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Catalyst Recycling via Hydrogen-Bonding-Based Affinity Tags

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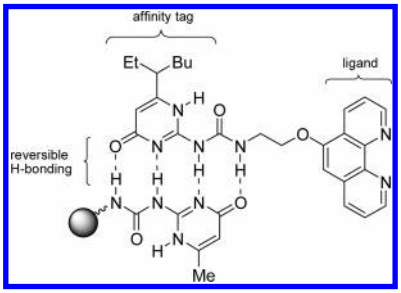
ABSTRACT



A novel procedure for catalyst recycling is described. Copper(I)-based catalysts, equipped with an affinity tag, are isolated from crude reaction mixtures on the basis of quadruple hydrogen-bonding interactions using a resin functionalized with complementary affinity tags. Recycled catalysts were successfully used to catalyze a tandem Sonogashira coupling/5-endo-dig cyclization and a Cu-catalyzed [3+2] Huisgen cycloaddition reaction in high yields.

The use of transition-metal-based catalysts in chemical processes is widespread because of an increasing amount of applications and a generally favorable atom economy. Drawbacks, however, are the high prices of the metal complexes and the often laborious removal of the metals from reaction mixtures. Facile isolation of catalysts and subsequent reuse is therefore an attractive goal to reduce both cost and waste. As a result, the development of new technology for catalyst recycling has been of interest for many researchers in the past decades.[1] A number of techniques to recycle metal-based catalysts have been developed over the years, such as covalent catalyst immobilization,[2] fluorous phase separation,[3] nanofiltration,[4] and ligand immobilization.[5]

Although significant progress has been made, there are still major shortcomings, including decreased activity of the catalyst and leaching of metal ions. In addition to the existing techniques, we designed a novel noncovalent linking concept for the recycling of catalysts on the basis of quadruple hydrogen bonding (Figure 1).[6] A ligand, generally used in homogeneous catalysis, is equipped with a hydrogen-bonding-based affinity tag (AT). The ligand is complexed to a metal, and the resulting catalyst can be applied in a homogeneous catalytic reaction in an organic solvent, assuming that the affinity tag does not affect its catalytic activity. After the catalytic reaction, the hydrogen-bonding properties of the AT allow facile isolation of the complex by binding it to a resin that contains a complementary hydrogen-bonding array (**1**). A simple filtration can be used to separate the soluble reaction products from the catalyst-containing solid support. Rinsing the polymer with a protic solvent causes cleavage of the hydrogen bonds between resin and the AT so that a second filtration yields only the tagged catalyst, which can then be directly used in the next catalytic reaction.

The AT that was selected to demonstrate the viability of this new purification method was the ureido[1*H*]pyrimidinone

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(1) For recent overviews, see, e.g.: (a) *Catalyst Separation, Recovery and Recycling-Chemistry and Process Design*; Cole-Hamilton, D. J., Tooze, R. P., Eds.; Springer, New York, 2006. (b) Yoshida, J.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693−3716.

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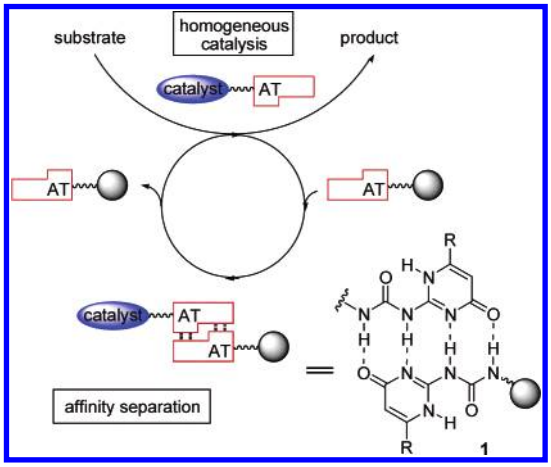


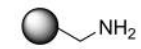
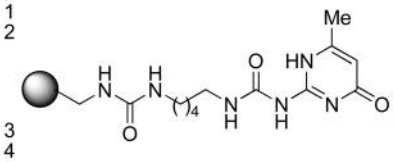
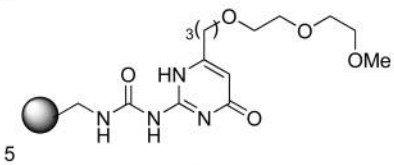
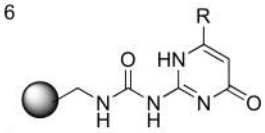
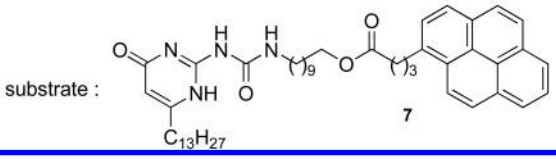
Figure 1. Principle of recycling by hydrogen bonds.

(UPy) group. This self-complementary UPy tag displays a remarkably high dimerization constant of $>10^7$ in chloroform.[7] We envisioned that functionalization of a solid support with a UPy tag, in combination with a complementary UPy-tagged catalyst, should give rise to a distinct affinity, leading to a reversible binding as described above.

Initially, an optimal AT-equipped resin system had to be developed. Therefore, both a flexible Merrifield resin (**2a**, 2% cross-linked) and a highly cross-linked, rigid ArgoPore resin (**2b**) were functionalized with different ATs and their complexation efficiency was evaluated. These complexation studies with the UV-active UPy-tagged compound **7**[8] were performed to determine which resin would be most suited to bind tagged compounds from a solution.

The different resins were added to a stock solution of **7** containing 4 equiv of binding sites relative to the amount of **7**. After 2 h of shaking, the resins were filtrated and the concentration of **7** in the filtrate was determined using UV measurements. The results are summarized in Table 1. The

Table 1. Initial Complexation Studies[a]

entry	resin-bound affinity tag	resin[b]	unbound substrate (mol %)
1		**2a**	90
2		**2b**	100
3		**3a**	100
4		**3b**	80
5		**4a**	100
6		**4b**	60
7		**5b**: R = $C_{13}H_{27}$	50
8		**6b**: R = Me	40
	substrate : 	**7**	

[a] Conditions: 4 equiv of binding sites on the resin (relative to the amount of **7**) in 1,2-dichloropropane, 2 h, room temperature. [b] **a**: 2% cross-linked Merrifield resin. **b**: ArgoPore resin.

high amounts of unbound substrate using Merrifield resins **3a** and **4a** (entries 3 and 5) led us to conclude that homodimerization on the solid support was a significant problem. Conceivably, the relatively flexible linker allowed the resin-bound ATs to dimerize, making binding of substrate molecules more difficult. This problem was partially solved by using a rigid ArgoPore resin with a low degree of functionalization (0.28 mmol of endgroups/g). In this case, the substrate was bound somewhat more efficiently, with a clear difference between the linker-bound UPy moiety (**3b**, entry 4) and the UPy that was directly attached to the resin (**4b**, entry 6). This observation confirmed the hypothesis of homodimerization on the resin. Finally, the best results were obtained using the same highly cross-linked ArgoPore resin in combination with alkyl-functionalized UPy moieties (**5a**,**b**). Because the side group on these UPy moieties did not have a large influence on the complexation, i.e., resins **5b** and **6b** performed equally well in binding substrate **7** (entries 7 and 8), the commercially available isocytosine (R = Me) was selected as the AT of choice for the catalyst recycling process. The functionalization procedure involved

(2) See, for example: (a) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Luis, S. V.; Martínez-Merino, V.; Mayoral, J. A. *J. Am. Chem. Soc.* **2005**, *70*, 5536−5544. (b) Kobayashi, S.; Akiyama, R. *Chem. Commun.* **2003**, *4*, 449−460. (c) Nagayama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2000**, *39* 567−569. (d) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147−4154.

(3) For reviews, see: (a) de Wolf, E.; van Koten, G.; Deelman, B. *Chem. Soc. Rev.* **1999**, *28*, 37−41. (b) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1175−1196. For some recent examples, see, e.g.: (a) Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636−1642. (b) Dinh, L. V.; Gladysz, J. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4095−4097.

(4) For a review, see: Dijkstra, H. P.; van Klink, G. P. M.; van Koten, G. *Acc. Chem. Res.* **2002**, *35*, 798−810. Recent examples: (a) Witte, P. T.; Chowdhury, S. R.; ten Elshof, J. E.; Sloboda-Rozner, D.; Neumann, R.; Alsters, P. L. *Chem. Commun.* **2005**, *9*, 1206−1208. (b) Aerts, S.; Weyten, H.; Buekenhoudt, A.; Gevers, L. E. M.; Vankelecom, I. F. J.; Jacobs, P. A. *Chem. Commun.* **2004**, *6*, 710−711. (c) De Smet, K.; Pleysier, A.; Vankelecom, I. F. J.; Jacobs, P. A. *Chem.−Eur. J.* **2003**, *9*, 334−338.

(5) For covalent examples, see, e.g.: (a) Belser, T.; Stöhr, M.; Pfaltz, A. *J. Am. Chem. Soc.* **2005**, *127*, 8720−8731. (b) Dai, L.-X. *Angew. Chem., Int. Ed.* **2004**, *41*, 5726−5729. (c) Bräse, S.; Dahmen, S.; Lauterwasser, F.; Leadbeater, N. E.; Sharp, E. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1849−1851. (d) Pugin, B. *J. Mol. Catal. A* **1996**, *107*, 273−279. For a noncovalent example, see: Chen, R.; Bronger, R. P. J.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *J. Am. Chem. Soc.* **2004**, *126*, 14557−14566.

(6) For a separation tag based on H-bonding, see: Zhang, K.; Fukase, M.; Izumi, Y.; Fukase, S.; Kusumoto *Synlett* **2001**, 590.

(7) (a) Folmer, B. J. B.; Sijbesma, R. P.; Versteegen, R. M.; van der Rijt, J. A. J.; Meijer, E. W. *Adv. Mater.* **2000**, *12*, 874−878. (b) Beijer, F. H.; Sijbesma, R. P.; Kooijman, H.; Spek, A. L.; Meijer, E. W. *J. Am. Chem. Soc.* **1998**, *120*, 6761−6769.

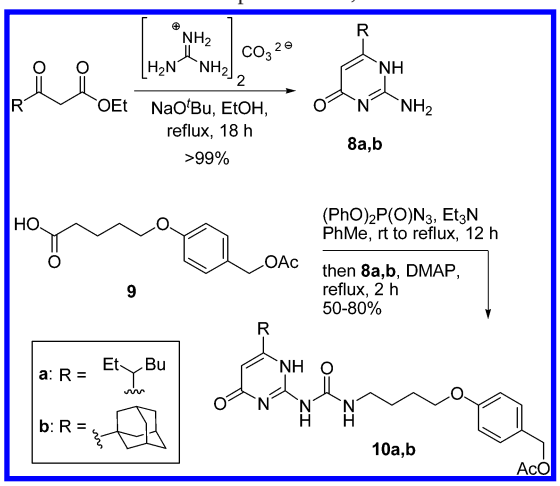
(8) Söntjens, S. H. M.; Sijbesma, R. P.; van Genderen, M. H. P.; Meijer, E. W. *J. Am. Chem. Soc.* **2000**, *122*, 7487−7493.

treatment of the ArgoPore resin with carbonyl diimidazole, followed by reaction with isocytosine, allowing a large-scale preparation of the resin-bound AT **6b**.[9]

Having the optimized resin system in hand, next we focused on identifying a suitable solution-phase AT. When using the same UPy group (R = Me) for this purpose, a very poor solubility of a variety of tagged compounds in virtually all common solvents was observed.

Therefore, we felt that switching to isocytosines with less polar and bulkier R-groups was necessary. The alternative isocytosines **8a** and **8b** were synthesized (R = (1-ethylpentyl) and 1-adamantyl, respectively) via condensation of the corresponding β-ketoester with guanidine carbonate (Scheme 1).[10] This standard reaction initially did not work in the case

Scheme 1. Synthesis of Isocytosines **8a**,**b** and UPy-Tagged Compounds **10a**,**b**

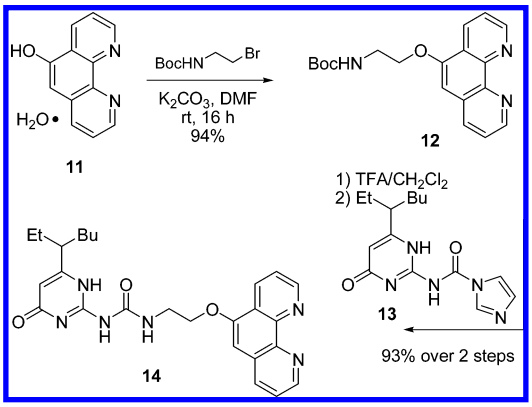


of the bulky adamantyl group but proceeded in excellent yield after addition of a stoichiometric amount of NaO^{t}Bu. The two new tagged compounds **10a** and **10b** were synthesized using these isocytosines in a one-pot procedure from carboxylic acid **9** by means of a Curtius rearrangement. The products were indeed soluble in a range of organic solvents, which is important for the scope of reactions that can be performed using UPy-tagged catalysts. When complexation experiments were carried out in chloroform using resin **6b** (10 equiv of binding sites relative to the amount of **10**), the substrates were bound in a quantitative manner after shaking for approximately 5 h. Upon washing the resin with chloroform, no notable leakage of these compounds from the polymer was observed. Importantly, the tagged compounds **10a** and **10b** were recovered in yields over 98% by shaking the resin in a mixture of DMF/MeOH (2:1 v/v) for 2 h, followed by filtration and evaporation.

This proof of principle set the stage for application of our affinity-based recovery method for catalysts, in which we focused on the functionalization of a ligand with the (1-ethylpentyl)-functionalized UPy tag.

The ligand we chose was 1,10-phenanthroline (phen), a well-known ligand for Cu-catalyzed cross-coupling reactions.[11] 1,10-Phenanthroline has been functionalized previously for immobilization purposes as reported by Canham et al., and we used their procedure to obtain compound **11**.[12] The alkylation of the phenolic hydroxyl group initially gave poor results, but via adjusting Canham's method by switching to other conditions (K_2CO_3 in DMF), the desired compound **12** was obtained in 94% yield (Scheme 2). After cleaving

Scheme 2. Synthesis of the UPy-Tagged Ligand **14**



the Boc group (TFA in CH_2Cl_2) to unveil the amine, we used the previously described carbonyl diimidazole activation to attach the required UPy tag.[9] Thus, the activated isocytosine **13** was obtained from **8a** and then reacted with the deprotected phenanthroline **12** to give the AT-bearing ligand **14** in excellent yield (93% over two steps).[13]

We decided to first test our new recycling concept on the copper(I)-catalyzed synthesis of 2-arylbenzo[*b*]furans as developed in the group of Venkataraman.[11a] This tandem Sonogashira coupling/5-endo-dig cyclization was carried out using $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst and 2 equiv of Cs_2CO_3 as a base in toluene (Table 2). Instead of isolating the copper(I) complex, it was formed in situ by stirring equimolar quantities of $Cu(PPh_3)_2NO_3$,[14] triphenylphosphine, and AT-ligand **14** in DMF, which immediately resulted in a clear yellow solution. To this solution, the other reagents were added, and using the same conditions as those described by Venkataraman, we obtained a complete conversion. This clearly indicates that the UPy tag does not interfere with the copper(I)-mediated coupling and that DMF can be used as a solvent for this cyclization process.

After an aqueous workup, the crude product was dissolved in chloroform and the AT-functionalized resin **6b** was added

(9) Keizer, H. M.; Sijbesma, R. P.; Meijer, E. W. *Eur. J. Org. Chem.* **2004**, 2553−2555.

(10) (a) Alker, D.; Campbell, S. F.; Cross, P. E.; Burges, R. A.; Carter, A. J.; Gardiner, D. G. *J. Med. Chem.* **1989**, *32*, 2381−2388. (b) Snell, B. K. *J. Chem. Soc. C* **1968**, 2367−2370.

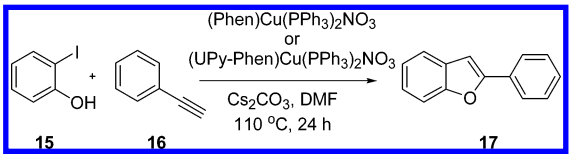
(11) See, e.g.: (a) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727−4729. (b) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315−4317.

(12) Slough, G. A.; Krchnak, V.; Helquist, P.; Canham, S. M. *Org. Lett.* **2004**, *6*, 2909−2912 and references therein.

(13) Because of slightly better solubility, we preferred to use the 1-ethylpentyl-substituted isocytosine **8a** instead of **8b**.

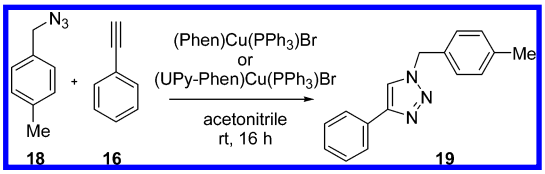
(14) All metal complexes in this article were synthesized as described by Venkataraman in ref 6 and used without further purification.

Table 2. Comparison among the Regular, the AT-Labeled, and the Recycled AT-Labeled Copper Catalysts



			isolated yield of **17**		
entry	catalyst	amount (mol %)	cycle 1	cycle 2	cycle 3
1	(phen)Cu(PPh_3)$_2NO_3$	10	>99%	–	–
2	(Upy-phen)Cu(PPh_3)$_2NO_3$	10	>99%	91%	68%

Table 3. Second Comparison among the Regular, the AT-Labeled, and the Recycled AT-Labeled Catalysts



			isolated yield of **19**		
entry	catalyst	amount (mol %)	cycle 1	cycle 2	cycle 3
1	(phen)Cu(PPh_3)Br	10	>99%	–	–
2	(Upy-phen)Cu(PPh_3)$_3$Br	10	>99%	>99%	>99%

to bind the catalyst via hydrogen bonding. After filtration, the product was isolated from the filtrate via evaporation and the resin was transferred to a mixture of DMF and methanol to cleave the hydrogen bonds. After filtering off the resin, the filtrate was concentrated and the crude catalyst was used in the next reaction.[15] The recycled catalyst remained active, although the yields dropped somewhat as indicated in Table 2, probably because of the harsh reaction conditions that may degrade the copper(I) complex.

To investigate the scope of this catalyst recycling procedure further, we decided to use AT-ligand **14** in a second copper(I)-catalyzed reaction. In 2002, both Meldal and Sharpless independently showed that a regioselective Huisgen [3+2] cycloaddition reaction could be performed under the influence of a copper(I) catalyst.[16] This method of preparing 1,2,3-triazoles has been widely used since then[17] and therefore forms an attractive application for our new procedure. For this reaction, we used the copper catalyst (Phen)Cu(PPh_3)Br,[14] which proved to be well-suited for the [3+2] cycloaddition reaction depicted in Table 3, and the desired product was isolated in quantitative yield.

Analogous to the aforementioned AT catalyst, the tagged CuBr-based catalyst was generated and used in the "click reaction' of substrates **16** and **18**. Again, a quantitative yield of **19** was obtained, showing the minimal influence of the tag on the outcome of the reaction. When the catalyst was recycled in the same way as previously described, initially low yields were encountered in the second reaction cycle. We reasoned that this could be due to undesired oxidation of the copper(I) species to inactive copper(II). This was overcome through the addition of 2 equiv of triphenylphosphine to the mixture to stabilize the Cu(I) complex so that complete conversions and excellent yields were obtained in the next two cycles as well (Table 3).[15] To quantify possible leakage of the catalyst during the recycling procedure, quantitative mass spectroscopy measurements were carried out. This showed that the amount of copper in the crude product was only 1.7% of the initial quantity, meaning that 98.3% of the catalyst was bound by the AT-bearing resin. This outcome, combined with the two aforementioned applications, clearly demonstrates that the viability of hydrogen-bonding-based catalyst recycling as a concept has been firmly established.

In summary, we have realized a novel concept of catalyst recycling based on hydrogen bonding, which is a potentially powerful method because the AT allows facile purification without affecting the catalyst. Furthermore, the tagged resin can be cleaned by simple rinsing with different solvents and reused without limitations. It is clear that other ligands may be equipped with the same AT to recycle different catalysts as well, and studies toward a broader application of this affinity protocol are currently ongoing in our laboratories.

Acknowledgment. These investigations were supported (in part) by The Netherlands Research Council for Chemical Sciences (CW) with financial aid from The Netherlands Technology Foundation (STW). J. Eygensteyn (Radboud University Nijmegen) is kindly acknowledged for performing the ICP-MS measurements.

Supporting Information Available: Experimental procedures and spectroscopic data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Following the same procedure with the nonfunctionalized resin **2b** did not result in any catalytic activity.

(16) (a) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057−3064. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(17) For some recent examples, see, e.g.: (a) Durán Pachón, L.; van Maarseveen, J. H.; Rothenberg, G. *Adv. Synth. Catal.* **2005**, *347*, 811−815. (b) Kaleta, Z.; Egyed, O.; Soós, T. *Org. Biomol. Chem.* **2005**, *3*, 2228−2230. (c) Lin, H.; Walsh, C. T. *J. Am. Chem. Soc.* **2004**, *126*, 13998−14003. (d) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Fréchet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928−3932. (e) Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflieg, P. J. L. M.; Blaauw, R. H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123−3126. (f) Dirks, A. J.; van Berkel, S. S.; Hatzakis, N. S.; Opsteen, J. A.; van Delft, F. L.; Cornelissen, J. J. L. M.; Rowan, A. E.; van Hest, J. C. M.; Rutjes, F. P. J. T.; Nolte, R. J. M. *Chem. Commun.* **2005**, 4172−4174.