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Preparation and evaluation of bipyridyl-tagged reagents and scavengers

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Abstract—The synthesis of three bipyridyl-tagged reagents and one scavenger is described. Of the three reagents, the carbodiimide derivative proved to be effective as a coupling reagent for amide formation and the removal of the coupling side product from the reaction mixture by complexation onto a Cu-derivatised resin has been successfully demonstrated. This purification process was thoroughly optimised using a DOE approach and the procedure subsequently applied to the use of a bipyridyl-tagged amine as an isocyanate scavenger. Preliminary results clearly demonstrate the potential of using chelation tags such as bipyridine units as a means for removing solution phase reagents and scavengers from reaction mixtures providing an attractive alternative to their resin-bound and fluorous-tagged counter-parts.

1. Introduction

In the past few years, technologies and strategies have been developed to produce large numbers of new compounds in a fast, clean and efficient way. Solid-phase organic synthesis is a widely used methodology but unfortunately, there are limitations to this approach, such as long reaction times and difficulties with monitoring the progress of reactions. New strategies have recently been developed in order to combine the benefits of solution-phase chemistry and the key advantages of solid-phase chemistry, using polymer-supported[1] and fluorous-tagged[2] reagents and scavenging agents. Each of these methods still has its disadvantages, the former being limited by slow reaction times and the requirement for excess reagent to be used in many cases, and the latter being expensive and requiring either solvent extraction or chromatography on fluorous silica as a means of purification. An alternative approach has recently been described by Ley and co-workers[3] who found that 4,4′-bis(hydroxymethyl)-2,2′-bipyridine was a suitable tag for substrates when employing a 'catch and release' synthesis strategy, followed by extraction of the bipyridyl tag onto a copper(II) chelated ion exchange resin and simple filtration to yield the desired products (Fig. 1). The benefits of this approach are that the reactions can be carried out in solution and purification achieved using cheap and readily available materials.

Encouraged by the report from Ley et al. we decided to investigate the possibility of using bipyridyl-tagged reagents and scavengers in synthesis. For the sake of simplicity, we opted to use a monofunctionalised bipyridine tag. This paper describes the synthesis of bipyridyl bound coupling reagents such as carbodiimide, HOBt and tetrafluorophenol analogues, and a bipyridyl bound scavenger. The objectives were the preparation of bipyridyl bound reagents and validation of their use in synthesis followed by purification using a Cu-derivatised resin.

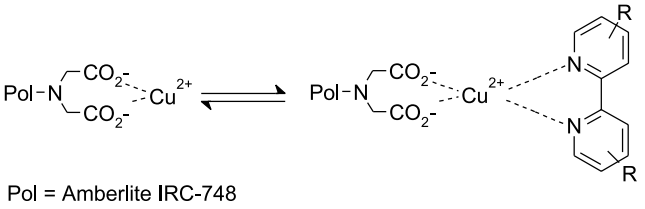

Figure 1. Chelation of bipyridyl unit using Cu-derivatised resin.

2. Results and discussion

Bipyridyl bound carbodiimide **1** and tetrafluorophenol **2** were the initial targets (Fig. 2). It was decided that the bipyridyl unit and the coupling reagent may be bound through an amide linkage, and that a spacer of two or three carbons would be ideal. The proposed synthetic routes involved bipyridyl bound amine **3** as a common intermediate for the synthesis of tetrafluorophenol **4**, hydroxybenzotriazole **5** and carbodiimide **6** (Fig. 3).

Keywords: Bipyridine; Reagent; Scavenger; Chelation-tagged.
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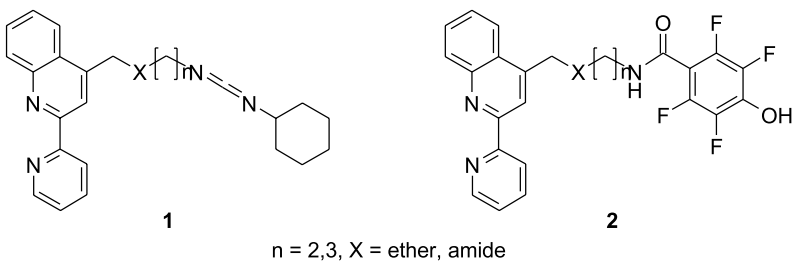


Figure 2.

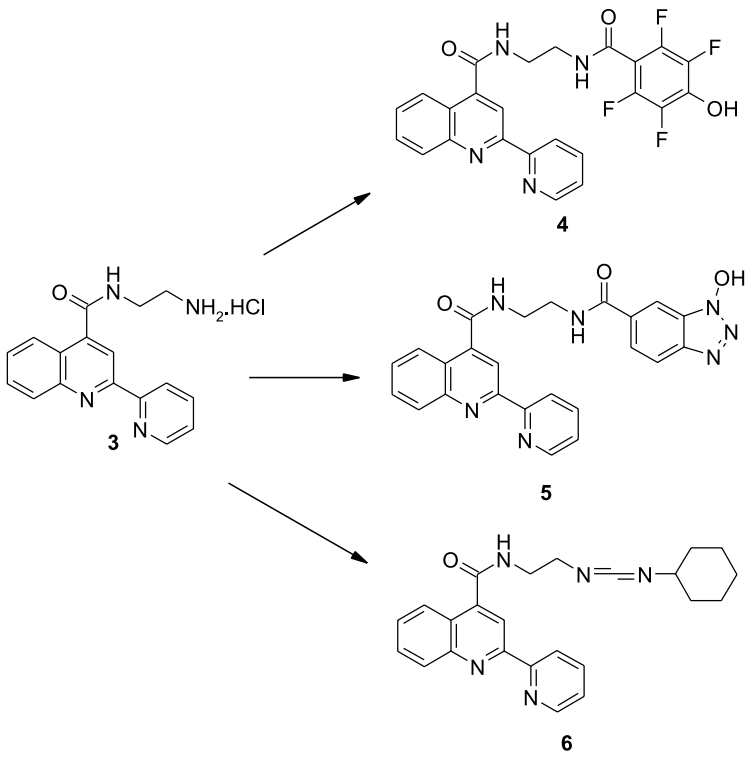
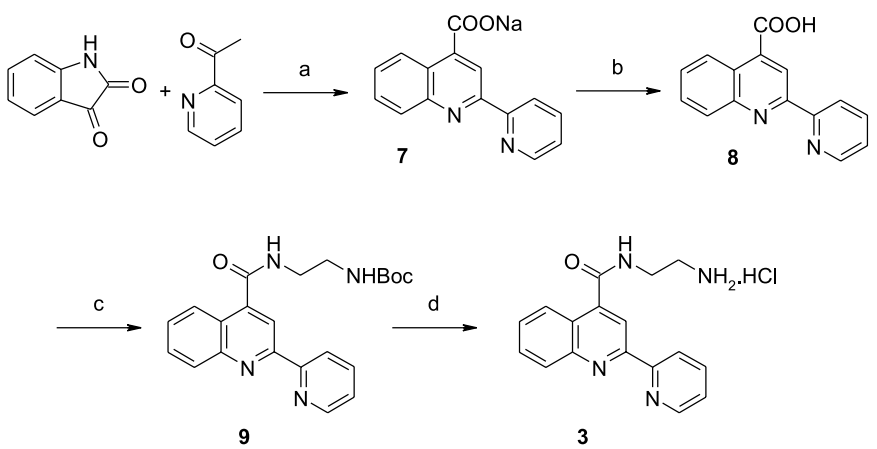
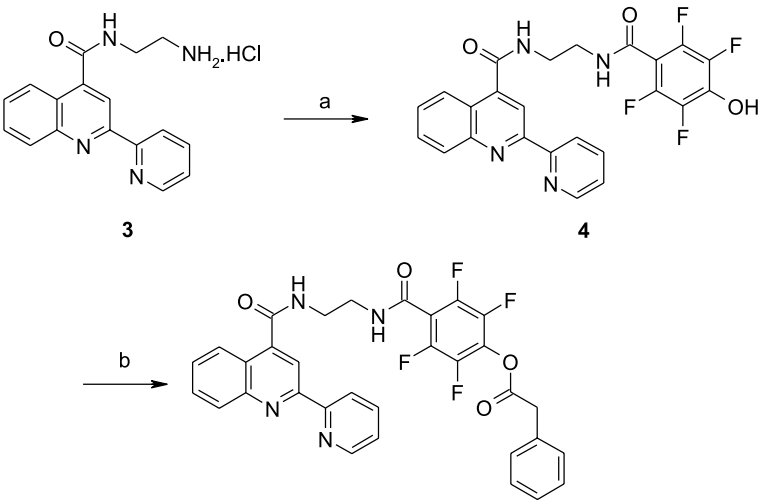


Figure 3.

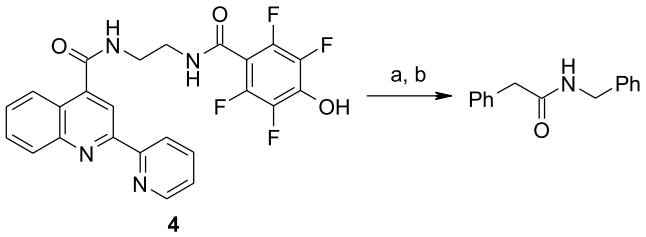
The bipyridyl bound amine **3** was synthesised from the 2-(2-pyridinyl)-4-carboxyquinoline **8**, easily obtained in two steps from commercial compounds according to the procedures described in a patent.[4] The bipyridyl bound amine **3** was then obtained through the coupling between the acid **8** and *N*-Boc-ethylenediamine (Scheme 1). The coupling step was quantitative and the HCl salt of the amine was easily obtained as a white solid upon treatment of compound **9** with HCl/Et_2O.



Scheme 1. (a) 33% NaOH, 62%; (b) 10% HCl, 89%; (c) *N*-Boc-ethylenediamine, EDC, HOBt, DMF, rt, 100%; (d) HCl 2 M/Et_2O, DCM, rt 100%.



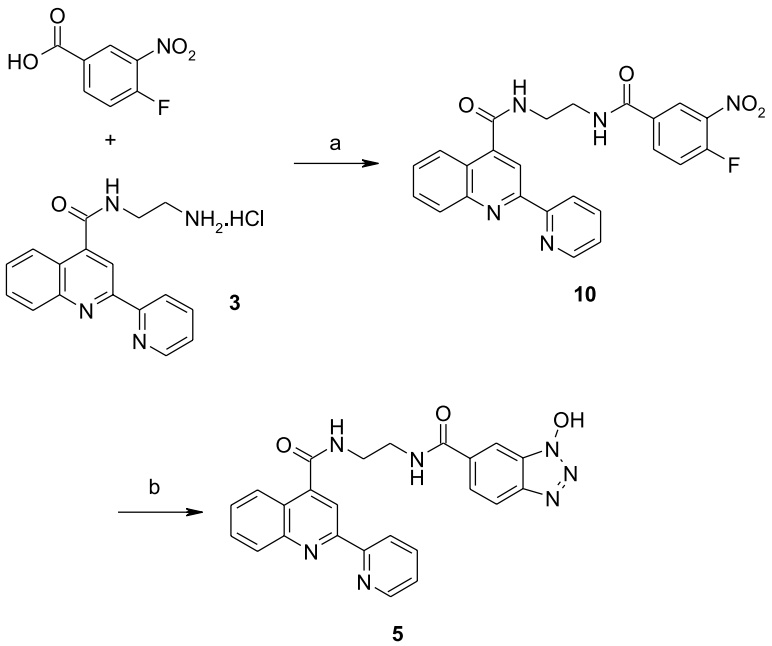
Scheme 2. (a) 2,3,5,6-Tetrafluoro-4-hydroxy benzoic acid, EDC, HOBt, Et_3N, DMF, 50 °C, 80%; (b) phenylacetic acid, PyBrop, DIPEA, DMF, rt.



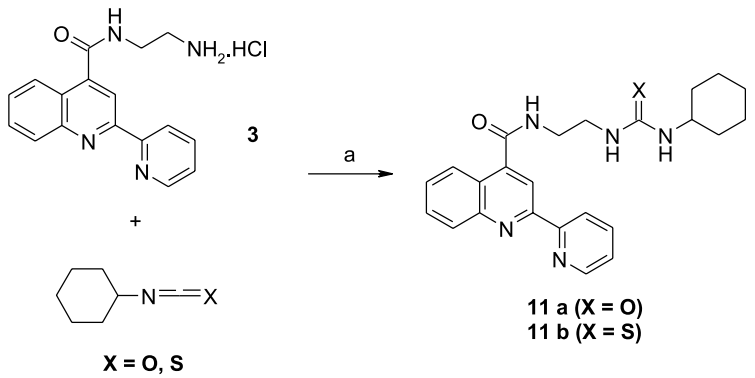
Scheme 3. (a) Phenylacetic acid, PyBrop, DIPEA, DMF, rt; (b) $BnNH_2$, rt, 35%.

The bipyridyl bound tetrafluorophenol analogue **4** was then synthesised[1,5] by coupling amine **3** and 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid (commercially available as a hydrate) in good yield (Scheme 2). Formation of the activated ester was then attempted with phenylacetic acid. Test reactions under different coupling conditions (PyBrop/DIPEA, TBTU/DIPEA, EDC/DIPEA in DMF) were investigated and showed the best result with PyBrop/DIPEA by LC–MS analysis. Unfortunately, although LC–MS showed the formation of the product, it was not possible to isolate it because of its poor stability. This may have been due to the competing formation of acyl pyridinium species in the reaction mixture. The formation of the activated ester and the displacement with benzylamine was then attempted as a one-pot procedure (Scheme 3). After work-up and purification by chromatography, the expected compound was isolated with 35% yield. Whilst this demonstrated that the bipyridyltagged tetrafluorophenol did function as a coupling reagent it was not considered useful as the activated esters could not be isolated and thus the utility of the bipyridyl tag could not be demonstrated.

In the literature, the use of a polymer supported 1-hydroxybenzotriazole derivative has been reported.[6a,6b] We thus decided to synthesise the bipyridyl bound HOBt derivative **5**



Scheme 4. (a) PyBrop, HOBt, DIPEA, DMF, rt, 100%; (b) hydrazine hydrate, EtOH, reflux, 36%.



Scheme 5. (a) Et_3N, DCM, rt, 92% (**11a**), 72% (**11b**).

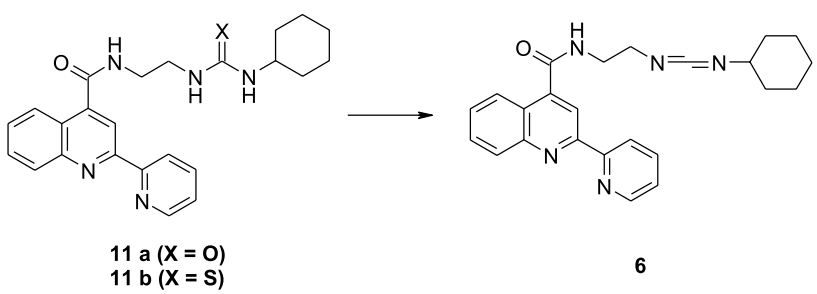
and assess it as a coupling reagent in the hope that it would yield more stable and isolable activated esters. The first step of the synthesis consisted in the coupling between the bipyridyl bound amine **3** and 4-fluoro-3-nitrobenzoic acid (Scheme 4). After purification by chromatography, the expected compound **10** was isolated in a quantitative yield. The second step involved cyclisation using hydrazine hydrate giving triazole **5** which was isolated with 36% yield. Formation of the activated ester was then attempted with Boc-Gly, using EDC/DIPEA in DMF as coupling conditions. Unfortunately, the desired product could not be isolated, probably for the same reason as the tetrafluorophenol derivative.

In light of these results, the synthesis and use of the bipyridyl bound carbodiimide **6** was then considered as this was expected to be much more stable than the activated esters. In order to synthesise this carbodiimide, the urea **11a** was prepared through the reaction between the amine salt **3** and cyclohexylisocyanate in the presence of triethylamine (Scheme 5). The expected compound was isolated as a white solid with an excellent yield. As the carbodiimide could potentially be obtained through the dehydration of the urea or the thiourea, the thiourea **11b** was also prepared through the reaction between the amine salt **3** and cyclohexylisothiocyanate in the presence of triethylamine. The expected compound was isolated as a white solid with 72% yield. Many different methods were attempted for the dehydration of the urea or thiourea (Scheme 6): TsCl under solid–liquid phase-transfer catalytic conditions,[7] TsCl/pyridine, MsCl/Et_3N/DMAP, $SOCl_2/Et_3N$, Ph_3PBr_2/Et_3N,[8] phosgene iminium chloride/Et_3N.[9] None of these methods gave the expected compound.

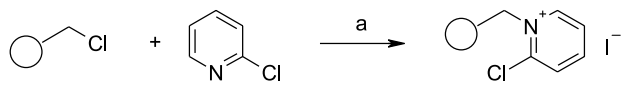
A further method was then attempted with the thiourea **11b**, using Mukaiyama's reagent[10] in solution. An analysis by IR showed the formation of the carbodiimide (stretch at 2121 cm^{-1}), but purification of the product was very difficult (removal of the reaction side-product). In the best conditions, pure carbodiimide was isolated after several stages of column chromatography in 61% yield. Due to these problems of purification, we then employed a polymer-bound Mukaiyama's reagent. This reagent was prepared through the reaction of Merrifield's resin and 2-chloropyridine in the presence of potassium iodide (Scheme 7). Further details relating to the preparation and use of this reagent will be described elsewhere. This reagent was then used for the dehydration of the thiourea **11b**. After filtration and washing of the resin, carbodiimide **6** was obtained in good yield.

Carbodiimide **6** was then tested as a coupling reagent in the reaction between phenylacetic acid and benzylamine. Several test reactions under different conditions were carried out. The use of carbodiimide in combination with DIPEA in DCM solvent gave the best results. After purification by chromatography, the expected compound was isolated with 28% yield. Having demonstrated that **6** could function as a coupling reagent we then carried out some reactions in which the crude reaction mixture was subjected to purification by extraction of the bipyridyl-tagged material onto a Cu-derivatised resin.

During the preliminary experiments of capture of the urea **11a** by the Cu-resin, it appeared that the poor solubility of this compound in DMF or DCM was a significant problem. Therefore, it was decided that a more soluble carbodiimide (and hence urea) should be prepared. It was thought that the introduction of a methyl group on the amide nitrogen would increase the solubility of the compound. A new bipyridyl bound amine, with three carbons as a spacer, could easily be obtained through the coupling between the acid **8** and the

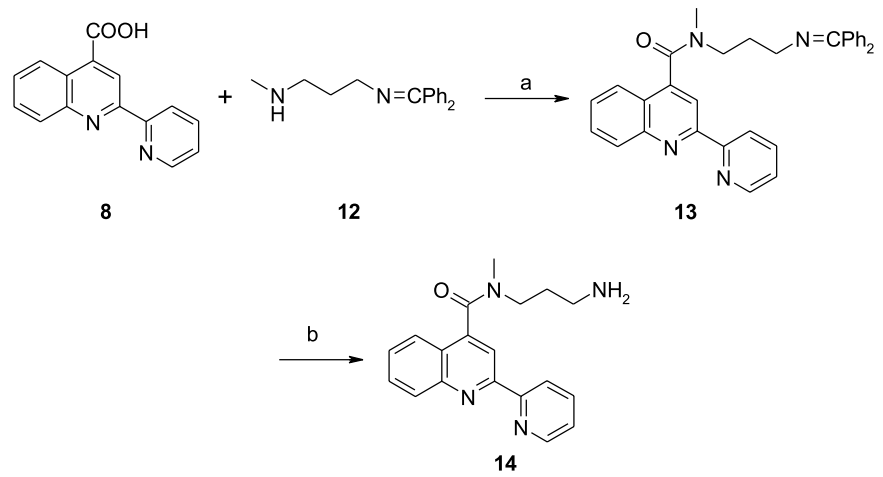


Scheme 6.



Scheme 7. (a) KI, DMF, 60 °C.

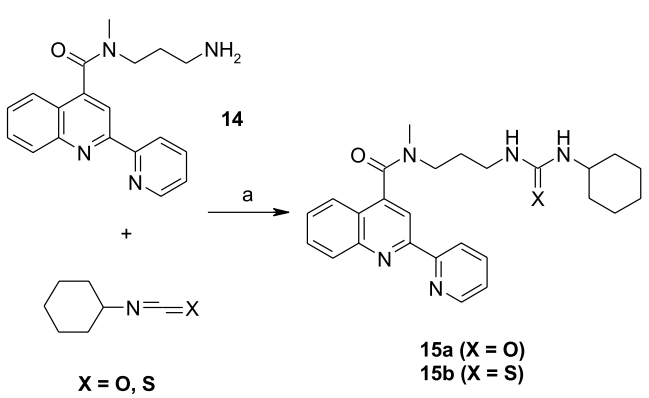
presence of a triethylamine salt impurity. In order to remove this impurity, different work-up conditions were tried: wash with a saturated bicarbonate solution or wash with water. In both cases, a significant loss of mass was observed, and the carbodiimide was partially decomposed.



Scheme 8. (a) EDC, HOBt, DMF, rt, 100%; (b) TFA/H_2O, DCM/THF, rt, 89%.

monoprotected *N*-Me-1,3-propanediamine **12**. For this purpose, the primary amine of the *N*-Me-1,3-propanediamine was protected as a benzophenone imine. The expected compound **12** was isolated with a quantitative yield. The bipyridyl bound amine intermediate **13** was then obtained through the coupling between the acid **8** and the monoprotected *N*-Me-1,3-propanediamine **12** (Scheme 8). The free amine **14** was easily obtained[11] by treatment of the coupled product with aqueous acid.

In order to test our hypothesis regarding solubility, the urea **15a** was then prepared through the reaction between the amine **14** and cyclohexylisocyanate (Scheme 9). The expected compound was isolated as a white solid with an excellent yield and was found to be readily soluble in DMF or DCM solvent. The corresponding carbodiimide was obtained from the thiourea **15b** which was prepared through the reaction between the amine **14** and cyclohexylisothiocyanate. Polymer-bound Mukaiyama's reagent was again used for the thiourea dehydration (Scheme 10). After filtration and wash of the resin, carbodiimide **16** was obtained in good yield but was contaminated by the



Scheme 9. (a) Et_3N, DCM, rt, 94% (**15a**), 75% (**15b**).

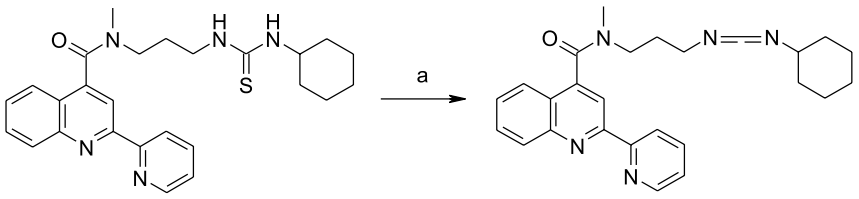
Finally use of a carbonate resin (prepared using Ambersep 900 OH and a solution of sodium carbonate) gave the pure carbodiimide **16** in 26% yield.

This compound was then used as a coupling reagent in a test reaction between phenylacetic acid and benzylamine. A classic work-up was done and after purification by chromatography, the expected coupled product was isolated with 40% yield. The same reaction was accomplished again, and then the Cu-resin was used to extract the side-product of the reaction (see Section 4). LC–MS analysis after 24 h of scavenging showed the coupled product and a small trace of the bipyridyl-tagged urea (<2% by UV in the LC trace). Evaporation of the reaction mixture gave a pink material which, after quick filtration through a plug of silica, to remove residual copper salts, gave the expected compound with 65% yield.

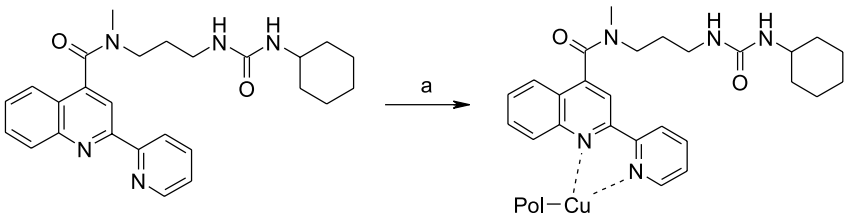
Whilst the carbodiimide could be used as a coupling reagent the difficulty of preparing this reagent and the moderate yield obtained for the coupling reaction led us to consider preparing bypyridyl tagged scavengers instead. We considered using bipyridyl bound amine **14**, which had already been prepared, as an isocyanate scavenger, as the resulting urea **15a** could be removed by extraction with the Cu-resin (Scheme 11). Tests for the capture of the urea **15a** were first accomplished in DCM and in DMF. In order to determine the best conditions for this scavenging a Design of experiments (DOE) approach using the MODDE software from Umetrics was employed.[†]

Experiments were designed which investigated the following parameters: solvent (DCM or DMF), resin quantity, time and amount of water added (Ley and co-workers had noted the requirement for the addition of water in their scavenging process[3]). The extent of scavenging was measured by

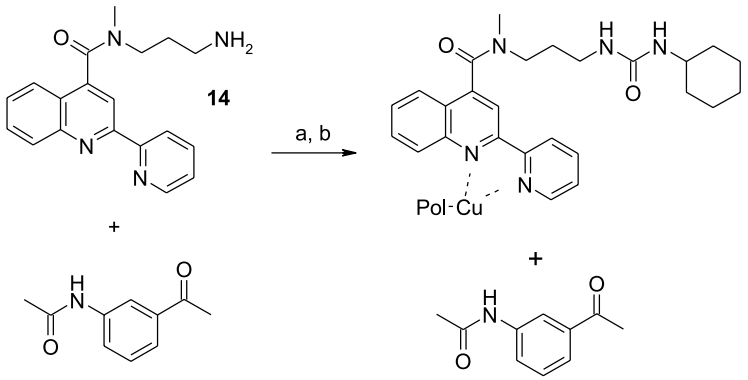
[†] For further information see www.umetrics.com



Scheme 10. (a) PS-Mukaiyama reagent, Et_3N, DMF, 45 °C, 26%.



Scheme 11. (a) DCM or DMF, Cu(II)-resin, 3-acetylacetanilide.



Scheme 12. (a) Cyclohexylisocyanate, DCM, Et_3N; (b) Cu(II)-resin.

LC–MS analysis giving the ratio of residual bipyridyl-tagged urea to an internal standard (3-acteylacetanilide). The use of DMF as a solvent was quickly eliminated due to problems with leaching of Cu from the resin resulting in the formation of blue solutions. A screen of 11 reactions was conducted based on a two-level full factorial design (with 3 centre points) varying the quantity of resin (2–10 g/mmol), amount of water added (10–50 μl) and the time (2–30 h) in DCM solvent. The results from this screen suggested that the main factors were the quantity of resin and the amount of water added. The optimiser function available in the MODDE software then enabled the identification of optimal scavenging conditions. These optimal conditions for scavenging were confirmed to be 10 g/mmol of resin (resin loading 2 mmol/g of Cu^{2+}), 1.8 mL/mmol water in DCM solvent for 24 h after a further two experiments had been conducted.

Once the optimum conditions for the scavenging of urea were established, it was then decided to test this method for isocyanate scavenging. Cyclohexylisocyanate was scavenged using the bipyridyl bound amine **14** in the presence of the internal standard (3-acetylacetanilide), and the thus formed urea was removed from the reaction mixture using the Cu-resin (Scheme 12). After 24 h, LC–MS of the reaction mixture showed that there was less than 5% of the urea remaining. After filtration and passing through a plug of silica (to remove residual copper slats) a white material was obtained, and NMR analysis showed clean 3-acetyl-acetanilide. The generality of this scavenging process is currently under investigation and will be reported in due course.

3. Conclusion

In the course of our investigation we have attempted the preparation of three bipyridyl-tagged reagents and one scavenger. Of the three reagents the carbodiimide derivative proved to be effective as a coupling reagent for amide formation and the removal of the coupling side product from the reaction mixture by complexation onto a Cu-derivatised resin was successfully demonstrated for this case. This said the difficulty of preparing this reagent and its moderate performance in an amide formation detracts from its utility as a coupling reagent of general use. We considered that the

use of such chelation tags for scavenging agents would be more effective. The copper-resin mediated purification process was thoroughly optimised using a DOE approach and the procedure was successfully applied to the use of a bipyridyl-tagged amine as an isocyanate scavenger. These preliminary results clearly demonstrate the potential of using chelation tags such as bipyridine units as a means for removing solution phase reagents and scavengers from reaction mixtures offering an attractive alternative to their resin-bound and fluorous-tagged counter-parts.

4. Experimental

4.1. General methods

All infrared spectra were recorded on a Nicolet 360 FT-IT spectrophotometer. All NMR were recorded on a Bruker AC 400 instrument at 293 K with solutions of compounds dissolved in $CDCl_3$ (unless stated otherwise), referenced to tetramethylsilane (δ 0.00 ppm). Mass spectra were recorded on a Z-spray mass spectrometer. Compounds were dissolved in 1:1 acetonitrile/water and ionised using an electrospray ionisation source and recorded in positive ion mode. Reactions were monitored by TLC using commercially available glass-backed plates (Merck). Column chromatography was carried out on silica gel 60 (40–63 μm, 60A, Fluorochem). All chemicals used in the reactions were reagent grade and used as purchased, except the *N*-Boc-ethylenediamine, and polymer supported Mukaiyama reagent which were synthesised in-house.

4.1.1. Sodium 2-(2-pyridinyl)-4-carboxyquinoline carboxylate 7. Isatin (16 g, 109 mmol) and 2-acetylpyridine (12 g, 99 mmol) were mixed in a beaker. To this mixture was quickly added, while stirring with a spatula, 60 g of a 33% sodium hydroxide solution, which had been previously cooled to 5 °C. The stirring was continued until the contents hardened (temperature 55 °C). 70 mL of water was then added, resulting in a red slurry. This material was then filtered, washed with ethanol (60 mL) and acetone until the filtrate was slightly pink. Crystallisation from hot water and then drying under high vacuum at 40 °C gave the product as a pink powder. Yield: 16.7 g (62%). ^{1}H NMR (400 MHz, CD_3OD) δ: 8.71 (m, 1H); 8.53 (m, 2H); 8.41 (dd, J=8.42, 0.82 Hz, 1H); 8.14 (m, 1H); 7.99 (m, 1H); 7.76 (m, 1H); 7.61 (m, 1H); 7.47 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ: 175.45, 157.54, 157.35, 150.49, 150.07, 149.73, 138.71, 130.95, 130.46, 128.19, 127.92, 126.32, 125.67, 123.28, 117.41. MS (ES+) m/z: 251 (M−Na+H$^+$). IR: 1573 cm^{-1} (COO$^-$). LC-AccMass: calcd for $C_{15}H_{10}N_2O_2$: 250.074. Found (M+2H−Na)$^+$: 251.08 (+1.1 mDa).

4.1.2. 2-(2-pyridinyl)-4-carboxyquinoline 8. To an aqueous solution of the carboxylate **8** (1 g, 3.68 mmol, dissolved in 20 mL of hot water) was added dropwise a 10% HCl solution to pH=7. Filtration of the solid, washing with acetone and then drying under high vacuum at 40 °C gave the product as a white solid. Yield: 816 mg (89%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.99 (s, 1H); 8.78 (m, 2H); 8.63 (d, J=7.96 Hz, 1H); 8.21 (d, J=7.96 Hz, 1H); 8.05 (ddd, J=7.73, 7.73, 1.74 Hz, 1H); 7.89 (ddd, J=8.37, 6.95, 1.37 Hz, 1H); 7.75 (ddd, J=8.39, 6.98, 1.35 Hz, 1H); 7.57 (ddd, J=7.48, 4.78, 1.12 Hz, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 167.44, 155.08, 154.28, 149.43, 148.15, 137.61, 136.89, 130.24, 129.90, 128.42, 125.53, 125.04, 124.49, 121.02, 119.30. MS (ES+) m/z: 251 (M+H$^+$). IR: 1699 cm^{-1} (COOH). LC-AccMass: calcd for $C_{15}H_{10}N_2O_2$: 250.074. Found (M+H)$^+$: 251.08 (+1.7 mDa).

4.1.3. Amide 9. To a solution of 2-(2-pyridinyl)-4-carboxyquinoline (200 mg, 0.8 mmol) in 4 mL of DMF were successively added *N*-Boc-ethylenediamine (140 μl, 0.88 mmol, 1.1 equiv.), EDC (169 mg, 0.88 mmol, 1.1 equiv.) and HOBt (119 mg, 0.88 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 5 h 30 min, then diluted with DCM and washed three times with water. Drying over $MgSO_4$, filtration and evaporation gave the crude material. Purification by chromatography on silica gel (2:3 hexane/EtOAc as eluent) gave the product as a white solid. Yield: 312 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.71 (m, 1H); 8.63 (m, 2H); 8.34 (dd, J=8.51, 0.91 Hz, 1H); 8.18 (d, J=8.25 Hz, 1H); 7.89 (ddd, J=7.73, 7.73, 1.74 Hz, 1H); 7.76 (ddd, J=8.42, 6.95, 1.42 Hz, 1H); 7.60 (ddd, J=8.37, 7.00, 1.28 Hz, 1H); 7.39 (ddd, J=7.50, 4.85, 1.19 Hz, 1H); 7.13 (bs, 1H, NH); 5.11 (bs, 1H, NH); 3.70 (m, 2H, NH−CH_2); 3.47 (m, 2H, NH−CH_2); 1.38 (s, 9H, Boc). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.22, 156.80, 155.56, 155.29, 148.86, 148.41, 142.34, 137.36, 130.12, 130.07, 127.88, 125.50, 124.55, 124.43, 122.07, 116.43, 41.09, 40.82, 29.70, 28.30. MS (ES+) m/z: 393 (M+H$^+$); 337 (M−tBu+H$^+$). IR: 3351, 2981 (NH), 1686, 1641 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{22}H_{24}N_4O_3$: 392.185. Found (M+H)$^+$: 393.19 (+0.2 mDa).

4.1.4. Amine hydrochloride salt 3. To a solution of the Boc-protected compound **9** (1.56 g, 3.97 mmol in 50 mL of DCM) was added 39 mL (20 equiv.) of a 2 M HCl solution in diethyl ether. The reaction mixture was stirred at rt for 1 h, and then filtered. Drying under high vacuum gave the product as a yellow solid. Yield: 1.3 g (99%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.09 (m, 1H); 8.70 (m, 3H); 8.14 (m, 6H); 7.83 (ddd, J=8.21, 7.07, 1.21 Hz, 1H); 7.67 (ddd, J=8.14, 7.14, 1.05 Hz, 1H); 7.59 (ddd, J=7.20, 5.10, 0.66 Hz, 1H); 3.60 (dd, J=11.98, 6.13 Hz, 2H, NH−CH_2); 3.02 (dd, J=11.85, 5.99 Hz, 2H, NH−CH_2). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.96, 147.98, 147.34, 142.93, 139.85, 130.67, 129.45, 128.21, 127.23, 125.72, 124.35, 122.31, 119.03, 116.97, 109.70, 38.30, 37.14. MS (ES+) m/z: 293 (M−HCl+H$^+$). IR: 3366, 2966 (NH), 1653 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{17}H_{16}N_4O$: 292.132. Found (M−HCl+H)$^+$: 293.14 (+0.9 mDa).

4.1.5. Urea 11a. To a solution of the bipyridyl bound amine hydrochloride salt **3** (500 mg, 1.52 mmol) in 25 mL of DCM was added cyclohexylisocyanate (215 μl, 1.67 mmol, 1.1 equiv.) and triethylamine (470 μl, 3.35 mmol, 2.2 equiv.). The reaction mixture was stirred at rt for 2 h 30 min. The reaction mixture was then filtered and the solid washed with DCM. Drying under high vacuum gave the product as a white solid. Yield: 583 mg (92%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.94 (t, J=5.12 Hz, 1H); 8.78 (d, J=4.30 Hz, 1H); 8.61 (m, 2H); 8.20 (m, 2H); 8.05 (ddd, J=7.75, 7.75, 1.62 Hz, 1H); 7.87 (ddd, J=8.14, 7.14, 1.05 Hz, 1H); 7.68 (ddd, J=8.00, 7.23, 0.82 Hz, 1H); 7.57 (ddd, J=7.30, 4.92, 0.80 Hz, 1H); 5.90 (m, 2H, NH); 3.40

(m, 2H); 3.27 (m, 2H); 1.74 (m, 2H); 1.61 (m, 2H); 1.51 (m, 1H); 1.28–1.02 (m, 5H). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.88, 157.51, 155.04, 154.62, 149.31, 147.56, 143.40, 137.51, 130.24, 129.56, 127.62, 125.63, 124.93, 124.23, 121.12, 116.09, 47.77, 45.56, 33.26, 30.65, 25.25, 24.48. MS (ES+) *m/z*: 418 (M+H$^+$). IR: 3241, 2927 (NH), 1627 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{24}H_{27}N_5O_2$: 417.216. Found (M+H)$^+$: 418.22 (+0.4 ppm).

4.1.6. Thiourea 11b. To a solution of the bipyridyl bound amine hydrochloride salt **3** (1 g, 3.04 mmol) in 50 mL of DCM was added cyclohexylisothiocyanate (475 μl, 3.34 mmol, 1.1 equiv.) and triethylamine (940 μl, 6.69 mmol, 2.2 equiv.). The reaction mixture was stirred at rt for 24 h, then washed with water, dried over $MgSO_4$ and evaporated. Purification by trituration in hexane gave the product. Yield: 856 mg (65%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.00 (t, *J*=5.12 Hz, 1H); 8.78 (m, 1H); 8.62 (m, 2H); 8.20 (2×d, *J*=8.28 Hz, 2H); 8.05 (ddd, *J*=7.75, 7.75, 1.67 Hz, 1H); 7.86 (ddd, *J*=8.37, 7.00, 1.33 Hz, 1H); 7.68 (ddd, *J*=8.16, 7.16, 1.07 Hz, 1H); 7.57 (ddd, *J*=7.46, 4.80, 1.10 Hz, 1H); 7.43 (bs, 2H, NH); 3.67 (m, 2H); 3.53 (m, 2H); 1.85 (m, 2H); 1.67–1.53 (m, 3H); 1.31–1.10 (m, 5H). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 167.04, 155.01, 154.60, 149.32, 147.58, 143.16, 137.53, 130.27, 129.57, 127.65, 125.63, 124.96, 124.21, 121.11, 116.21, 32.23, 30.66, 25.13, 24.53, 22.02. MS (ES+) *m/z*: 434 (M+H$^+$). IR: 3239, 2929 (NH), 1646 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{24}H_{27}N_5OS$: 433.194. Found (M+H)$^+$: 434.20 (+0.3 ppm).

4.1.7. Carbodiimide 6. To a solution of the thiourea **11b** (100 mg, 0.23 mmol) in 8 mL of DMF were added the polymer-supported Mukaiyama's reagent (892 mg, 10 equiv.) and triethylamine (64 μl, 0.46 mmol, 2 equiv.). The reaction mixture was agitated in a FlexChem oven at 45 °C for 4 h. The resin was then filtered and washed with DMF, MeOH (3 times). After evaporation, the residue was taken in 5 mL of DCM. 750 mg of carbonate resin (previously washed with DCM) was added and the mixture was stirred at rt for 1 h. Filtration and evaporation gave the product. Yield: 19 mg (21%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.73 (m, 1H); 8.67 (m, 2H); 8.34 (dd, *J*=8.46, 0.87 Hz, 1H); 8.21 (m, 1H); 7.90 (ddd, *J*=7.73, 7.73, 1.83 Hz, 1H); 7.78 (ddd, *J*=8.37, 6.91, 1.42 Hz, 1H); 7.62 (ddd, *J*=8.37, 6.95, 1.33 Hz, 1H); 7.39 (ddd, *J*=7.48, 4.78, 1.17 Hz, 1H); 6.61 (bs, 1H, NH); 3.72 (m, 2H); 3.59 (m, 2H); 1.88–1.83 (m, 2H); 1.64–1.59 (m, 2H); 1.48 (m, 1H); 1.31–1.10 (m, 5H). IR: 3267, 2926 (NH), 2116 (N=C=N), 1649 (C=O) cm^{-1}.

4.1.8. Protected amine 12. To a solution of *N*-methyl-1,3-propanediamine (500 mg, 5.67 mmol) in 10 mL of DCM was added benzophenone imine (950 μl, 5.67 mmol, 1 equiv.) under inert atmosphere. The reaction mixture was stirred at rt for 24 h, and then diluted with 20 mL of DCM. Three washes with a 1% bicarbonate solution followed by drying over $MgSO_4$ and evaporation gave the product as a yellow oil. Yield: 1.36 g (95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (m, 2H); 7.39 (m, 6H); 7.16 (m, 2H); 3.43 (t, *J*=6.82 Hz, 2H, $-CH_2-CH_2-CH_2-$); 2.66 (t, *J*=7.04 Hz, 2H, $-CH_2-CH_2-CH_2-$); 2.42 (s, 3H, CH_3); 1.87 (ddd, *J*=13.95, 6.95, 6.95 Hz, 2H, $-CH_2-CH_2-CH_2-$); 1.60 (bs, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.42, 130.07, 129.92, 128.51, 128.39, 128.28, 128.08, 127.75, 52.12, 50.41, 36.18, 30.87. MS (ES+) *m/z*: 253 (M+H$^+$). IR: 2930, 2781 (NH), 1619 (C=N) cm^{-1}. LC-AccMass: calcd for $C_{17}H_{20}N_2$: 252.163. Found (M+H)$^+$: 253.17 (−0.6 mDa).

4.1.9. Amide 13. To a solution of 2-(2-pyridinyl)-4-carboxyquinoline **8** (200 mg, 0.8 mmol) in 4 mL of DMF were successively added protected *N*-methyl-1,3-propanediamine **12** (222 mg, 0.88 mmol, 1.1 equiv.), EDC (169 mg, 0.88 mmol, 1.1 equiv.) and HOBt (119 mg, 0.88 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 20 h, then diluted with DCM and washed three times with water. Drying on Na_2SO_4, filtration and evaporation gave the crude material. Purification by chromatography on silica gel (1:4 hexane/EtOAc as eluent) gave the product. Yield: 318 mg (100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70–6.80 (m, 19H); 3.72 (t, *J*=7.36 Hz, 2H, $-CH_2-CH_2-CH_2-$); 3.49 (t, *J*=6.77 Hz, 2H, $-CH_2-CH_2-CH_2-$); 3.18 (s, 3H, CH_3); 3.04 (m, 2H, $-CH_2-CH_2-CH_2-$). MS (ES+) *m/z*: 485 (M+H$^+$).

4.1.10. Amine 14. To a solution of amide **13** (2.36 g, 4.88 mmol) in 50 mL of DCM and 50 mL of THF were added 8 mL of water and 8 mL of TFA. The reaction mixture is stirred at rt for 2 h. After evaporation of the solvents, the crude material was taken in water and washed three times with TBME. The aqueous phase was then poured into a saturated bicarbonate solution, then extracted with DCM and dried with K_2CO_3. Evaporation and drying under high vacuum gave the product. Yield: 1.39 g (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.72 (m, 1H); 8.66 (m, 1H); 8.52 (m, 1H); 8.20 (m, 1H); 7.92–7.72 (m, 3H); 7.59 (m, 1H); 7.38 (m, 1H); 3.79 (t, *J*=7.04 Hz, 1H); 3.25 (m, 2H); 2.97–2.84 (m, 5H); 2.49 (m, 1H); 1.91 (m, 1H); 1.66 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.71, 155.88, 155.65, 149.18, 148.14, 143.60, 137.01, 130.33, 130.15, 127.80, 124.85, 124.61, 124.34, 121.79, 115.86, 39.23, 36.64, 36.48, 31.43. MS (ES+) *m/z*: 321 (M+H$^+$). IR: 3306, 2929 (NH), 1628 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{19}H_{20}N_4O$: 320.164. Found (M+H)$^+$: 321.17 (−0.5 mDa).

4.1.11. Urea 15a. To a solution of the bipyridyl bound amine **14** (200 mg, 0.62 mmol) in 10 mL of DCM was added cyclohexylisocyanate (88 μl, 0.69 mmol, 1.1 equiv.) and triethylamine (95 μl, 0.69 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 24 h. The reaction mixture was washed with water, dried on $MgSO_4$ and evaporated. Purification by chromatography on silica gel (with MeOH 3% in DCM as eluent) gave the product. Yield: 260 mg (94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (m, 2H); 8.55 (m, 1H); 8.22 (m, 1H); 7.99–7.74 (m, 3H); 7.61 (m, 1H); 7.48–7.38 (m, 1H); 5.62 (bs, 1H, NH); 4.08 (m, 1H); 3.79 (m, 1H); 3.52–3.38 (m, 2H); 3.24 (s, 3H, Me); 1.92 (m, 4H); 1.73–1.49 (m, 3H); 1.42–1.10 (m, 4H). MS (ES+) *m/z*: 445 (M+H$^+$).

4.1.12. Thiourea 15b. To a solution of the bipyridyl bound amine **14** (1.2 g, 3.76 mmol) in 60 mL of DCM was added cyclohexylisothiocyanate (800 μl, 5.64 mmol, 1.5 equiv.). The reaction mixture was stirred at rt for 30 h, then washed with water, dried on $MgSO_4$ and evaporated. Purification by

chromatography on silica gel (85:15 EtOAc/hexane as eluent) gave the product. Yield: 1.3 g (75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.70 (m, 2H); 8.50 (s, 1H); 8.23 (m, 1H); 7.88 (m, 1H); 7.78 (m, 2H); 7.63 (m, 1H); 7.40 (m, 2H); 5.92 (bs, 1H, NH); 3.88 (m, 2H); 3.77 (m, 2H); 2.89 (s, 3H, Me); 2.03 (m, 3H); 1.73–1.49 (m, 3H); 1.42–1.10 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.02, 155.88, 155.45, 149.21, 148.20, 142.84, 137.12, 130.58, 130.32, 128.07, 124.52, 124.34, 123.82, 121.79, 115.97, 44.31, 41.12, 36.85, 32.72, 25.99, 25.33, 24.38. MS (ES+) *m/z*: 462 ($M+H^+$). IR: 3297, 2923 (NH), 1620 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{26}H_{31}N_5OS$: 461.225. Found $(M+H)^+$: 462.23 (−0.4 ppm).

4.1.13. Carbodiimide 16. To a solution of the thiourea **15b** (100 mg, 0.22 mmol) in 8 mL of DMF were added the polymer-supported Mukaiyama's reagent (892 mg, 10 equiv.) and triethylamine (60 μl, 0.43 mmol, 2 equiv.). The reaction mixture was agitated in a FlexChem oven at 45 °C for 4 h. The resin was then filtered and washed with DMF, MeOH (3 times). After evaporation, the residue was taken in 5 mL of DCM. 750 mg of carbonate resin (previously washed with DCM) was added and the mixture was stirred at rt for 1 h. Filtration and evaporation gave the product. Yield: 24 mg (26%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.68 (m, 2H); 8.50 (m, 1H); 8.20 (m, 1H); 7.87 (m, 1H); 7.75 (m, 2H); 7.58 (m, 1H); 7.35 (m, 1H); 3.76 (t, J=7.41 Hz, 1H); 3.44 (t, J=6.68 Hz, 1H); 3.25 (m, 2H); 3.01 (m, 1H); 2.95–2.81 (m, 4H); 2.08–0.81 (m, 11H). IR: 2121 (N=C=N), 1628 (C=O) cm^{-1}.

4.1.14. Bipyridyl-tagged tetrafluorophenol 4. To a solution of the bipyridyl bound amine hydrochloride salt **3** (424 mg, 1.29 mmol) in 8 mL of DMF was added triethylamine (400 μl, 2.84 mmol, 2.2 equiv.), 2,3,5,6-tetrafluoro-4-hydroxybenzoic acid (500 mg, 2.19 mmol, 1.7 equiv.), EDC (272 mg, 1.42 mmol, 1.1 equiv.) and HOBt (192 mg, 1.42 mmol, 1.1 equiv.). The reaction mixture was stirred at 50 °C for 24 h. After evaporation, the residue was taken in water (3 mL), triturated, then filtered and washed five times with water (10 mL) to give the product. Yield: 497 mg (80%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 8.99 (bs, 1H); 8.90 (bs, 1H); 8.76 (d, J=4.48 Hz, 1H); 8.62 (m, 2H); 8.20 (2×d, J=8.37, 8.37 Hz, 2H); 8.05 (ddd, J=7.68, 7.68, 1.33 Hz, 1H); 7.86 (t, J=7.64 Hz, 1H); 7.67 (t, J=7.55 Hz, 1H); 7.56 (dd, J=7.04, 5.31 Hz, 1H); 3.53 (m, 4H). ^{13}C NMR (100 MHz, d_6-DMSO) δ: 166.95, 158.07, 155.05, 154.61, 149.29, 147.58, 143.17, 137.52, 130.27, 129.55, 127.60, 125.65, 124.93, 124.21, 121.12, 116.21; 38.75; 38.70. ^{19}F NMR (376 MHz, d_6-DMSO) δ: −144.3; −161.2. MS (ES+) *m/z*: 485 ($M+H^+$). IR: 3273 (NH), 1646 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{24}H_{16}F_4N_4O_3$: 484.116. Found $(M+H)^+$: 485.12 (−2.0 ppm).

4.1.15. Amide 10. To a solution of the bipyridyl bound amine salt **3** (500 mg, 1.52 mmol) in 5 mL of DMF was added DIPEA (795 μl, 4.56 mmol, 3 equiv.). After 5 min, 4-fluoro-3-nitrobenzoic acid (309 mg, 1.67 mmol, 1.1 equiv.), PyBrop (1.06 g, 2.28 mmol, 1.5 equiv.) and HOBt (308 mg, 2.28 mmol, 1.5 equiv.) were added and the reaction mixture was stirred at rt for 66 h. After evaporation of the DMF, the residue was taken in DCM and washed with water. Drying on $MgSO_4$ and evaporation gave the crude material. Purification by chromatography on silica gel (with MeOH 4% in DCM as eluent) gave the product. Yield: 698 mg (100%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.05 (m, 2H, NH); 8.76 (m, 1H); 8.67 (dd, J=7.32, 2.29 Hz, 1H); 8.62 (m, 2H); 8.33 (m, 1H); 8.17 (m, 2H); 8.05 (ddd, J=7.75, 7.75, 1.76 Hz, 1H); 7.85 (ddd, J=8.44, 6.98, 1.40 Hz, 1H); 7.75 (dd, J=11.21, 8.74 Hz, 1H); 7.63 (ddd, J=8.30, 6.93, 1.21 Hz, 1H), 7.56 (ddd, J=7.43, 4.83, 1.12 Hz, 1H); 2.89 (m, 2H, NH–CH_2); 2.55 (m, 2H, NH–CH_2). MS (ES+) *m/z*: 460 ($M+H^+$). IR: 2967 (NH), 1704, 1615 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{24}H_{18}FN_5O_4$: 459.134. Found $(M+H)^+$: 460.14 (+0.9 ppm).

4.1.16. Hydroxybenzotriazole 5. To a solution of amide **10** (700 mg, 1.52 mmol) in 17 mL of EtOH was added hydrazine hydrate (3.315 mL, 106 mmol, 70 equiv.). The mixture was stirred under reflux for 5 h, and then the solvent was removed by rotary evaporation. The residue was taken in 20 mL of cold water and acidified with HCl 1.5 M to pH~4. The product precipitated and was isolated by filtration. Drying under high vacuum at 40 °C gave the product. Yield: 245 mg (36%). ^{1}H NMR (400 MHz, d_6-DMSO) δ: 9.06 (m, 1H); 8.94 (m, 1H); 8.76 (d, J=4.03 Hz, 1H); 8.62 (m, 2H); 8.28 (s, 1H); 8.16 (m, 2H); 8.05 (m, 2H); 7.95 (m, 1H); 7.84 (m, 1H); 7.58 (m, 1H). MS (ES+) *m/z*: 454 ($M+H^+$). IR: 3271 (OH), 2921 (NH), 1639 (C=O) cm^{-1}. LC-AccMass: calcd for $C_{24}H_{19}N_7O_3$: 453.155. Found $(M+H)^+$: 454.16 (−3.1 ppm).

4.1.17. Amide formation using carbidiimide 16 and subsequent chelation purification. To a solution of phenylacetic acid (21 mg, 0.15 mmol) in 420 μl of DCM was added carbodiimide **16** (74 mg, 0.17 mmol, 1.1 equiv.). After agitation at rt for 10 min, benzylamine (17 μl, 0.15 mmol, 1 equiv.) and DIPEA (30 μl, 0.17 mmol, 1.1 equiv.) were added. After 18 h, the reaction mixture was transferred to a fritted syringe containing 1.70 g (10 g/mmol) of Cu-resin with 6.98 mL of DCM and 310 μl of water (1.8 mL/mmol). This mixture was rotated at rt for 24 h. Filtration and evaporation gave a crude material which was taken in DCM and filtered through a plug of silica. This purification gave the clean-coupled product. Yield: 23 mg (65%). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.37–7.05 (m, 10H, Ph), 5.58 (bs, 1H, N*H*), 4.40 (d, 2H, CH_2, J=5.83 Hz), 3.55 (s, 2H, CH_2). LC–MS: calcd for $C_{15}H_{15}NO$: 225.29. Found 226.25 $(M+H)^+$.

4.1.18. Copper(II)-containing beads. Amberlite IRC-718 beads (160 mL) were washed three times with methanol, then shaken for 1 h in a 2 M aqueous solution of copper sulfate (50 g, 100 mL).The blue beads were filtered and washed with water (3×100 mL) followed by TBME (3×100 mL). Drying under high vacuum at 60 °C gave 47.02 g of resin (loading 2 mmol/g of Cu^{2+}).

4.1.19. Isocyanate scavenging. To a solution of cyclohexylisocyanate (18 μl, 0.14 mmol) and 3-acetylacetanilide (50 mg, 0.28 mmol, 2 equiv.) in 2.5 mL of DCM was added the bipyridyl bound amine **14** (50 mg, 0.156 mmol, 1.1 equiv.) and triethylamine (20 μl, 0.14 mmol, 1 equiv.). After 6 h, the reaction mixture was transferred to a fritted syringe containing 1.42 g (10 g/mmol) of Cu-resin with

4.2 mL of DCM and 280 μl of water (1.8 mL/mmol). This mixture was rotated at rt for 24 h. Filtration and evaporation gave a crude material which was taken in DCM and filtered through a plug of silica. This purification gave the 3-acetylacetanilide, clean by NMR.

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