Available online at www.sciencedirect.com

ScienceDirect

Mendeleev Commun., 2016, **26**, 477–479

Mendeleev Communications

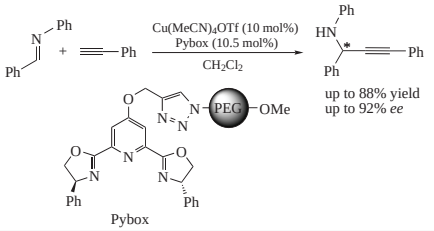
Poly(ethylene glycol)-supported chiral pyridine-2,6-bis(oxazoline): synthesis and application as a recyclable ligand in Cu^{I}-catalyzed enantioselective direct addition of terminal alkynes to imines

Elena A. Tarasenko and Irina P. Beletskaya*

Department of Chemistry, M. V. Lomonosov Moscow State University, 119991 Moscow, Russian Federation. Fax: +7 495 939 3618; e-mail: beletska@org.chem.msu.ru

DOI: 10.1016/j.mencom.2016.11.005

Pyridine-2,6-bis(oxazoline) immobilized on a soluble support, *viz.*, poly(ethylene glycol) methyl ether with M_n = 5000 Da, has been synthesized for the first time. The efficiency of its application as a chiral ligand in Cu^{I}-catalyzed direct addition of terminal alkynes to imines and the feasibility of its recycling at least in three cycles have been shown.

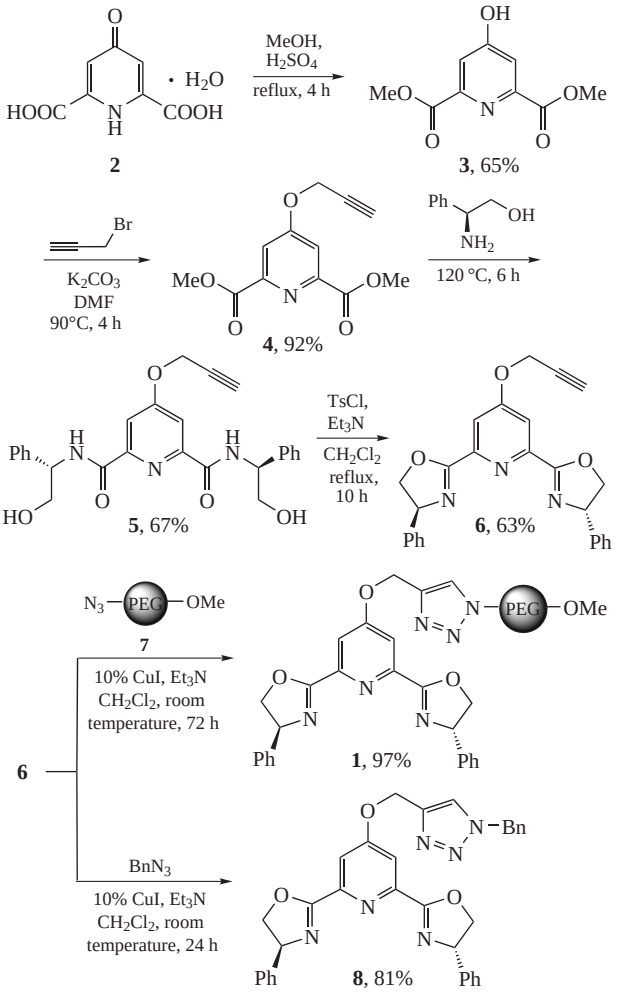


Pyridine-2,6-bis(oxazolines) (Pybox) belong to an important class of tridentate chiral ligands with C_2 symmetry. They form chiral complexes with ions of many metals and are widely used in asymmetric catalysis.[1–3] Pyridine-2,6-bis(oxazolines) are obtained from the corresponding (*R*)- and (*S*)-amino alcohols that are usually commercially available, which allows one to synthesize Pybox ligands both as (*R*,*R*) and (*S*,*S*) isomers. As a result, the use of these ligands in enantioselective reactions makes it possible to obtain the products in both enantiomeric forms.

Since the synthesis of Pybox ligands is a multistep process, it is beneficial from economical and ecological standpoints to use them repeatedly, which is achieved by their immobilization on various supports.[4] Mayoral[5] in 2002 was the first to perform such immobilization by copolymerization of the 4-vinylpyridine-2,6-bis(oxazoline) derivative with styrene and divinylbenzene. Later, Pybox ligands were grafted on TentaGel resin,[6] Wang resin,[7] polystyrene,[8] Merrifield resin,[9] silica gel coated magnetic Fe_3O_4 nanoparticles.[10] Immobilization was also performed by electrostatic interaction of Cu^{I}- and Cu^{II}-Pybox complexes with silica gel[11] and using ionic liquids as the support.[12,13] In all these cases, the immobilized Pybox-based catalysts mentioned above were insoluble in organic solvents, *i.e.*, the reactions were carried out under heterogeneous conditions. However, some examples are available when aza-box ligands[14,15] and box-ligands[16] were immobilized on a soluble support, *viz.*, poly(ethylene glycol) (PEG). This allows one to perform chemical reactions under homogeneous conditions and separate the catalyst by precipitation, *e.g.*, with diethyl ether and then re-use it.

In this study, we performed the immobilization of a pyridine-2,6-bis(oxazoline) derivative on poly(ethylene glycol) monomethyl ether with M_n = 5000 Da ($MeOPEG_{5000}$) and studied the efficiency and feasibility of recycling the complex of this ligand with copper(I) triflate, as well as the feasibility of recycling the ligand itself in the enantioselective addition of phenylacetylene to *N*-benzylideneaniline.

To perform grafting of the Pybox moiety to $MeOPEG_{5000}$, we chose popular and reliable Cu^{I}-catalyzed azide-alkyne cycloaddition (CuAAC, a click-reaction).[17–21] It is often used in the covalent immobilization of homogeneous catalysts and ligands,[22] *e.g.*, in the immobilization of an aza-box-ligand on PEG[15] and Pybox[9] on Merrifield resin.



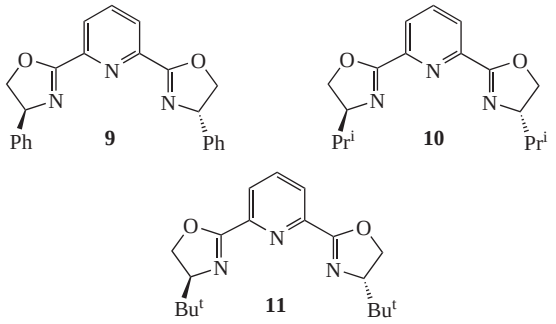
Scheme 1

Immobilized Pybox **1** was synthesized in five steps from commercially available chelidamic acid hydrate **2** (Scheme 1). At the first step, reflux in methanol in the presence of sulfuric acid gave dimethyl chelidamate **3**, which was then propargylated. Propargyl derivative **4** was heated with (*S*)-phenylglycinol without a solvent to afford diamide **5**. Treatment of the latter with tosyl chloride followed by reflux in CH_2Cl_2 resulted in the closure of the oxazoline rings to give Pybox ligand **6** containing a triple bond.

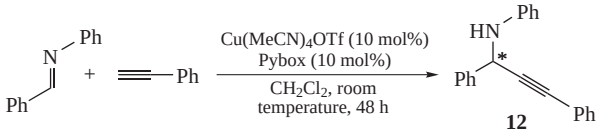
The immobilization was performed by the click reaction between propargyloxy derivative **6** and $MeOPEG_{5000}$-azide **7** in CH_2Cl_2 in the presence of catalytic amounts of CuI and excess Et_3N at room temperature for 72 h. The target ligand **1** was isolated by precipitation with diethyl ether from CH_2Cl_2 after preliminary washing of the reaction mixture with 0.1 M aqueous solution of EDTA-Na_2 to remove copper. Analysis of isolated product **1** by IR spectroscopy has shown the lack of the absorption band around 2100 cm^{-1}, which is characteristic of the azido group and is observed in the spectrum of the original $MeOPEG_{5000}$-azide **7**. ^1H NMR spectroscopic data also confirmed the purity of compound **1**. The integral intensity of the methoxy group in $MeOPEG_{5000}$ matched the integral intensities of the Pybox moiety (see Online Supplementary Materials).

We chose the direct enantioselective addition of terminal acetylenes to imines to produce non-racemic propargyl amines,[23–26] structural fragments of many biologically active and natural compounds, as the model reaction for testing the ligand we obtained. The addition of terminal alkynes to imines catalyzed by complexes of Cu^I with Pybox ligands usually occurs in high yields and with rather high enantioselectivity.[27–31]

In contrast to the previous studies where complexes with benzene $(CuOTf)_2 \cdot C_6H_6$ or toluene $(CuOTf)_2 \cdot PhMe$ were used as the source of CuOTf, we applied the acetonitrile complex of copper(I) triflate. Therefore, we first tested $Cu(MeCN)_4OTf$ with non-immobilized Pybox ligands **9**–**11** containing various substituents at 4-position of the oxazoline rings in the reaction of phenylacetylene with *N*-benzylideneaniline (Scheme 2, Table 1).



All the complexes obtained *in situ* from $Cu(MeCN)_4OTf$ and Pybox ligands **9**–**11** demonstrated high reactivity, while compounds **9** and **11** provided high enantioselectivity as well (entries 1 and 3). Immobilized ligand **1** differs from Pybox ligands **9**–**11**, first, by the presence of an oxygen atom at 4-position of the pyridine ring; this oxygen atom enriches the ligand with electrons and thus makes its complex with Cu^I a weaker Lewis acid. Second, the click reaction creates a triazole linker that is also able to coordinate Cu^I. In order to estimate the effect of the factors mentioned above on the course of the reaction, we



Scheme 2

Table 1 Enantioselective addition of phenylacetylene to *N*-benzylideneaniline catalyzed by Cu^I–Pybox **8**–**11** complexes.[a]

Entry	Pybox	Conversion[b] (%)	Yield[b,c] (%)	*ee*[d] (%)
1	**9**	96	96 (89)	93
2	**10**	96	91 (85)	72
3	**11**	100	96 (92)	94
4	**8**	99	95 (90)	96

[a] Reaction conditions: *N*-benzylideneaniline (0.25 mmol), phenylacetylene (0.375 mmol), CH_2Cl_2 (1 ml). [b] Determined by ^1H NMR analysis of the crude product. [c] Isolated yields after column chromatography are given in parentheses. [d] Determined by chiral HPLC.

synthesized the low-molecular analogue **8** (see Scheme 1). The activity of the complex based on ligand **8** and $Cu(MeCN)_4OTf$ was found to be comparable to that of complexes of other Pybox ligands and had the highest enantioselectivity (entry 4). Thus, the triazolylmethoxy group at 4-position of the pyridine ring in a Pybox ligand has no adverse effect on the chosen model reaction.

The use of the immobilized Pybox **1** in the addition of phenylacetylene to *N*-benzylideneaniline has shown (Table 2) that the polymeric support based on PEG slows the reaction down considerably, both in comparison with Pybox ligands **8**–**11** and with analogues immobilized on an insoluble support.[9,10] This is apparently due to a considerable increase in the viscosity of the reaction mixture obtained. Furthermore, PEG can coordinate Cu^I similarly to crown ethers. In fact, conversion in 7 days at room temperature was only 30% (entry 1), while the enantiomeric excess decreased from 96 to 84% as compared to the same reaction with non-immobilized ligand **8** (Table 1, entry 4). Twofold dilution of the reaction mixture raised the conversion to 47% and *ee* to 92% (see Table 2, entry 2). However, subsequent dilution decreased the conversion again but did not affect the enantiomeric excess (entry 3).

An attempt to reduce the viscosity by decreasing the concentration of PEG in the mixture, *i.e.*, by diminishing the catalyst loading to 5 mol% (entry 4) in comparison with the initial 10 mol% (entry 2), also led to lower conversion. A decrease in viscosity and an increase in conversion to 93 or 94% (depending on dilution) can be attained by performing the reaction at 50 °C (entries 5 and 6). Unfortunately, an attempt to reuse the catalyst after separating it by precipitation from the reaction mixture with diethyl ether resulted in the conversion as small as 36 or 23% (entries 5 and 6, 2nd cycle). This is probably due to the oxidation of Cu^I to Cu^{II} during the isolation of the immobilized complex. A decrease in the product yield and enantioselectivity in this reaction, though not so considerable, was also observed previously with Pybox ligands immobilized on insoluble supports.[9,10]

In view of the unsatisfactory results of the studies on catalyst reuse, we studied whether it is possible to recycle ligand **1** under

Table 2 Cu^I-immobilized Pybox **1** complex catalyzed enantioselective addition of phenylacetylene to *N*-benzylideneaniline.[a]

Entry	Temperature	Time/ days	Volume of CH_2Cl_2/ml	Conversion[b] (%)	*ee*[c] (%)
1	Ambient	7	1	30	84
2	Ambient	7	2	47	92
3	Ambient	7	3	26	92
4[d]	Ambient	7	2	33	90
5	50 °C	4	1	93 (36)[e]	87 (81)[e]
6	50 °C	7	2	94 (23)[e]	90 (76)[e]

[a] Reaction conditions: *N*-benzylideneaniline (0.25 mmol), phenylacetylene (0.375 mmol), $Cu(MeCN)_4OTf$ (10 mol%), Pybox **1** (10.5 mol%). [b] Determined by ^1H NMR analysis of the crude product. [c] Determined by chiral HPLC. [d] 5 mol% of $Cu(MeCN)_4OTf$ and 5.25 mol% of Pybox **1** were used. [e] The values for the second cycle of the catalyst are given in parentheses.

Table 3 Recycling of Pybox ligand **1** in enantioselective addition of phenylacetylene to *N*-benzylideneaniline.[a]

Cycle	Conversion[b] (%)	Isolated yield[c] (%)	*ee*[d] (%)
1	93	83	90
2	91	82	90
3	97	88	91

[a]Reaction conditions: *N*-benzylideneaniline (0.25 mmol), phenylacetylene (0.375 mmol), $Cu(MeCN)_4OTf$ (10 mol%), Pybox **1** (10.5 mol%), CH_2Cl_2 (2 ml), 50 °C, 7 days. [b]Determined by ^1H NMR analysis of the crude product. [c]After column chromatography. [d]Determined by chiral HPLC.

the conditions of entry 6 (Table 2). To do so, after the reaction was completed, the catalyst was separated by precipitation with diethyl ether, redissolved in CH_2Cl_2 and thoroughly washed with 0.1 M aqueous solution of EDTA-Na_2 to remove copper. After drying and solvent evaporation, the ligand was reused upon addition of a new portion of $Cu(MeCN)_4OTf$, the solvent and reactants (Table 3).

The results have shown that the immobilized ligand is sufficiently stable during the reaction and its isolation. So it can be used repeatedly. The product yield and enantiomeric excess did not change considerably in three successive cycles. In this case, both the yields and *ee* values are comparable to those obtained using Pybox ligands immobilized on insoluble supports.[9,10]

In conclusion, we were the first to synthesize a Pybox ligand immobilized on a soluble support, *viz*., poly(ethylene glycol) methyl ether with M_n = 5000 Da. The efficiency of the complex obtained *in situ* from this immobilized Pybox ligand and $Cu(MeCN)_4OTf$ in enantioselective direct addition of alkynes to imines has been estimated. The product of addition of phenylacetylene to *N*-benzylideneaniline has been obtained in yields up to 88% and *ee* up to 92%. The ligand can be recycled at least in three successive cycles without a decrease in the product yield or enantioselectivity.

This work was supported by the Russian Science Foundation (grant no. 14-23-00186).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2016.11.005.

References

1 G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev*., 2003, **103**, 3119.
2 H. A. McManus and P. J. Guiry, *Chem. Rev*., 2004, **104**, 4151.
3 B. D. Ward and L. H. Gade, *Chem. Commun.*, 2012, **48**, 10587.
4 J. M. Fraile, J. I. García and J. A. Mayoral, *Coord. Chem. Rev*., 2008, **252**, 624.
5 A. Cornejo, J. M. Fraile, J. I. García, E. García-Verdugo, M. J. Gil, G. Legarreta, S. V. Luis, V. Martínez-Merino and J. A. Mayoral, *Org. Lett*., 2002, **4**, 3927.
6 S. Lundgren, S. Lutsenko, C. Jonsson and C. Moberg, *Org. Lett.*, 2003, **5**, 3663.
7 A. Weissberg, B. Halak and M. Portnoy, *J. Org. Chem*., 2005, **70**, 4556.
8 A. Cornejo, J. M. Fraile, J. I. Garcia, M. J. Gil, S. V. Luis, V. Martinez-Merino and J. A. Mayoral, *J. Org. Chem*., 2005, **70**, 5536.
9 M. Tilliet, S. Lundgren, C. Moberg and V. Levacher, *Adv. Synth. Catal*., 2007, **349**, 2079.
10 T. Zeng, L. Yang, R. Hudson, G. Song, A. R. Moores and C. J. Li, *Org. Lett*., 2011, **13**, 442.
11 C. McDonagh, P. O'Conghaile, R. J. M. Klein Gebbink and P. O'Leary, *Tetrahedron Lett*., 2007, **48**, 4387.
12 J. Lu, S. J. Ji and T. P. Loh, *Chem. Commun*., 2005, 2345.
13 B. Karimi, A. Maleki, D. Elhamifar, J. H. Clark and A. J. Hunt, *Chem. Commun*., 2010, **46**, 6947.
14 M. Glos and O. Reiser, *Org. Lett*., 2000, **2**, 2045.
15 A. Gissibl, M. G. Finn and O. Reiser, *Org. Lett*., 2005, **7**, 2325.
16 R. Annunziata, M. Benaglia, M. Cinquini, F. Cozzi and M. Pitillo, *J. Org. Chem.*, 2001, **66**, 3160.
17 V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem. Int. Ed*., 2002, **41**, 2596.
18 C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem*., 2002, **67**, 3057.
19 *Click Chemistry for Biotechnology and Materials Science*, ed. J. Lahann, John Wiley & Sons, Chichester, 2009.
20 M. Meldal and C. W. Tornøe, *Chem. Rev*., 2008, **108**, 2952.
21 P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev*., 2013, **113**, 4905.
22 A. E. Fernandes, A. M. Jonas and O. Riant, *Tetrahedron*, 2014, **70**, 1709.
23 L. Zani and C. Bolm, *Chem. Commun*., 2006, 4263.
24 G. Blay, A. Monleón and J. Pedro, *Curr. Org. Chem*., 2009, **13**, 1498.
25 B. M. Trost and A. H. Weiss, *Adv. Synth. Catal*., 2009, **351**, 963.
26 W.-J. Yoo, L. Zhao and C.-J. Li, *Aldrichimica Acta*, 2011, **44**, 43.
27 C. Wei and C.-J. Li, *J. Am. Chem. Soc.*, 2002, **124**, 5638.
28 C. Wei, J. T. Mague and C.-J. Li, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5749.
29 A. Bisai and V. K. Singh, *Org. Lett*., 2006, **8**, 2405.
30 M. Panera, J. Diez, I. Merino, E. Rubio and M. P. Gamasa, *Inorg. Chem*., 2009, **48**, 11147.
31 J. Liu, B. Liu, X. Jia, X. Li and A. S. C. Chan, *Tetrahedron: Asymmetry*, 2007, **18**, 396.

Received: 27th July 2016; Com. 16/5009