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Application of tartarate derived bidentate bioxazolines in enantioselective addition of terminal alkynes to imines

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ABSTRACT

A series of highly efficient and inexpensive bioxazoline ligands were easily synthesized from tartaric acid and further explored for enantioselective addition of terminal alkynes to imines in combination with copper(II) salts. This is the first ever report showing application of bidentate bioxazoline ligands in the synthesis of propargylamines with good enantioselectivity.

Chiral propargylamines are one of the most important synthetic building blocks for the preparation of nitrogen heterocycles,[1] natural products,[2] and biologically active molecules.[3] Addition of metal acetylide to imine is the convenient and powerful method for the preparation of propargylamines and their derivatives.[4]

Enantioselective synthesis of propargylamines was achieved by Li and co-workers[5] using 1,3-bis(oxazolin-2-yl)pyridine ligands (pybox, **1**)[6] (Fig. 1) and copper salts led to the development of a three-component reaction of aldehyde, amine, and alkyne. Apart from pybox ligands, several catalysts were reported for the synthesis of chiral propargylamines.[7] Application of bidentate bis(oxazoline) ligands (**2**), which are privileged ligands to induce good enantioselectivity in propargylamine synthesis was not successful (<5% ee).[5,8] Similarly ligand **4** which is derived from tartaric acid and amenable to modification was completely overlooked by the research community because of its inability to promote mechanis-

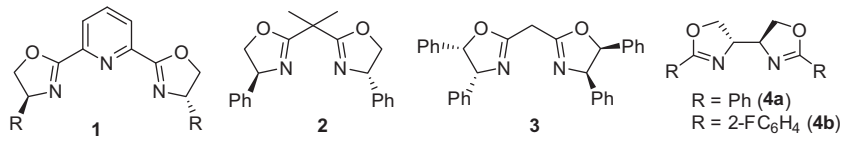
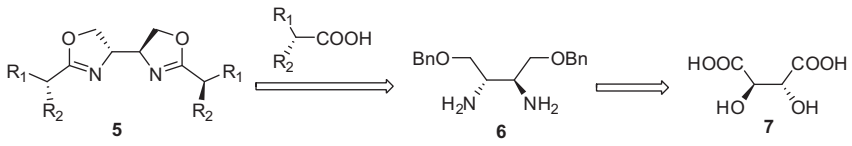


Figure 1. Structure of various bis(oxazoline) ligands.



Scheme 1. Retrosynthesis of bidentate bioxazoline.

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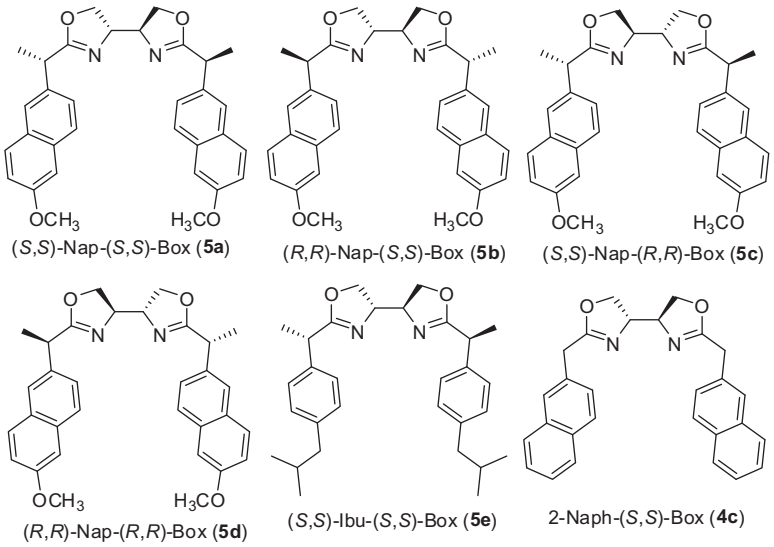


Figure 2. Structure of tartarate derived bioxazoline ligands.

tically different asymmetric transformations with good enantioselectivity.[9]

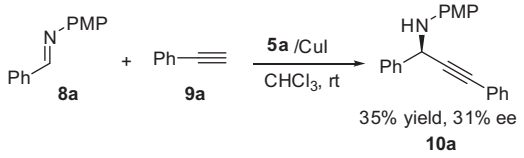
In our lab we re-designed tartaric acid derived bioxazoline ligand (**4**) by introducing another stereogenic center as shown in ligand **5** near the coordination sphere (Scheme 1). This modification mitigated the poor chirality transfer of ligand **4**, in asymmetric transformations.

The application of newly developed bioxazoline ligands **5** (Fig. 2) in asymmetric catalysis was successfully demonstrated in copper catalyzed enantioselective Henry reaction and good enantioselectivities with a broad range of substrates were achieved.[10] We applied the same ligand to achieve asymmetric allylic alkylation (AAA) with >95% ee.[11] Since the amino acid derived bidentate bis(oxazolines) **2** and **3** are inefficient in catalyzing enantioselective synthesis of propargylamines, we decided to explore the efficiency of tartaric acid derived bidentate bioxazoline **5** for the same synthesis. Only unnatural and highly expensive amino acid (*tert*-leucine, phenylglycine) derived pybox ligands **1** are responsible for very good enantioselectivity to synthesize propargylamines, whereas our catalytic system was prepared using inexpensive and naturally available tartaric acid. This makes tartarate derived bidentate bioxazoline **5** as an alternative in terms of price and availability to achieve enantioselective synthesis of chiral propargylamines.

An initial exploration of enantioselective propargylamine synthesis was carried out using ligand **5a** which was identified as a suitable ligand for the asymmetric Henry reaction. The reaction of phenylacetylene (**9a**) and imine **8a** was performed in chloroform ($CHCl_3$) at 25 °C using 5 mol % CuI and 10 mol % of **5a**. The desired product **10a** was obtained with 35% yield and 31% enantiomeric excess after 72 h (Scheme 2).

This superiority of ligand **5a** over bis(oxazoline) ligands **2** & **3** encouraged us to optimize the reaction conditions further to increase enantioselectivity of the product.

In an attempt to enhance the efficiency of the reaction, we carried out the reaction in one pot manner using benzaldehyde (**11a**),



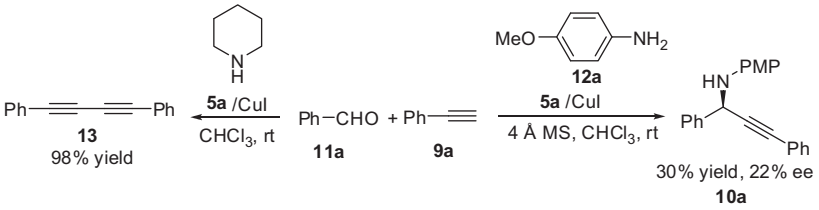
Scheme 2. Copper catalyzed enantioselective addition of alkyne to imine.

4-methoxyaniline (**12a**), and phenylacetylene (**9a**) under similar reaction conditions. Propargylamine **10a** with 22% enantioselectivity in low yield (30%) was obtained (Scheme 3). Apart from low yield, very low enantioselectivity was also observed when compared with the addition of alkyne to imine **8a** (Scheme 2). Use of cyclic amines such as piperidine and pyrrolidine instead of anilines led to the formation of 1,3-diynes (Scheme 3).[12] These two demerits forced us to optimize reaction conditions by using the preformed imine **8a**.

Other Cu(I) and Cu(II) pre-catalysts such as Cu(OTf), CuCl, CuBr, $Cu(PF_6)(CH_3CN)_4$, $Cu(OTf)_2$, $Cu(ClO_4)_2{\cdot}6H_2O$, and $Cu(OAc)_2{\cdot}H_2O$ were investigated in this reaction in order to choose a suitable metal partner (Table 1). Except $Cu(OAc)_2{\cdot}H_2O$, every other copper salts catalyzed the formation of propargylamine **10a** in moderate to good yields. Among them $Cu(ClO_4)_2{\cdot}6H_2O$ fared better in inducing enantioselectivity (43%) at ambient temperature (Table 1 entry 8). Further attempts to enhance enantioselectivity by reducing the temperature to 0 °C were not fruitful. Even after 2 days, no formation of propargylamine **10a** was observed (Table 1, entry 9).

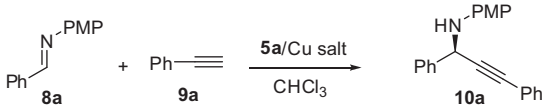
5 mol % of $Cu(ClO_4)_2{\cdot}6H_2O$ with 10 mol % of **5a** at ambient temperature furnished the target product **10a** with better enantioselectivity (81% yield, 52% ee) (Table 1, entry 10). After identification of $Cu(ClO_4)_2{\cdot}6H_2O$ as a suitable metal partner and 25 °C as an optimal reaction temperature we went ahead to choose the appropriate reaction medium (Table 2).

Under the same reaction conditions optimized previously, a profound solvent effect on the yield and the enantioselectivity was observed. No product was isolated when the reaction was carried out in acetonitrile, acetone, and dimethoxyethane (DME) (Table 2, entries 4, 6, and 9). Reaction in dichloroethane, diethyl ether, and tetrahydrofuran (THF) contrived only a trace amount of propargylamine **10a** in TLC visualization and hence no attempts were made to isolate the product (Table 2, entries 3, 8, and 10). Up to 70% yield was obtained with toluene, *tert*-butyl methyl ether (TBME), and dimethylformamide (DMF) as a reaction medium but very poor enantioselectivity was observed (up to 17%) in these cases (Table 2, entries 5, 7, and 11). Excellent conversion (up to 87%) was observed only in chlorinated solvents such as dichloromethane and chloroform. Enantioselectivity observed in chloroform was better (52%) (Table 2, entry 1) than of enantioselectivity in dichloromethane (29%) (Table 2, entry 2). Thus chloroform was identified as the most suitable reaction medium for the enantioselective synthesis of propargylamines using ligand **5a**.



Scheme 3. One-pot enantioselective propargylamine reaction.

Table 1
Optimization studies of enantioselective propargylamine reaction[a]

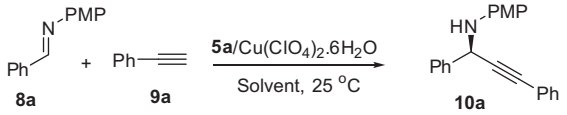


Entry	Cu salt	Time (h)	L/M	*T* (°C)	Yield[c] (%)	ee[d] (%)
1	CuCl	24	1:1	25	65	20
2	CuBr	24	1:1	25	72	26
3	CuI	24	1:1	25	35	31
4	Cu(OTf)	24	1:1	25	81	27
5	$Cu(PF_6)(CH_3CN)_4$	24	1:1	25	47	7
6	$Cu(OAc)_2{\cdot}H_2O$	48	1:1	25	—	—
7	$Cu(OTf)_2$	24	1:1	25	87	27
8	$Cu(ClO_4)_2{\cdot}6H_2O$	24	1:1	25	89	43
9	$Cu(ClO_4)_2{\cdot}6H_2O$	48	1:1	0	—	—
10[b]	$Cu(ClO_4)_2{\cdot}6H_2O$	36	2:1	25	81	52

[a] Reactions were performed on a 1 mmol scale: Cu salt (5 mol %) and ligand **5a** (5 mol %) were stirred in $CHCl_3$ (3 mL) under Ar at 25 °C. After a stirring period of 3 h, imine **8a** (1 equiv) and **9a** (1.5 equiv) were added.
[b] 5 mol % of Cu salt and 10 mol % of ligand were used.
[c] Isolated yields after chromatography.
[d] Absolute configurations of the product **10a** were assigned as ***R*** by the reported HPLC retention times in the literature.

After optimizing the reaction conditions systematically, we proceeded to optimize the ligand structure in order to identify the matched pair of diastereomeric ligand to achieve the higher enantioselectivity possible. All four different diastereomeric ligands (**5a–5d**) (Fig. 2) were obtained using respective starting materials and were evaluated in the enantioselective synthesis of propargylamine **10a**. From these results we came to know that only ligand **5a** induced good asymmetry (52% ee, Table 3, entry 1)

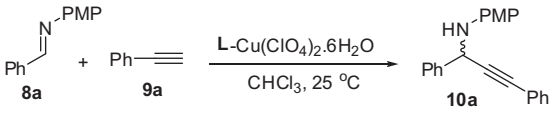
Table 2
Effect of solvents on enantioselective propargylamine reaction[a]



Entry	Solvent	Time (d)	Yield[b] (%)	ee (%)
1	Chloroform	2	81	52
2	Dichloromethane	2	87	29
3	Dichloroethane	4	<5	—
4	Acetonitrile	4	—	—
5	Toluene	3	68	17
6	Acetone	4	—	—
7	TBME	3	38	15
8	Diethyl ether	4	<5	—
9	DME	4	—	—
10	THF	4	<5	—
11	DMF	3	70	4

[a] Ratio of **5a**, $Cu(ClO_4)_2{\cdot}6H_2O$, **8a**, and **9a** was 0.1:0.05:1:1.5 in 3 mL of solvent.
[b] Isolated yield.

Table 3
Evaluation of box ligands in asymmetric propargylamine reaction[a]



Entry	Ligand	Time (d)	Yield[b] (%)	ee (%)
1	**5a**	2	81	52 (*R*)
2	**5b**	2	65	29 (*R*)
3	**5c**	2	75	24 (*S*)
4	**5d**	2	72	27 (*S*)
5	**5e**	3	78	27 (*R*)
6	**4a**	2	71	0
7	**4b**	2	68	0
8	**4c**	3	68	0

[a] Ratio of ligand, $Cu(ClO_4)_2{\cdot}6H_2O$, **8a**, and **9a** was 0.1:0.05:1:1.5 in 3 mL of $CHCl_3$.
[b] Isolated yield.

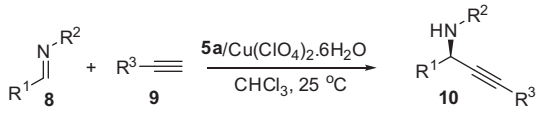
when compared to the other diastereomers (**5b–5d**) (Table 3, entries 2–4) including ligand **5e** (Table 3, entry 5). Also, the absolute configuration of the product was identified as ***R*** configuration. This is in accordance with our previous results that the absolute configuration was dictated by the chirality of oxazoline backbone, and not of the chirality possessed by chiral appendage.

To prove the essentiality of additional chiral appendage, we also carried out the transformation using control ligands **4a**, **4b**, and **4c**. All these ligands failed to induce the enantioselectivity (Table 3, entries, 6–8). This proves unequivocally that chiral appendage is essential for asymmetric induction to synthesize chiral propargylamines. This result is no different from our earlier observation for the Henry reaction.[10]

With these optimized conditions in hand, we proceeded to evaluate the scope of enantioselective propargylamine formation for various terminal acetylenes with structurally diverse imines.[13] Addition of phenylacetylene (**9a**) to imine derived from simple aromatic substrates such as benzaldehyde and aniline resulted in the formation of **10b** with very good enantioselectivity (80% ee) (Table 4, entry 1), whereas imine **8a** formed from *p*-methoxyaniline showed only 52% enantioselectivity in the formation of the corresponding propargylamine **10a** (Table 4, entry 2). Since, electron releasing group diminished the enantioselectivity we carried out the reaction using electron deficient imine **8c** with 4,4′-dichloro substitution to the formation of **10c**. Unfortunately electron withdrawing substituents did not induce good enantioselectivity in the formation of the corresponding propargylamine **10c**. Only moderate yield and enantioselectivity were obtained in this case (Table 4, entry 3). To diversify the scope of substrates further we also made sulfonyl imine **8d** from the corresponding sulfonamide. But there was no formation of product even after 4 days, when imine **8d** was used as a substrate (Table 4, entry 4).

Various aldehydes were reacted with aniline to prepare structurally diverse imines for the enantioselective addition of phenyl-

Table 4
Enantioselective alkynylation of imines with (*S*,*S*)-Nap-(*S*,*S*)-Box (**5a**)[a]



Entry	R^1	R^2	R^3	Time (d)	Product	Yield[b] (%)	ee (%)
1	Ph	Ph	Ph	2	**10b**	72	80
2	Ph	4-$OMeC_6H_4$	Ph	4	**10a**	81	52
3	4-ClC_6H_4	4-ClC_6H_4	Ph	2	**10c**	69	66
4	Ph	Ts	Ph	4	**10d**	—	—
5	4-PhC_6H_4	Ph	Ph	3	**10e**	76	70
6	4-$OMeC_6H_4$	Ph	Ph	4	**10f**	67	10
7	2-$OMeC_6H_4$	Ph	Ph	4	**10g**	—	—
8	4-ClC_6H_4	Ph	Ph	2	**10h**	81	64
9	4-BrC_6H_4	Ph	Ph	2	**10i**	86	60
10	4-$NO_2C_6H_4$	Ph	Ph	2	**10j**	78	64
11	Ph	Ph	$SiMe_3$	3	**10k**	77	52

[a] Ratio of **5a**, $Cu(ClO_4)_2{\cdot}6H_2O$, **8**, and **9** was 0.1:0.05:1:1.5 in 3 mL of $CHCl_3$.
[b] Isolated yields after chromatography.

acetylenes. Addition of phenylacetylene to 4-phenyl substituted imine made from 4-phenylbenzaldehyde and aniline resulted in the formation of **10e** with 76% yield with good enantioselectivity (70%) (Table 4, entry 5). As observed in the case of anilines electron releasing substituents at the aldehyde part also diminished the enantioselectivity when compared with electron withdrawing substitutions. Imine **8f** with *p*-methoxy substitution on the aldehyde part yielded 67% of propargylamine **10f** with only 10% enantioselectivity (Table 4, entry 6). Similarly imine **8g** synthesized using 2-methoxybenzaldehyde and aniline did not react well under our catalytic system even after 4 days (Table 4, entry 7). Imines **8h–8j** having electron withdrawing groups such as Cl, Br, and NO_2 on the aldehyde part, furnished corresponding propargylamines **10h–10j** with almost similar enantioselectivities of 60–64% and yields 78–86% (Table 4, entries 8, 9, and 10). To extend the substrate scope further, we employed TMS-acetylene **9b** instead of phenylacetylene (**9a**). The reaction was carried out using imine **8k** with TMS-acetylene **9b** which yielded 52% enantioselectivity with 77% yield of **10k** (Table 4, entry 11). Thus a broad range of imines underwent alkyne addition to afford propargylamines in good yields with moderate to very good enantioselectivity.

In conclusion, we applied a new class of bidentate bioxazoline ligands to synthesize optically active propargylamines. Further optimization of the ligand structure might evolve this bioxazoline as a viable competitor for pybox in terms of price and availability of the chiral sources. Currently efforts are dedicated in our lab to utilize bioxazoline **5a**, in various asymmetric transformations.

Acknowledgments

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13. *General procedure for the enantioselective synthesis of propargylamine derivatives (**10a–10k**) catalyzed by the Cu(II)–**5a** complex*: A solution of ligand **5a** (0.05 mmol, 5 mol %) and $Cu(ClO_4)_2{\cdot}6H_2O$ (0.1 mmol, 10 mol %) in dry chloroform (3 mL) was stirred at room temperature for 60 min. Imine (1 mmol) and an alkyne (1.5 mmol) were added, and the whole mixture was stirred at 25 °C for 2–4 days. After completion of the reaction (monitoring by TLC), the mixture was concentrated in vacuo and purified over silica gel by column chromatography (10–20% EtOAc in hexane) yielding pure propargylamine (**10a–10k**).