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The synthesis of chiral *N*-tosylatedaminoimine ligands and their application in enantioselective addition of phenylacetylene to imines

Bao Liu,[a] Juntao Liu,[a] Xian Jia,[c] Ling Huang,[a] Xingshu Li[a,*] and Albert S. C. Chan[a,b,*]

[a]*School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 51006, China*
[b]*Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China*
[c]*Shenyang Pharmaceutical University, Shenyang, PR China*

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Abstract—A class of new chiral tridentate *N*-tosylatedaminoimine ligands were synthesized and used in the Cu(I)-catalyzed enantioselective addition of phenylacetylene to imines. Good enantioselectivities in up to 91% ee were obtained.

1. Introduction

Asymmetric catalytic reactions have attracted much attention in recent years because of their great potential in making higher-value-added products. Many chiral ligands have been synthesized and applied in various asymmetric reactions over the past few decades.[1] However, only in recent years, limited organometallic systems have been developed to catalyze the addition of alkynes to imines[2] to produce propargylamines, which are important synthetic intermediates in the construction of biologically active nitrogen-containing compounds and natural products.[3] Li et al. developed a Cu(I) complex of pyridyl-bisoxazoline, which catalyzed the direct alkyne addition to imines with high ee's and good yields.[4] Hoveyda reported a Zr-catalyzed enantioselective addition of a range of mixed alkynylzinc reagents to various arylimines with a chiral amino acid-based ligand.[5] Knochel et al. described the addition of functionalized alkynes to enamines catalyzed by Cu(I)-Quinap complexes.[6] Carreira et al. developed a new atropisomeric P,N ligand (Pinap) and used it in the CuBr-catalyzed three-component reaction of dibenzylamine, aldehydes and various acetylenes.[7] We developed a versatile catalytic synthesis of enantiomerically enriched β,γ-alkynyl α-amino acid derivatives by realizing the direct asymmetric alkynylation of α-imino ester.[8] Benaglia et al. reported an enantioselective synthesis of propargylamines catalyzed by copper(I)-bisimine complexes with up to 85% ee.[9] Very recently, Bolm et al. developed a one-pot, enantioselective synthesis of *N*-aryl propargylic amines using alkynylation reagents in combination with aldehydes and *o*-methoxyaniline as starting materials.[10]

In contrast to the enantioselective alkynylation of aldehydes in which considerable progress has been made in recent years, the enantioselective alkynylzinc addition to imines still remains less developed. One of the targets in our study of catalytic asymmetric synthesis is the development of effective chiral ligands that can be easily prepared and successfully applied in asymmetric synthesis. Herein we report our preliminary study using new chiral mixed *N*-tosylatedaminoimine ligands in the Cu(I) catalyzed enantioselective addition of alkynes to imines.

2. Results and discussions

The alkyne additions to imines were usually slow and generally required 3–4 days at room temperature,[3,4a,5,7] which was mainly due to the inert nature of the imines towards the addition. In a preliminary screen study to develop a simple and active catalyst system for this reaction, we chose TsDPEN **1**, Salen **2**, camphorsulfonamide **3**, mixed *N*-tosylatedaminoimine **4** and its analogue **5** as chiral ligands. *N*-Benzylideneaniline was used as the model substrate and toluene was used as the reaction solvent for

* Corresponding authors. Tel.: +86 2035693517 (X.L); e-mail addresses: xsli219@yahoo.com; bcachan@polyu.edu.hk

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the Cu(I) catalyzed enantioselective addition of alkynes to imines. The results showed that when **1** and **2** were used as ligands, either poor enantioselectivity or undesired side products were obtained. Chiral camphorsulfonamide ligand **3**, which was effective in the Cu(II)-catalyzed asymmetric alkynylation of ketones,[8] was not very successful and low ee's were observed (Fig. 1).

On the other hand, the use of new tridentate mixed *N*-tosylatedaminoimine ligands gave moderate yields and ee's (Table 1, entry 5, 51% isolated yield and 65% ee). Some factors governing the enantioselectivities of the reaction were subsequently examined with tridentate mixed *N*-tosylated-aminoimine ligands and the results are shown in Table 1. The temperature effect was rather significant for the reaction; it could proceed smoothly at room temperature although a low yield was obtained at 0 °C. The ee values attained herein were found to be sensitive to the choice of solvents. At room temperature, the use of toluene, ether, hexane, dichloromethane and tetrahydrofuran gave the

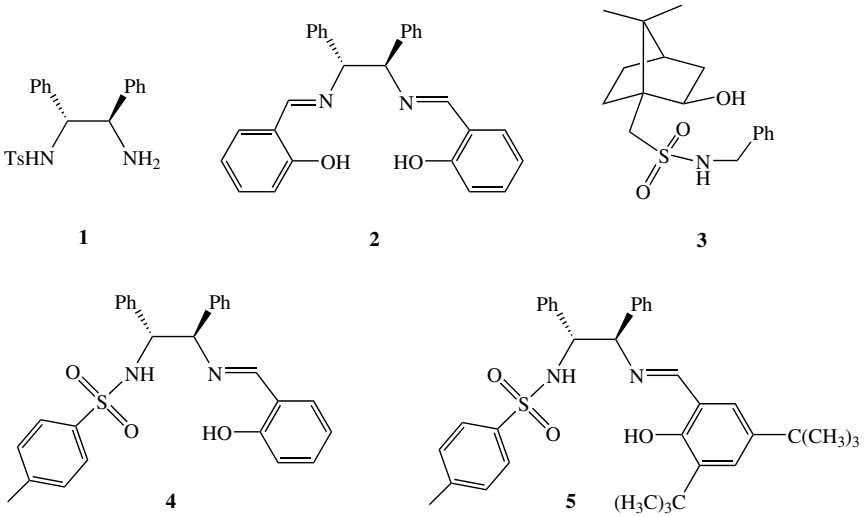
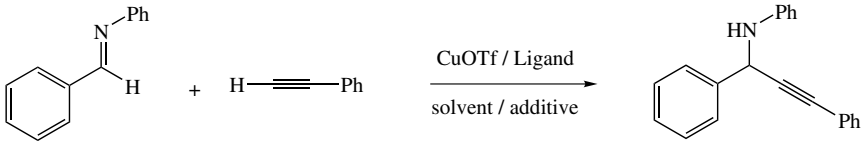


Figure 1.

Table 1. Enantioselective addition of phenyl acetylene to *N*-benzylindeneaniline in various reaction conditions[a]



Entry	Ligands	Solvents	Time (h)	Additive	Yield[b] (%)	ee[c] (%)
1	1	Toluene	36	—	52	5
2	2	Toluene	36	—	53	9
3	3	Toluene	36	—	84	0
4	4	Toluene	36	—	65	55
5	5	Toluene	36	—	51	65
6[d]	5	Toluene	36	—	32	46
7	5	Toluene	24	—	41	63
8	5	THF	36	—	69	41
9	5	CH_2Cl_2	36	—	85	5
10	5	EtOEt	36	—	57	10
11	5	Hexane	36	—	71	0
12	5	Toluene	24	CH_3ONa	10	0
13	5	Toluene	24	$(CH_3)_3COK$	47	29
14	5	Toluene	24	$(CH_3)_3CONa$	82	0
15	5	Toluene	24	*n*-BuLi	12	25
16	5	Toluene	24	Et_3N	32	42
17	5	Toluene	24	$Zn(Me)_2$	76	85
18[e]	5	Toluene	24	$Zn(Me)_2$	Trace	—
19[f]	5	Toluene	24	$Zn(Me)_2$	49	68

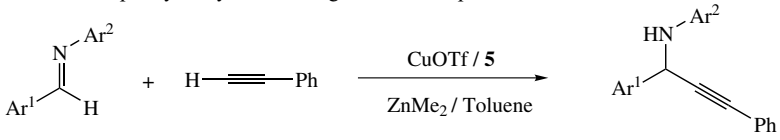
[a] All reactions were carried out with 20 mol % CuOTf and ligands at room temperature.
[b] Isolated yields after purification by flash chromatography.
[c] Enantiomeric excess was determined by HPLC with a chiracel OD column.
[d] 10 mol % of catalyst was used.
[e] Carried out without CuOTf.
[f] 10 mol % of $Zn(Me)_2$ was used.

product with ee's ranging from 5% to 65% and chemical yields from 51% to 85%. Toluene was the best solvent for this reaction. Base additives such as CH_3ONa, $(CH_3)_3CONa$, $(CH_3)_3COK$, *n*-BuLi and Et_3N were also investigated but no positive effects were found for accelerating the reaction or improving the enantioselectivities (entries 12–16, CH_3ONa, 10% yield with 0% ee; $(CH_3)_3CONa$, 82% yield with 5% ee; $(CH_3)_3COK$, 47% yield with 29% ee; *n*-BuLi, 12%yield with 25% ee; Et_3N, 32% yield with 68% ee). As organozinc reagents are highly selective and widely used in nucleophilic addition to carbonyl compounds, we attempted to apply alkynyl zinc reagents to the reaction. When the alkynyl zinc reagent was prepared using a known procedure (phenylacetylene reacted with dimethylzinc) and then used in the enantioselective addition to imines, the reaction was finished in 24 h with good enantioselectivity (85% ee) and yield (76%). The procedure was very simple: to a mixture of imine, copper(I) triflate benzene complex and chiral ligand was added an alkynylzinc reagent and the reaction was carried out at room temperature for 24 h and worked up to obtain the required product.[9] Only trace amounts of the product were detected when the reaction was carried out in the absence of copper(I) triflate benzene complex (entry 18). The result indicated that copper(I) was very important for catalyzing this reaction. At the same time, decreasing the amount of dimethyl zinc led to lower yields and enatioselectivity (e.g., 10 mol % dimethyl zinc and phenylacetylene as a nucleophilic reagent gave 49% yield with 68% ee, entry 19). This was probably due to dimethyl zinc acting solely to deprotonate the alkyne to form an alkynylzinc reagent in the reaction.

Having established the optimal reaction conditions for conversion of the model substrate *N*-benzylideneaniline, various imines derived from aromatic aldehydes and amines were treated with phenylacetylene in the presence of dimethylzinc catalyzed by Cu(I)-tridentate mixed *N*-tosylatedamineimine ligand **5** and the results obtained are listed in Table 2. Most imines derived from aniline and substituted aldehydes in the reaction gave moderate to good ee values (entries 1–5, 50–87% ee) except in the case of 4-chlorobenzaldehyde (entry 6). On the other hand, imines derived from substituted anilines and benzaldehyde also provided similar results (entries 7–9, 62–86% ee with 58–87% yield).

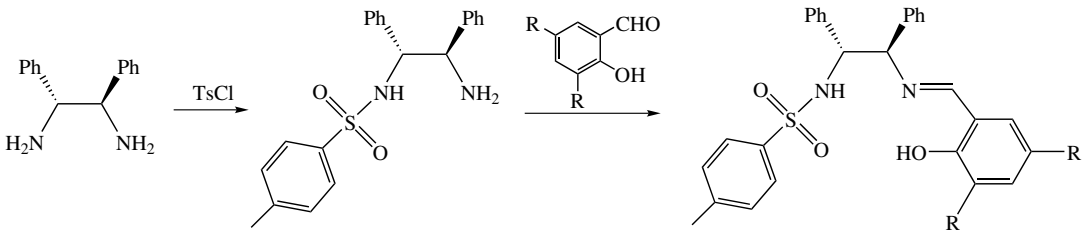
The synthesis of the new tridentate mixed *N*-tosylatedaminoimine ligand was simple. (*R*,*R*)-1,2-Diphenylethane-1,2-diamine (*R*,*R*)-DPEDA, a commercially available chiral starting material, was reacted with toluenesulfonic acid chloride to afford TsDPEN in good yield according to a known procedure.[10] TsDPEN then was allowed to react with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde in the presence of anhydrous sodium sulfate in methanol to give a nearly quantitative yield of the desired product[11] (Scheme 1).

Table 2. Enantioselectivity of the addition of phenylacetylene with ligand **5** in the presence of $ZnMe_2$



Entry	Substrates	Yield[a] (%)	ee[b] (%)
1	Ph–CH=N–Ph	76	85
2	4-$MeOC_6H_4$–CH=N–Ph	68	83
3	2-$MeOC_6H_4$–CH=N–Ph	79	80
4	4-$NO_2C_6H_4$–CH=N–Ph	73	87
5	2-ClC_6H_4–CH=N–Ph	52	50
6	4-ClC_6H_4–CH=N–Ph	60	24
7	Ph–CH=N-(4-$CH_3C_6H_4$)	58	77
8	Ph–CH=N-(4-$CH_3OC_6H_4$)	87	86
9	Ph–CH=N-(4-ClC_6H_4)	72	62
10	4-ClC_6H_4–CH=N-(4-ClC_6H_4)	65	91
11	4-$MeOC_6H_4$–CH=N-(4-$CH_3OC_6H_4$)	63	83

[a] Isolated yields after purification by flash column chromatography.
[b] Enantiomeric excess was determined by HPLC with a chiracel OD column.



4: R = H; **5**: R = $C(CH_3)_3$

Scheme 1.

3. Conclusion

In conclusion, we have developed a new class of chiral tridentate *N*-tosylatedaminoimine ligands, which are effective in the production of propargylic amines with good enantioselectivities and yields. Further studies on the scope and mechanism of this reaction are currently underway.

4. Experimental

4.1. General methods

All reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. THF was distilled and dried before use. Reagents were purchased from either Acros or Aldrich and used without further purification except for the aldehydes, which were redistilled before use. NMR spectra were recorded on a Varian-500 spectrometer. Optical rotations were measured with a Perkin–Elmer model 341 polarimeter at 20 °C. HPLC analyses (Chiralcel OD or OD-H column from Daicel, IPA–hexane as eluent) were performed using a Waters™ 600 HPLC with Waters™ 486 Tunable Absorbance Detector.

4.2. The preparation of chiral ligands

4.2.1. Chiral ligand 4. To a solution of 2.00 g, (5.46 mmol) of (*R*,*R*)-TsDPEN[12] in 40 mL of methanol were added 0.67 g, (5.5 mmol) of 2-hydroxy-benzaldehyde and 3.57 g of anhydrous Na_2SO_4 (30 mmol). The reaction mixture was stirred and refluxed until the reactants disappeared (usually requires about 8 h, as monitored by TLC). After cooling to room temperature, the mixture was filtrated and the solvent was removed in vacuo to afford chiral (*R*,*R*)-**4** as a yellow solid (2.54 g, 99%). Mp = 155–156 °C. $[\alpha]_D^{20} = +12.1$ (*c* 3.0, CH_2Cl_2). Anal. Calcd for $C_{28}H_{26}N_2O_3S$: C, 71.46; H,5.57; N, 5.95. Found: C, 71.31; H, 5.28; N, 5.76. IR *v*: 3281(m), 3034(w), 2956(s), 1626(s), 1451(m), 1161(s), 1056(w), 928(w), 818(w), 773(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ: 8.16 (s, 1H), 7.42 (d, $J = 8.4$ Hz, 2H), 7.25 ± 7.00 (*c*, 13H), 6.89 (d, $J = 8.3$ Hz, 2H), 5.22 (d, $J = 6.0$ Hz, 1H), 4.79 (dd, $J = 6.0$ Hz, $J' = 7.2$ Hz, 1H), 4.58 (d, $J = 5.7$ Hz, 1H), 2.32 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), δ: 167.3, 160.9, 138.6, 137.8, 137.2, 133.1, 132.2, 129.5, 128.6, 127.7, 63.7, 21.9 ppm.

4.2.2. Chiral ligand 5. Prepared according to the procedures of chiral ligand **4** to afford a yellow solid (2.34 g, 98%). Mp = 99–101 °C. $[\alpha]_D^{20} = +17.9$ (*c* 3.0, CH_2Cl_2). Anal. Calcd for $C_{36}H_{42}N_2O_3S$: C, 74.19; H,7.26; N, 4.81. Found: C, 74.24; H, 7.31; N, 4.72. IR *v*: 3283(m), 3032(w), 2957(s), 1626(s), 1455(m), 1160(s), 1056(w), 928(w), 811(w), 773(w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ: 8.18 (s, 1H), 7.40 (dd, $J = 6.6$ Hz, $J' = 1.5$ Hz, 3H), 7.25–7.02 (m, 10H), 6.95 (dd, $J = 1.8$ Hz, $J' = 2.1$ Hz, 3H), 5.13 (d, $J = 6.6$ Hz, 1H), 4.71 (dd, $J = 10.5$ Hz, $J' = 3.6$ Hz, 1H), 4.53 (d, $J = 5.7$ Hz, 1H), 2.34 (s, 3H), 1.49 (s, 9H), 1.28 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$), δ: 168.8, 158.0, 143.1, 140.6, 138.9, 137.9, 137.1, 136.9, 127.9, 63.9, 35.5, 34.5, 31.8, 29.9, 21.9 ppm.

4.3. General procedure for the enantioselective alkynylation of imines

A typical procedure was as follows. Phenylacetylene (0.033 mL, 0.3 mmol) and a solution of 2.0 M dimethylzinc in toluene (0.15 mL, 0.3 mmol) were added to a dry flask at room temperature under N_2 with continued stirring for 15 min to prepare an alkynylzinc reagent. Imine (0.2 mmol) was added to the catalyst solution which was made from copper(I) triflate benzene complex (0.04 mmol), chiral ligand (0.04 mmol) and toluene (0.5 mL). The alkynylzinc reagent was added to the mixture of the catalyst and substrate via a syringe. After being stirred at room temperature for a specified period of time, the reaction mixture was quenched with water, extracted with dichloromethane and concentrated in vacuo. The extracts were applied directly onto a silica gel column by flash chromatography (1:50 ethyl acetate/petroleum ether as eluents) to give the desired product. The enantiomeric excess was determined by chiral HPLC, using a Chiralcel OD column (4.6 mm * 250 mm) with 5% isopropanol in hexane as eluents.

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