamination pathway.

Baoguo Zhao et.al.[24] synthesized a class of axially chiral pyridoxamines **92a-f**. It was done by the reaction of bromopyridine **86** and naphthalenyl boronic acid **87** that gave biaryl dialdehyde **88** in a 29% yield. Treatment of **88** with 1 equiv of (*S*)-tert-butylsulfinamide and subsequent reduction with $NaBH_4$ gave a pair of TLC-separable diastereoisomers (*R*, *S*)-**89** and (*S*, *S*)-**89**. The enantiopure compound (*R*, *S*)-**89** or (*S*, *S*)-**89** on oxidation with MnO_2, reductive amination, and deprotection with acid to form the desired chiral pyridoxamines **92a−f** as HCl salts (scheme 12). The pyridoxamines exhibited high catalytic activity and excellent enantioselectivity in asymmetric transamination of α-keto acids **93**, to give various α-amino acids in 67−99% yields with 83−94% ee's. N-Methyl amine analog of **92** i.e. **92a** was demonstrated to be the best catalyst for transamination reaction, affording high yield of 96% with excellent enantioselectivities of 89%. under the optimized reaction conditions (scheme 13). The lateral amine arm likely participates in cooperative catalysis as the Lys residue does in biotic transamination and has an crucial impact on the transamination in terms of activity and enantioselectivity.



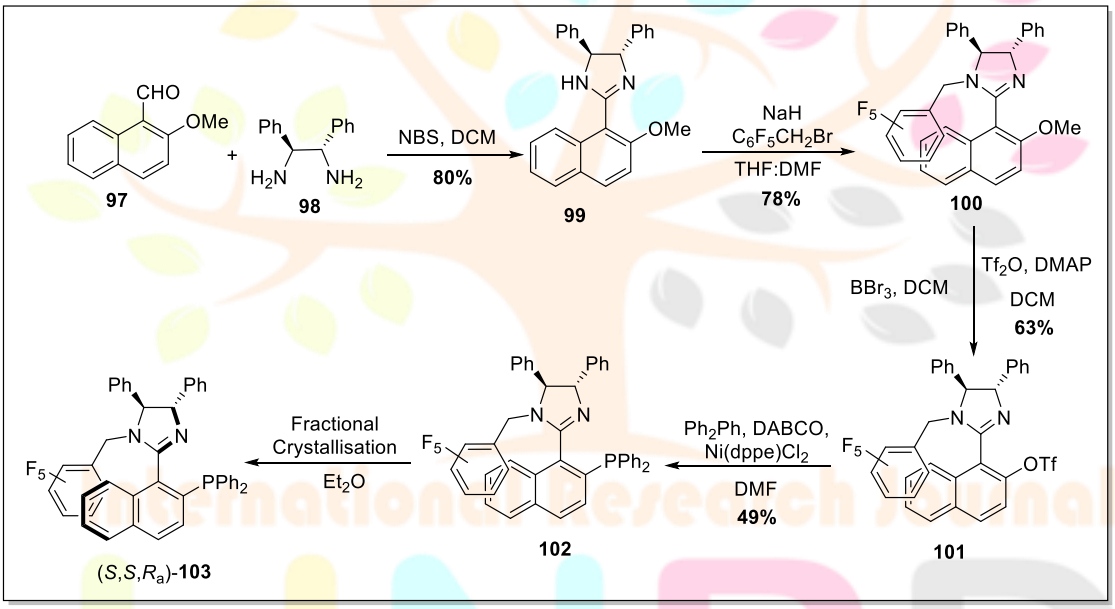
Scheme 12. Synthesis of Chiral Pyridoxamines **92a−f**



Scheme 13. Pyridoxamine **92a** Catalysed Asymmetric Transamination of α-Keto Acid

3.7 Coupling reaction

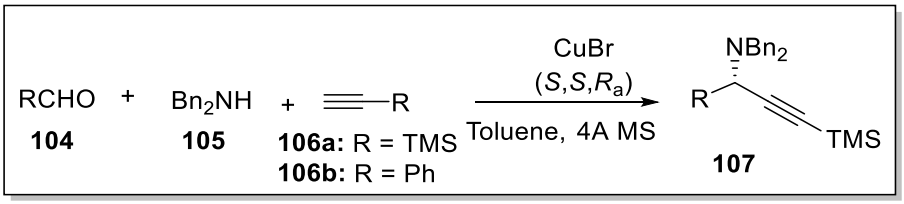
A coupling reactions are the reactions where two fragments are joined together with the help of a metal catalyst. These reactions are employed in the preparation of pharmaceuticals routinely. Conjugated polymers are prepared using this technology as well. Aponick and co-workers [25] stated the elegant synthesis of the new axially chiral P, N-ligand StackPhos, (*S*, *S*, R_s)-**103** containing a five membered imidazole moiety. The ligand synthesis began with cyclization of 2-methoxy-1-napthaldehyde **97** with (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (DPEDA), **98** and was mediated by NBS ,lead the formation of corresponding 2-substituted imidazoline, **99** in 80% yield (Scheme 14). Then the imidazoline **99** was treated with pentafluorobenzyl bromide to afford the benzylated imidazoline **100** in 78% yield. In Demethylation reaction, BBr_3 in heptane and the crude naphthol product was exposed to reaction with Tf2O in the presence of 4-dimethylaminopyridine (DMAP) to furnish the corresponding triflate **101** (63% yield over two steps). There was smooth formation of ligand 102 in 49% yield (scheme 14) by nickel-catalyzed cross-coupling reaction between triflate **101** and Ph_2PH. The fractional crystallization using Et_2O in >99.5% de (scheme 14) resolved the atropdiastereomeric mixture to major atropdiastereomer (*S*, *S*, *Ra*)-**103**

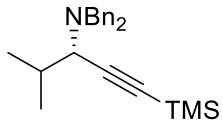
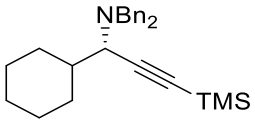
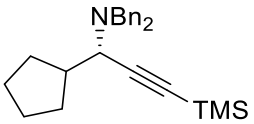
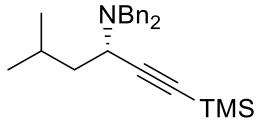
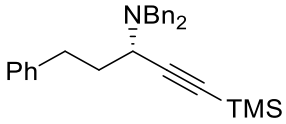
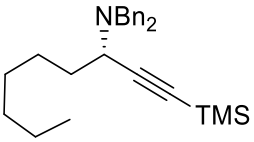
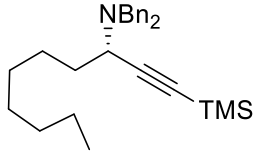
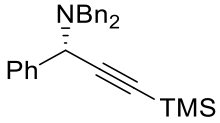
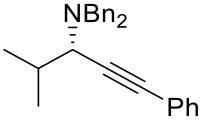


Scheme 14. Synthesis of Ligand, (*S*, *S*, R_a)-**103**

The novel chiral ligand (*S*, *S*, R_a)-**103** tested in asymmetric catalysis for the A3 coupling (aldehyde, amine and alkyne). Using optimized conditions, the reaction possibilty with aldehydes and alkynes was determined s(Table 14). The reaction seems to be general for a variety of aliphatic aldehydes **104 (b-i)** resulting to the formation of propargylic amine **107 (b-i)** in excellent enantioselectivities (up to 97.5%, S-isomer) and yields (up to 98%). Aliphatic aldehydes such as **104b** and **104c** containing an α-substituent afforded the products **107b** and **107c** in excellent ee's (97.5 and 92.9%) and good to excellent yields (90 and 70%). Linear-chain aliphatic aldehydes such as **104d-104g** also afforded product **107d-107g** in excellent ee's (97.1, 95.3, 94.3 and 93.6%) and good to excellent yields (98, 84, 86 and 66%). With ligand (*S*, *S*, *Ra*)-**103**, no significant α-substituent effect was observed for the enantioselectivity unlike the related P, N-ligands. The reaction employing benzaldehyde **104h** was found to be slow under these conditions giving product **107h** in only 23% yield and 65.1% ee. Additionally, changing the alkyne to phenyl acetylene 10b and reaction with aldehyde 8a provided the expected product 1**07i** in 80.5% ee and 95% yield.

Table 14. Substrate Scope for A3 Coupling



 **107a**, yield = 89% **ee** = 98.1%	 **107b**, yield = 90% **ee** = 97.5%	 **107c**, yield = 70% **ee** = 92.9%
 **107d**, yield = 98% **ee** = 97.1%	 **107e**, yield = 84% **ee** = 95.3%	 **107f**, yield = 86% **ee** = 94.3%
 **107g**, yield = 66% **ee** = 93.6%	 **107h**, yield = 23% **ee** = 65.1%	 **107i**, yield = 95% **ee** = 80.5%

4. Conclusion

The review report clearly illustrated the significance of axially chiral amines as the competent catalyst and a strong ligand in combination with suitable metal. The utility of axially chiral amines in asymmetric catalysis of enantioselective hydrogenation reaction, allylic substitution reaction, asymmetric mannich reaction, kinetic resolution, conjugate addition reaction, transamination reaction and coupling reaction have been briefly presented. This short review unlock opportunity for researchers to develop modified axially chiral amines and induce desired features needed for the progress of suitable catalysts/ ligands for the wide range of chiral organic transformation.

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