DOI: 10.1002/adsc.200700112

Polymer-Bound Pyridine-Bis(oxazoline). Preparation through Click Chemistry and Evaluation in Asymmetric Catalysis

Mélanie Tilliet,[a,b] Stina Lundgren,[b] Christina Moberg,[b,*] and Vincent Levacher[a,*]

[a] Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, IRCOF, CNRS, Université et INSA de Rouen. B.P. 08, 76131 Mont-Saint-Aignan Cédex, France
Fax: (+33)-(0)-2-3552-2962; e-mail: vincent.levacher@insa-rouen.fr

[b] KTH School of Chemical Science and Engineering, Organic Chemistry, 100 44 Stockholm, Sweden; e-mail: kimo@kth.se

Received: February 28, 2007; Revised: July 6, 2007; Published online: September 11, 2007

Supporting information for this article is available on the WWW under http://asc.wiley-vch.de/home/.

Abstract: A pyridine-bis(oxazoline) ligand was efficiently immobilized by copper(I)-catalyzed azide-alkyne cycloaddition onto a polystyrene resin. The so obtained click-pybox resin **1a** was associated with various metal salts ($YbCl_3$, $LuCl_3$, CuOTf) and the resulting resin-bound catalysts were explored in ring-opening of cyclohexene oxide, silylcyanation of benzaldehyde and alkynylation of imines. These new polymer-supported catalysts exhibit good to excellent performances in terms of catalytic activity, enantioselectivity and recyclability.

Keywords: asymmetric catalysis; click chemistry; copper(I); immobilization; lanthanides; pybox

In recent years, pyridine-2,6-bisoxazoline (pybox) derivatives have emerged as a popular class of tridentate ligands, highly efficient in a large range of asymmetric catalytic processes.[1] The demands for economical, eco-friendly and recyclable polymer-supported catalysts led some groups to investigate various strategies to attach pybox ligands on solid supports.[2] The first immobilization of pybox was reported by Mayoral et al. by means of copolymerization of 4-vinylpybox derivatives with styrene and divinylbenzene.[2a,b] Moberg et al. subsequently reported the grafting of pybox ligands onto a TentaGel resin *via* the formation of ester bonds.[2c] Finally, Portnoy at al. reported a five-step solid-phase synthesis of various pybox ligands from a Wang trichloroacetimidate resin.[2d] Although these polymer-supported pybox ligands demonstrated promising results in a number of transformations, all these approaches suffer from serious drawbacks and limitations, regarding either the number of steps or the stability of the linker connecting pybox to the polymeric matrix. We report herein a rapid and straightforward method for the preparation of a new polystyrene-supported pybox by means of "click chemistry".[3] The performance of the resulting click-pybox resin **1a** was investigated in asymmetric ring opening of cyclohexene oxide,[4] silylcyanation of benzaldehyde,[5] and alkynylation of imines.[6]

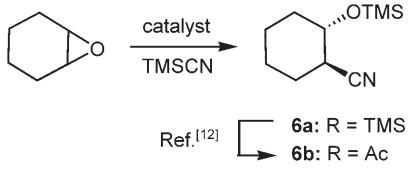
We were especially interested in investigating the Cu(I)-catalyzed "click" azide-alkyne cycloaddition,[7] since the resulting triazole ring connecting the ligand to the polymer is formed in high yield and under mild conditions,[8] providing a stable linker compatible with various reaction conditions. The robustness of this triazole linker and the simplicity of the method make this approach very attractive for accessing new polymer-supported catalysts. This strategy has recently been exploited with success for the immobilization of hydroxyproline,[9a] TEMPO,[9b] P,N-ligands,[9c] aza(bisoxazoline)[9d] and *Cinchona* alkaloid derivatives.[9e]

The click-pybox resin **1a** was uneventfully prepared in a three-step sequence from the readily available 4-bromo-substituted phenyl-pybox **2**[2c] and polystyrene-supported azide **5**,[10] using the Gmeiner CuI protocol.[8] The required "alkyne anchor" was installed through a Sonogashira cross-coupling between **2** and (trimethylsilyl)acetylene in refluxing CH_2Cl_2 in the presence of 2 mol% $Pd(PPh_3)_2Cl_2$, 4 mol% CuI, and a large excess of NEt_3. The resulting 4-[(trimethylsilyl)-ethynyl]-pybox **3** was subsequently, without further purification, desilylated by TBAF affording 4-ethynyl-pybox **4** in 50% yield over the two steps. The "click-immobilization" of pybox **4** with the polystyrene-supported resin **5** was then accomplished in THF at 35 °C for 3 days in the presence of excess DIEA and a catalytic amount of CuI.[8] Analysis of resin **1a** by IR spectroscopy showed complete disappearance of the typical azide stretch vibration (2090 cm^{-1}), consistent with the smooth formation of the triazole ring. The estimated pybox loading based on elemental analysis (6.79% N; 0.8 mmol $g)^{-1}$ demonstrated that "click-immobilization" occurred in essentially quantitative yield (theoretical loading: 0.8 mmol $g)^{-1}$. For compari-

son, monomeric ligand **1b** was also prepared from 4-ethynyl-pybox **4** and benzyl azide under the same conditions in 82% yield (Scheme 1).

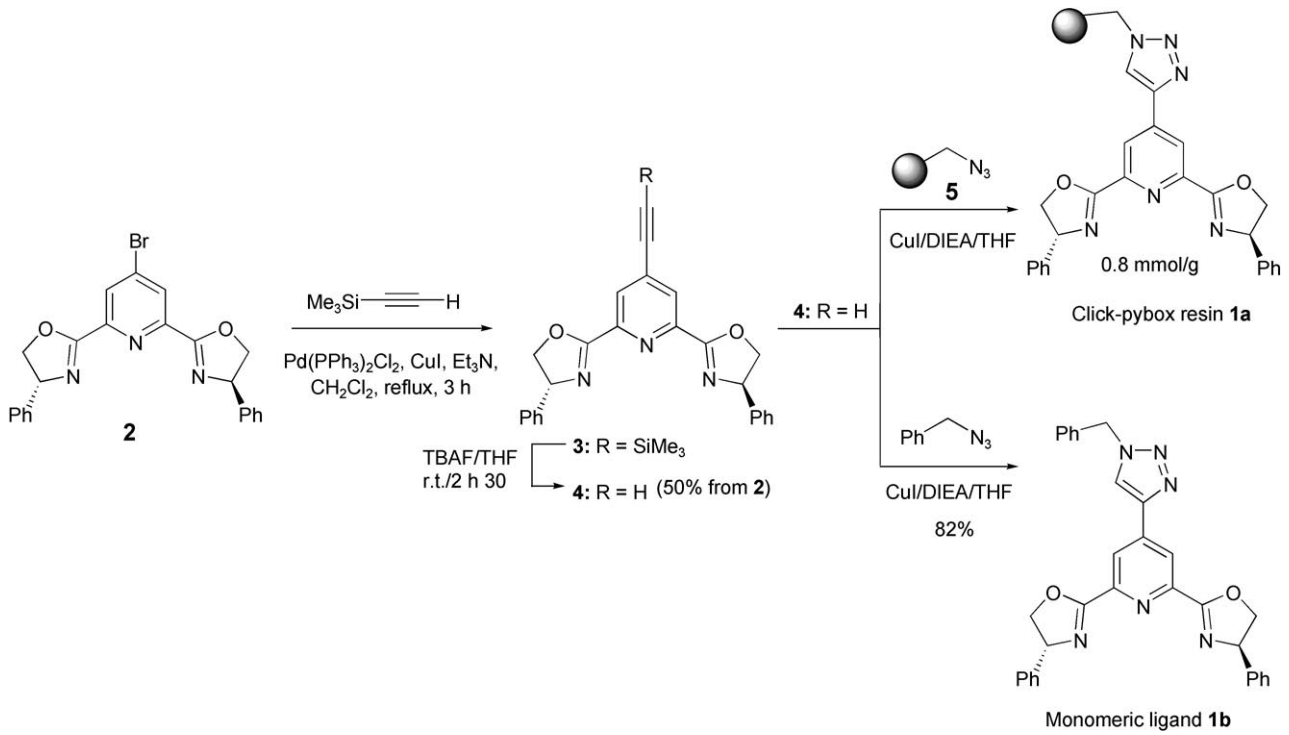
The click-pybox resin **1a** was first evaluated in the ring opening of cyclohexene oxide (Table 1). The asymmetric ring opening of *meso* epoxides with TMSCN has previously been found to be catalyzed by pybox-lanthanide complexes affording β-trimethylsilyloxy nitrile ring-opened products in high yields and fair to good enantioselectivities.[4] Given that a systematic evaluation of $LnCl_3$ revealed that $YbCl_3$ and $LuCl_3$ furnished the highest *ee*s, both lanthanide chloride salts were selected in this study. The resin-bound pybox **1a** was first incubated with a THF solution of $YbCl_3$, filtered and washed. Ring opening of cyclohexene oxide in CH_2Cl_2 was accomplished in the presence of 10 mol% of the resulting resin-bound catalyst and 1.2 equivs. of TMSCN at room temperature. The β-trimethylsilyloxy nitrile **6a** was obtained in 98% conversion and 64% *ee* within 1 hour (entry 1). When the click-pybox resin **1a** was treated with $LuCl_3$ and involved in the ring opening of cyclohexene oxide under the same conditions, β-trimethylsilyloxy nitrile **6a** was obtained in 97% conversion and 57% *ee* (entry 2). The same experiments conducted with ligand **1b** under homogenous conditions afforded comparable conversions and enantioselectivities (entries 3 and 4). These results are very similar to those reported in the literature with the parent phenyl-pybox ligand,[4] indicating that neither the presence of a triazole linker nor the heterogeneous conditions perturb the performance of the catalyst. However, attempts to reuse the resin-bound catalyst after simple filtration and washings with CH_2Cl_2 resulted in a drastic drop of the enantioselectivity, while the conversion

Table 1. Click-pybox resin **1a**-mediated asymmetric ring opening of cyclohexene oxide.[a]



Entry	Catalyst	Run	Conversion [%][b]	*ee* [%][c]
1	**1a**-$YbCl_3$	1	98	64
2	**1a**-$LuCl_3$	1	97	57
3	**1b**-$YbCl_3$	1	98	65
4	**1b**-$LuCl_3$	1	98	55
5	**1a**-$YbCl_3$	2	97	21
6	**1a**-$YbCl_3$	3	95	7
7	**1a**-$YbCl_3$	4	98	4
8	**1a**-$YbCl_3$	5	97	4

[a] All reactions were carried out in CH_2Cl_2 at room temperature for 1 hour using 10 mol% of catalyst, 1.2 equivs. of TMSCN.
[b] Conversion determined by GC-MS analysis.
[c] Enantiomeric excess determined by chiral GC after derivatization of **6a** into **6b** according to ref.[12]



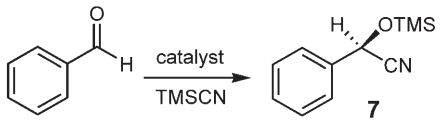
Scheme 1. Preparation of click-pybox resin **1a** and monomeric ligand **1b**

remained unaffected after five consecutive runs (entries 5–8).[11]

We then turned our interest to the enantioselective silylcyanation of benzaldehyde (Table 2). Enantiomerically pure cyanohydrins represent an important class of chiral building blocks in organic synthesis.[13] The use of pybox-lanthanide complexes in enantioselective silylcyanation of aldehydes has been reported earlier, providing cyanohydrins with fair to good enantioselectivities (up to 89% *ee*).[5] We have previously demonstrated that cyanohydrins could be obtained with similar enantioselectivities (81% *ee*) by conducting the reaction under heterogeneous conditions with Tentagel-supported pybox ligands.[2c] In the present context, we were interested in testing the newly prepared click-pybox resin **1a** in order to compare its performance with the earlier reported Tentagel-supported pybox. In contrast to what was observed with pybox-ytterbium complexes under homogeneous conditions[5] and with Tentagel-supported pybox ligands,[2c] the use of acetonitrile as solvent led to a modest *ee* and rather low conversion (entry 1). The sluggish reaction rate can be explained by the poor swelling properties of the polystyrene matrix in acetonitrile. To overcome this problem, the reaction was then carried out in a mixture of acetonitrile and CH_2Cl_2. The acetonitrile-CH_2Cl_2 ratio was optimized to ensure a good compromise between resin swelling and compatibility of the solvent with the reaction of interest. Under optimized solvent conditions, $YbCl_3$ and $LuCl_3$ salts were tested with click-pybox resin **1a**. Reactions were conducted at room temperature in the presence of 10 mol% polystyrene-bound pybox **1a** and 5 mol% $LnCl_3$. Both $YbCl_3$ and $LuCl_3$ complexes provided comparable results. As judged by GC-MS analysis, the reactions were completed within 1.5 h, affording cyanohydrin **7** with 87% and 78% conversions, respectively (entries 2 and 6). These conversions are similar to those observed with the Tentagel-supported pybox ligand previously reported by us,[2c] whereas the enantioselectivity of the click-pybox resin revealed to be somewhat lower, affording cyanohydrin **7** with 65% and 69% *ee* (entries 2 and 6). In four consecutive runs, the polymer-supported catalysts could be easily recovered by simple filtration and recycled, although the catalytic activity was somewhat reduced presumably due to some leaching of the metal (entries 2–9). We were pleased to note that *ee*s obtained from the recycled catalysts were appreciably improved, reaching the same level of induction as that recorded with the Tentagel-supported pybox ligands previously reported (entries 5 and 9).[14]

Lastly, we examined the performance of click-pybox resin **1a** in enantioselective alkynylation of imines (Table 3 and Table 4). Chiral propargylic amines are useful building blocks and important precursors for the preparation of various nitrogen-containing products.[15] Catalytic alkynylation of imines by pybox-Cu(I) complexes has been reported earlier

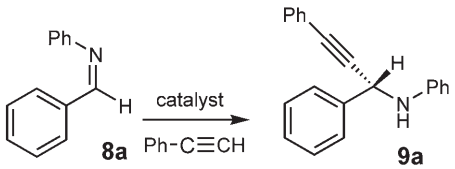
Table 2. Click-pybox resin **1a**-mediated asymmetric silylcyanation of benzaldehyde.[a]



Entry	Catalyst	Run	Conversion [%][b]	*ee* [%][c]
1[d]	**1a**-$YbCl_3$	1	55	32
2	**1a**-$YbCl_3$	1	87	67
3	**1a**-$YbCl_3$	2	76	73
4	**1a**-$YbCl_3$	3	70	75
5	**1a**-$YbCl_3$	4	70	78
6	**1a**-$LuCl_3$	1	78	69
7	**1a**-$LuCl_3$	2	73	75
8	**1a**-$LuCl_3$	3	70	77
9	**1a**-$LuCl_3$	4	68	78

[a] All reactions were carried out in acetonitrile: CH_2Cl_2 (3:2) at room temperature for 1.5 h using 1.2 equivs. of TMSCN, 10 mol% polymer-bound ligand **1a** and 5 mol% $LnCl_3$.
[b] Conversion determined by GC-MS analysis.
[c] Enantiomeric excess determined by chiral GC.
[d] Only acetonitrile used as solvent.

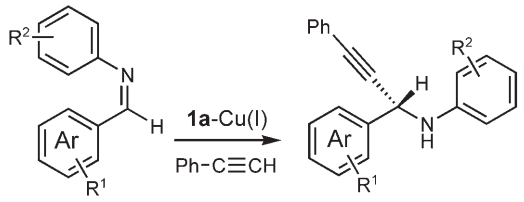
Table 3. Click-pybox resin **1a**-mediated enantioselective addition of phenylacetylene to benzylidene aniline **8a**.[a]



Entry	Catalyst	Run	Conversion [%][b]	*ee* [%][c]
1	**1b**-Cu(I)	1	100	96
2	**1a**-Cu(I)	1	100	88
3	**1a**-Cu(I)	2	98	83
4	**1a**-Cu(I)	3	99	81
5	**1a**-Cu(I)	4	95	80
6	**1a**-Cu(I)	5	49	9
7[d]	**1a**-Cu(I)	1	100	89

[a] All reactions were carried out in dichloroethane at room temperature for 48 h using 1.5 equivs. of phenylacetylene, 10 mol% polymer-bound ligand **1a** and 10 mol% CuOTf.
[b] Conversion determined by ^{1}H NMR of the crude product.
[c] Enantiomeric excess determined by chiral HPLC
[d] Polymer-supported catalyst from entry 6 after washings with pyridine/methanol/CH_2Cl_2 and reloading with copper triflate

Table 4. Click-pybox resin **1a**-mediated enantioselective alkynylation of imines **8a–h**.[a]



8a – h **9a – h**

Entry	Substrate	R^1	R^2	Conversion [%][b]	*ee* [%][c]
1	**8a**	H	H	**9a**: 100	88
2	**8b**	4-Cl	H	**9b**: 85	90
4	**8c**	4-Et	H	**9c**: 84	90
5	**8d**	4-F	H	**9d**:78	84
7	**8e**	Ar = α-naphthyl	H	**9e**:100	81
9	**8f**	H	4-*t*-Bu	**9f**: 73	88
10	**8g**	H	4-Et	**9g**: 93	88
11	**8h**	H	4-OMe	**9h**: 73	80

[a] All reactions were carried out in dichloroethane at room temperature for 48 h using 1.5 equivs. of phenylacetylene, 10 mol% polymer-bound ligand **1a** and 10 mol% CuOTf.

[b] Conversion determined by ^{1}H NMR of the crude product.

[c] Enantiomeric excess determined by chiral HPLC.

and represents one of the rare enantioselective processes available today for the preparation of this class of compounds with high enantioselectivity.[6] Portnoy et al. have recently reported the use of polystyrene-supported pybox-Cu(I) complexes in enantioselective additions of phenylacetylene to *N*-arylimines.[2d] The authors obtained 83% *ee* for the reaction of phenylacetylene and *N*-benzylideneaniline with their best catalyst, but had problems with recycling.

Alkynylation of *N*-benzylideneaniline **8a** was performed at room temperature in dichloroethane in the presence of 10 mol% of the resin-supported catalyst, generated in situ from the click-pybox resin **1a** and copper triflate. The aminoalkyne **9a** was obtained in quantitative conversion and 88% *ee* (Table 3, entry 2), whereas under homogeneous conditions pybox **1b** afforded *ee*s up to 96% (Table 3, entry 1). After filtration, the recycled catalyst could be reused in three consecutive runs with no apparent loss of the catalytic activity, while the enantioselectivity decreased somewhat from 88% to 80% *ee* (Table 3, entries 2–5). A marked drop of both the conversion and enantioselectivity was observed in run 5 (Table 3, entries 6), probably due to partial oxidation of the active catalytic copper(I) species to copper(II). We next examined the possibility to recycle the metal-free click-pybox resin **1a** by successive washings (pyridine/methanol/dichloromethane) of the deactivated supported catalyst from run 6. Interestingly, when recharged with copper triflate, both the catalytic activity and enantioselectivity of the resulting polymer-supported catalyst were fully re-established (Table 3, entry 7).

To illustrate the performance and the effectiveness of the click-pybox resin **1a**, various *N*-arylimines **8a–h** were tested in this reaction (Table 4). In this set of experiments, resin **1a** was washed and recharged with copper triflate between each experiment as reported above. The corresponding propargylic amines **9a–h** were obtained in high conversions and good enantioselectivities ranging from 80% to 90% *ee* (Table 4, entries 1–11). Although the enantioselectivity remained to some extent inferior to that generally observed under homogeneous conditions,[6] the click-pybox resin **1a** offered markedly higher enantioselectivities to those usually obtained by Portnoy's supported catalyst and showed superior recyclability of the catalyst.

In summary, we have shown for the first time that click chemistry provides a useful strategy for immobilizing pybox ligands on a polystyrene resin for asymmetric catalytic applications. The grafting occurred cleanly, under mild conditions, affording the click-pybox resin **1a** with an estimated pybox loading of 0.8 mmol g^{-1}. Various polymeric metal complexes could be pre-formed and exploited in a number of catalytic benchmark reactions. Ring-opening of cyclohexene oxide and silylcyanation of benzaldehyde with TMSCN were first surveyed in the presence of polymer-supported pybox-lanthanide complexes. In both cases, comparable reactivity and level of asymmetric induction were obtained when compared with parent pybox ligands under homogeneous conditions. The polymeric complex of click-pybox resin **1a** with copper triflate was then successfully used in enantioselective addition of imines, affording the corresponding propargylic amines with high enantioselectivities (up to 90% *ee*). In all cases, the metal-free resin **1a** could be easily recycled by simple washings of the supported catalyst. With the exception of ring opening of cyclohexene oxide catalyzed by lanthanide complexes, in all other cases, the polymer-supported catalyst could be recovered by simple filtration and reused at least in four consecutive runs with no significant erosion of the conversion and enantioselectivity, without adding further metal salts.

Experimental Section

General Remarks

The Merrifield resin (1.2 mmol g^{-1}, cross-linked with 1% DVB) was purchased from Fluka. The following compounds were prepared according to literature methods: 4-bromopybox **2**,[2c] azidomethylpolystyrene **5**.[10] All other chemicals were purchased and used without further purification. ^1H and ^{13}C NMR were recorded on a Bruker Avance 300 with chloroform-d_1 ($\delta = 7.26$, ^1H; $\delta = 77.0$, ^{13}C) as internal standard unless otherwise indicated. The IR spectra were recorded on a Perkin–Elmer Paragon 500. Elemental analyses were performed by the University of Rouen Microanalytical Service Laboratory on a Carlo Erba 1160. Mass spectrometry was performed by the University of Rouen Spectroscopy Center. Electron impact (EI) and chemical ionization (IC) spectra were performed on a JEOL JMS AX-500 spectrometer. Routine monitoring of reaction was performed by TLC, using 0.2 Kieselgel 60 F_{254} precoated aluminium sheets, commercially available from Merck. Flash chromatographies were performed on Gerudan SI-60 (70–230 mesh ASTM) from Merck. Tetrahydrofuran (THF) was distilled on sodium-benzophenone ketyl under nitrogen, CH_2Cl_2 from NaH, and MeCN from CaH_2. Resin **1a** was prepared on the First Mate apparatus from Argonaut. All heterogeneous catalytic reactions with resin **1a** were performed on a Quest 210 Parallel Synthesizer from Argonaut.

Preparation of the Resin-Supported Pybox (1a)

Azidomethylpolystyrene **5** (1.2 mmol g^{-1}, 500 mg, 0.6 mmol), pybox **4** (475 mg, 1.2 mmol), CuI (12 μmol, 23 mg), and DIEA (0.986 g, 7.6 mmol) were weighed into the reaction vessel (16 × 115 mm test tube). After adding THF (15 mL), the reaction vessel was equipped with an agitation magnet, topped with a Teflon cap and fitted with the parallel reflux bar of the First Mate®. The resulting mixture was stirred at 35 °C for 3 days. The beads were filtered, successively washed with pyridine (5 × 6 mL), methanol (5 × 6 mL), and CH_2Cl_2 (5 × 6 mL) then dried at room temperature under vacuum overnight to afford resin **1a**. Anal. found: N 6.79% corresponding to 0.8 mmol of pybox/g of resin. IR (KBr): $\nu = 3063$, 3026, 2921, 2852, 1945, 1871, 1808, 1639, 1603, 1565, 1512, 1492, 1475, 1450, 1401, 1345, 1311, 1258, 1227, 1184, 1150, 1102, 1045, 1028, 978, 947, 923, 898, 746, 695, 606, 530 cm^{-1}.

General Procedure for Lanthanide-Catalyzed Ring-Opening of Cyclohexene Oxide Using Click-Pybox Resin 1a

Polymer-supported pybox **1a** (150 mg, 0.8 mmol g^{-1}, 0.12 mmol) and $LnCl_3$ (0.10 mmol) were mixed in dry THF (6 mL) and agitated for 1.5 h at room temperature. THF was filtered off and the supported catalyst was rinsed twice with dry THF (2 × 5 mL) under N_2. The resin was then dried thoroughly before adding CH_2Cl_2 (2 mL). Cyclohexene oxide (102 μL, 1.00 mmol) was then added followed by TMSCN (160 μL, 1.20 mmol). The mixture was stirred at room temperature and the reaction rate was monitored by GC-MS. Each sample was filtered through a plug of silica before analysis by GC-MS. After each run, the solvent was filtered off and the resin was rinsed twice with CH_2Cl_2 (2 mL). Enantiomeric excesses were determined after derivatization of **6a**, by adding $Sc(OTf)_3$ (4.9 mg, 0.01 mmol) and acetyl chloride (0.1 mL, 2 mmol) to the filtrate and the resulting mixture was stirred for 2.5 h.[10] The resulting β-acetyloyl nitrile **6b** was obtained with quantitative conversion. Enantiomeric excesses of **6b** were determined by GC using a chiral column [Chiraldex, G-TA (gamma cyclodextrin trifluoroacetyl), 30 m × 0.25 mm, 120 °C, t_R (*minor*) = 19 min, t_R (*major*) = 27 min].

General Procedure for Lanthanide-Catalyzed Asymmetric Addition of TMSCN to Benzaldehyde Using Click-Pybox Resin 1a

Polymer-supported pybox **1a** (30 mg, 0.8 mmol g^{-1}, 0.024 mmol) and $LnCl_3$ (0.01 mmol) were transferred to a reaction vessel and agitated for 1 h in dry MeCN (0.4 mL) and dry CH_2Cl_2 (0.6 mL) under nitrogen. After adding benzaldehyde (106 mg, 0.1 mmol) and TMSCN (12 mg, 0.12 mmol), the reaction mixture was stirred at room temperature and conversions were determined by GC-MS. After each run, the solvent was filtered off, the resin was rinsed twice with CH_3CN (2 mL) and dried before being used in another run. Enantiomeric excesses were determined by GC analyses using a chiral column [Chiraldex, G-TA (gamma cyclodextrin trifluoroacetyl), 30 m × 0.25 mm, 115 °C, t_R (*R*) = 12 min, t_R (*S*) = 14 min].

General Procedure for Cu(I)-Catalyzed Asymmetric Alkynylation of Imines Using Click-Pybox Resin 1a

Polymer-supported pybox **1a** (30 mg, 0.8 mmol g^{-1}, 0.024 mmol), CuOTf (10 mg, 0.02 mmol), phenylacetylene (33 μL, 0.3 mmol), and imine (0.2 mmol) were transferred to a reaction vessel and agitated for 24 h in dry dichloroethane (1 mL). The resin was filtered and washed with CH_2Cl_2 (2 × 10 mL). The crude material was purified by flash chromatography on silica gel (eluent: pure cyclohexane then 1% EtOAc in cyclohexane). Enantiomeric excesses were determined by chiral HPLC (Daicel Chiralcel OD column). The polymer could either be reused directly or rinsed successively with pyridine, methanol and dichloromethane and then reloaded with the metal salt.

Supporting Information

Experimental procedures for compounds **3**, **4**, **1b**, *rac*-propargylic amines **9a–h**. Spectroscopic data for all compounds (including ^1H NMR spectra of **4**, **1b**, IR spectra of **5**, **1a, b** and **4**).

Acknowledgements

We thank the CNRS, the région Haute-Normandie, EGIDE and the Swedish Foundation for Strategic Research for financial and technical support. M. T. thanks the CNRS and EGIDE for a grant.

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[11] $YbCl_3$ may be imprisoned in the polymer matrix after partial decomplexation from the pybox ligand. The presence of uncomplexed $YbCl_3$ in the polymer would promote the ring-opening of cyclohexene oxide in the next run, however without any stereoselectivity. This scenario would explain that while the conversion of the reaction remains unaltered between two consecutive runs, a significant drop of the stereoselectivity was observed. A control experiment conducted under homogenous conditions in the presence of a suspension of $YbCl_3$ in CH_2Cl_2 showed that the reaction was completed in 16 h at room temperature.

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