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Asymmetric addition of alkynes to imines in water catalyzed with a recyclable Cu(I)–bis(oxazoline) and stearic acid system

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

[a]*School of Pharmaceutical Science, Sun Yat-Sen University, Guangzhou 51006, China*
[b]*Shenyang Pharmaceutical University, Shenyang, PR China*
[c]*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*

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Abstract—Stearic acid and its zinc salt were used as additives in the enantioselective alkyne addition to imines catalyzed by copper(I)–bis(oxazoline) (box) in water. The reactions took place smoothly with good yields and high enantioselectivities (up to 97% ee). Good enantioselectivities were maintained in a catalyst recycle study.

1. Introduction

Chiral propargylamines are important synthetic intermediates for the construction of biologically active nitrogen-containing compounds and natural products.[1–3] In contrast to extensive studies on the asymmetric alkynylation of aldehydes,[4] only a limited number of catalyst systems have been reported for the addition of acetylenes to imines. 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.[5] Hoveyda reported a Zr-catalyzed enantioselective addition of a range of mixed alkynylzinc reagents to various arylimines with a chiral amino acid-based ligand.[6] Knochel et al.[7] described the addition of functionalized alkynes to enamines catalyzed by Cu(I)–Quinap complexes. Carreira et al. developed a new atropisomeric P,N ligand (Pinap), structurally related to Quinap, which showed similar reactivity and stereochemical efficiency in promoting the CuBr-catalyzed three-component reaction of dibenzylamine, aldehydes and various acetylenes.[8] Recently, Afonso et al. reported the enantioselective alkyne addition to imines catalyzed by copper(I)–pyridylbis(oxazoline) (pybox), performed in the ionic liquid 1-*n*-butyl-3-methyl imidazolium bis(trifluoromethylsulfonyl)imide [bmim][NTf_2].[9]

Water as a solvent in chemical reactions has many advantages over the usual organic solvents. It is safe, nontoxic, very economical and environmentally friendly. From an industrial point of view, the low solubility of many organic compounds in water makes it possible to form a two-phase system that allows an easy separation of the products from the water-soluble organometallic catalyst by simple phase separation. However, the low solubility of many organic compounds in water also limits its application in various chemical transformations. To circumvent this problem, surfactants, which improve the solubility of organic materials or form a colloidal dispersion with them in water, have been used in some reactions such as the Diels–Alder reaction,[10] aldol reactions,[11] Suzuki coupling,[12] alkylation,[13] asymmetric hydrogenation[14] and transfer hydrogenation.[15]

On the other hand, the recycle or reuse of the chiral catalyst in organic reactions has attracted much attention in recent years. Many methods such as the immobilization of the catalyst on homogenous or heterogeneous supports,[16] solvent extractions based on the large different affinities of the catalysts and the reaction products in each liquid phase have been developed. Supercritical CO_2 ($scCO_2$),[17] fluorinated solvents[18] and room temperature ionic liquids (RTILs)[19] are typical examples. Herein, we report our preliminary studies on the enantioselective addition of alkynes to imines in water, catalyzed with Cu(I)–bis(oxazoline) using stearic acid as the surfactant.

* Corresponding author. Tel.: +86 2035693517; e-mail: xsli219@yahoo.com

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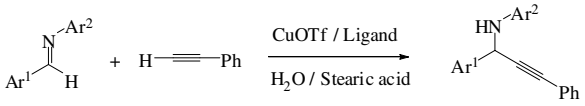
2. Results and discussion

The alkyne addition to imines in water was slow and generally needed 2–4 days.[5] We believed this reaction could be accelerated by using a surfactant, which formed a colloidal dispersion with the alkyne and imines in water. PEG was initially used as a surfactant for the addition of alkynes to imines with a chiral bis(oxazolinyl) CuOTf catalyst. The results were quite unsatisfactory: both the chemical yields and the enatioselectivities in aqueous solutions containing 5%, 25% and 50% PEG aqueous solution were low. The cationic surfactant, cetyltrimethylammonium bromide (CTAB), which was effective in the asymmetric transfer hydrogenation of ketones, gave very good chemical yields[19] but no enantioselectivity. Other cationic surfactants, such as dodecyltrimethyl ammonium bromide (DATB), cetyltrimethyl ammonium chloride (CATC) and tetrabutyl ammonium bromide (TBAB) afforded similar results. On the other hand, sodium dodecyl sulfate (SDS), sodium dodecylbenzenesulfonate (SDBS) and sodium carboxymethyl cellulose (SCMC) provided low to modest chemical yields and low ee's. However, when stearic acid and zinc stearate were used as the surfactant in the reaction, both enatioselectivity and chemical yields were greatly improved. Furthermore, the asymmetric addition of alkynes to imines could be completed within 24 h with an 85% ee and 86% yield, which were substantially superior to that obtained without the surfactant (48 h, 80% ee and 77% yield) (Table 1).

The recycling of Cu(I)–bis(oxazoline) was investigated with imine-1 and imine-2 as the substrates and 0.12 equiv of stearic acid as surfactant. The procedure for recycling of the reaction was very simple: hexane was added to extract the product after each batch reaction and the residue containing the catalyst was reused by changing fresh *N*-benylideneaniline and phenylacetylene for the next cycle. The enantioselectivities (78–85% ee) were quite consistent (Table 2).

Table 2. Recycle of catalyst with stearic acid as surfactant in water



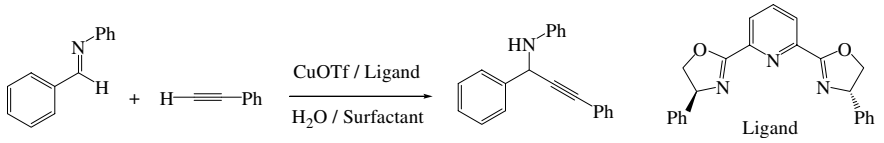
Imine-**1**: $Ar^1 = Ar^2 = Ph$;
Imine-**2**: $Ar^1 = 4\text{-}CH_3C_6H_4$, $Ar^2 = Ph$

Cycle	Imine	Time (h)	Yield[a] (%)	ee[b] (%)
1	Imine-**1**	24	67	78
2	Imine-**1**	24	78	85
3	Imine-**1**	24	75	85
4	Imine-**1**	24	62	80
5	Imine-**1**	24	45	79
1	Imine-**2**	24	70	97
2	Imine-**2**	24	83	97
3	Imine-**2**	24	78	96
4	Imine-**2**	24	75	95

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

Table 3 shows the results of the addition of phenylacetylene to a series of substrates in water with Cu(I)–bis(oxazoline)

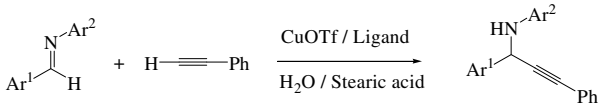
Table 1. Screening of surfactants as additives for the enantioselective alkynylation of imines



Entry	Surfactants	Time[a] (h)	Yield[b] (%)	ee[c] (%)
1	—	48	77	80
2	5% PEG[d]	48	52	38
3	25% PEG	48	30	35
4	50% PEG	48	12	35
5	100% PEG[e]	48	—	—
6	SDS	48	32	26
7	SDBS	48	68	35
8	TBAB	24	87	2
9	CTAB	24	90	0
10	DTAB	24	83	0
11	CTAC	24	80	5
12	CMC	48	38	12
13	Calcium stearate	48	69	79
14	Sodium stearate	48	35	82
12	Zinc stearate	48	88	80
13	Stearic acid	24	86	85
14	D-Camphorsulfonic acid	24	80	30

[a] All reactions were carried out with 10 mol % CuOTf and 10 mol % Ph–Pybox in water at room temperature.
[b] Isolated yields after purification by flash chromatography.
[c] Enantiomeric excess was determined by HPLC with a chiracel OD column.
[d] 5% PEG-400 aqueous solution (m/m).
[e] PEG-400 was used as solvent.

Table 3. Enantioselectivity of the addition of phenylacetylene with catalyst and stearic acid in water



Entry	Ar^1	Ar^2	Yield[a] (%)	ee[b] (%)
1	C_6H_5	C_6H_5	86	85
2	C_6H_5	4-$CH_3C_6H_4$	80	88
3	C_6H_5	4-$CH_3OC_6H_4$	85	86
4	C_6H_5	4-ClC_6H_4	60	35
5	4-$CH_3C_6H_4$	C_6H_5	80	97
6	2-ClC_6H_4	C_6H_5	78	86
7	2-$CH_3OC_6H_4$	C_6H_5	83	62
8	4-$CH_3OC_6H_4$	C_6H_5	89	90
9	4-$CH_3C_6H_4$	4-$CH_3C_6H_4$	82	94
10	4-$CH_3OC_6H_4$	4-$CH_3C_6H_4$	81	91
11	3,5-Di-$CH_3C_6H_3$	C_6H_5	83	95
12	3,5-Di-$CH_3C_6H_3$	4-$CH_3C_6H_4$	85	85

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

as the catalyst precursor and stearic acid as the additive. The reactions took place smoothly to give propargylamines in good yield and high enantioselectivity in most cases. The results also revealed that an electron donating group on the phenyl ring of the substrates enhanced the enatioselectivity, while an electron-withdrawing group gave somewhat negative effects. The best ee value was obtained in the addition to the imine formed by 4-methylbenzyl aldehyde and aniline (entry 5, 97% ee).

3. Conclusion

In conclusion, we have developed an efficient catalytic system for the enantioselective alkyne addition to imines consisting of copper(I)–bis(oxazoline) (box) and stearic acid or its zinc salt as additives. The reactions proceeded smoothly with good yield and high enantioselectivity in water and the catalyst could be reused several times.

4. Experimental

4.1. General procedure for the enantioselective alkynylation of imines

To a mixture of imine (0.2 mmol), copper(I) triflate benzene complex (0.02 mmol), chiral ligand (0.02 mmol) and water (0.5 mL) were added phenylacetylene (0.033 mL, 0.3 mmol) and the surfactant (0.002 mmol). The mixture was stirred at room temperature for a specified period of time, and then extracted with dichloromethane. After concentration in vacco, the extracts were directly applied onto a silica gel column for flash chromatography (1:50 ethyl acetate/petroleum ether as eluent). 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.

4.2. General procedure for recycle of catalyst with stearic acid in water

To a mixture of *N*-benylideneaniline (180 mg, 1 mmol), copper(I) triflate benzene complex (50 mg, 10 mol %), chiral ligand (37 mg, 10 mol %) and water (5 mL) in a 10 mL round bottom flask, were added phenylacetylene (0.165 mL, 1.5 mmol) and stearic acid (28 mg, 10 mol %). The mixture was stirred at room temperature for 24 h, and then extracted with hexane (5 mL × 3). The combined organic phase was concentrated under reduced pressure, and purified by chromatography through silica gel (1:50 ethyl acetate/petroleum ether as eluents) to give the propargylamine. The residue containing catalyst was reloaded with *N*-benylideneaniline (180 mg, 1 mmol) and phenylacetylene (0.165 mL, 1.5 mmol) for the next cycle reaction and the process was repeated for five times. The ee values were determined by chiral HPLC analysis using a Chiralcel OD column (4.6 mm * 250 mm, 5% isopropanol in hexane as eluents).

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