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Fluorous Phase-Switching of Pyridyl-Tagged Substrates/Products

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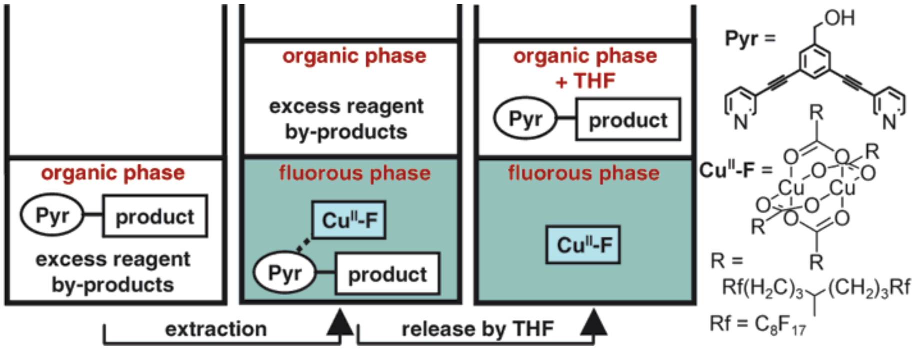
ABSTRACT



A bis-monopyridyl Wang-type tag was prepared for application in the hydrocarbon/perfluorocarbon phase-switching of substrates/products. This "catch-and-release" strategy relies on the reversible coordination of the tag to a fluorous copper(II)–carboxylate complex. A hydantoin was prepared in high yield and purity by a four-step protocol where the intermediates were purified by the straightforward liquid/liquid phase-switching process.

The search for rapid and efficient protocols for the purification of organic compounds is a major concern of modern chemistry.[1] Homogeneous "molecular approaches" have been developed in which the phase separation is driven by a small functional group called a phase tag.[2] Among the various tags developed to favor aqueous-phase extraction, the dimethyl-(2-pyridyl)silyl tag developed by Yoshida and co-workers is the prototypical example of a masked phase tag, which allows products to be switched between organic solvents and aqueous solution.[2,3] Pyridine-containing ligands were also used as masked phase tags for substrates.[4] In that case, a resin functionalized with iminodiacetic groups and loaded with copper(II) ions was employed as a solid support to trap substrates/products linked to a 4,4′-bis(hydroxymethyl)-2,2′-bipyridine tag.

In a previous report we described an unprecedented example of hydrocarbon/perfluorocarbon phase-switching of pyridyl-tagged porphyrin and C_{60} fullerene.[5] This "catch-and-release" approach took advantage of both pyridyl and fluorous tags, the latter being widely used in phase separation

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[2] Yoshida, J.-I.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693−3716.

[3] Reviews: Yoshida, J.-I.; Itami, K. J. *Synth. Org. Chem. Jpn.* **2001**, *59*, 1086−1094. (b) Itami, K.; Mitsudo, K.; Nokami, T.; Kamei, T.; Koike, T.; Yoshida, J.-I. *J. Organomet. Chem.* **2002**, *653*, 105−113.

[4] Ley, V. L.; Massi, A.; Rodriguez, F.; Horwell, D. C.; Lewthwaite, R. A.; Pritchard, M. C.; Reid, A. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1053−1055.

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[6] Selected examples: (a) Zhang, W.; Lu, Y. *Org. Lett.* **2003**, *5*, 2555−2558. (b) Manzoni, L. *Chem. Commun.* **2003**, 2930−2931. (c) Chen, C. H.-T.; Zhang, W. *Org. Lett.* **2003**, *5*, 1015−1017. (d) Zhang, W.; Luo, Z.; Chen, C. H.-T.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 10443−10450. (e) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36. (f) Luo, Z. Y.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766−1769. (g) Studer, A.; Hadida, S.; Ferritto, R.; Kim, S.-Y.; Jeger, P.; Wipf, P.; Curran, D. P. *Science* **1997**, *275*, 823−826. (h) Curran, D. P.; Ferrito, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937−4940. (c) Röver, S.; Wipf, P. *Tetrahedron Lett.* **1999**, *40*, 5667−5670. (i) Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 5139−5142. (j) Wipf, P.; Reeves, J. T. *Tetrahedron Lett.* **1999**, *40*, 4649−4652. (k) Wipf, P.; Reeves, J. T.; Balachandran R.; Giuliano, K. A.; Hamel, E.; Day, B. W. *J. Am.*

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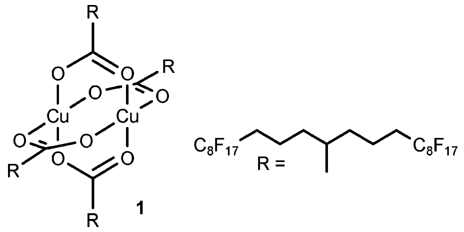
procedures for substrates.[6] Pyridyl tag activation was realized by pyridine coordination to the "heavy" fluorous copper(II)−carboxylate complex **1** (Scheme 1). Due to the high lability of monopyridyl ligands, porphyrin release was carried out by simply adding THF in excess to the biphasic system, a competitive pyridine ligand for copper. As previously described, the use of THF as an unmasking agent allowed recycling of the copper(II)−fluorous phase for subsequent catch-and-release experiments with the same efficiency.[5]

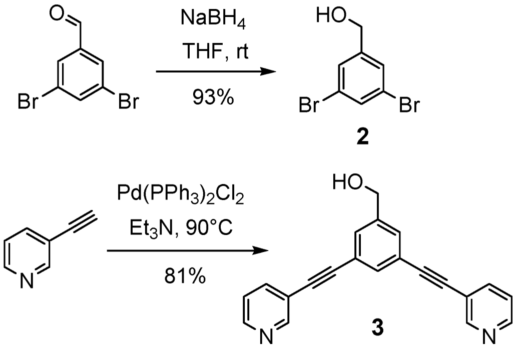
Scheme 1



1

On the basis of our previous results, we assumed that a bis-monopyridyl benzyl alcohol Wang-type tag such as **3** could be used in association with a perfluorocarbon solution of **1** for the separation and recovery of substrates/products (Scheme 2). Acethylenic groups were introduced as rigid spacers between the pyridines to ensure minimum steric hindrance upon coordination of **3** with two bulky copper(II) complexes. The moderate reactivity of the acetylenic bonds toward a rather wide range of reaction conditions and the facile formation of ethylenic-aromatic carbon−carbon bonds appeared as additional attractive features. The bis-monopyridyl benzyl alcohol tag **3** was prepared by a two-step procedure in 75% overall yield from commercially available 3,5-dibromobenzaldehyde and 3-ethynylpyridine (Scheme 2).

Scheme 2. Synthesis of Bis-monopyridyl Benzyl Alcohol Tag **3**



2

3

The alcohol **2**, obtained in 93% yield by reduction with sodium borohydride, was subjected to Sonogashira coupling conditions, affording the desired pyridyl-tagged benzyl alcohol in 81% yield.

The efficiency of the hydrocarbon/perfluorocarbon phase-switching of **3** was then evaluated accurately by UV−visible spectroscopy. Aliquots of complex **1** (from 0.50 to 1.50 equiv with respect to **3** in solution in perfluorodecalin) were added successively to a chloroform solution of **3** (12.4 mM). Upon stirring of the biphasic system, the extraction of **3** was followed by the disappearance in the chloroform phase of its characteristic 286 nm absorption band ($\epsilon_{286} = 49\ 300\ \mathrm{M}^{-1}\ \mathrm{cm}^{-1}$). It was found that only 1.1 equiv of complex **1** was necessary to quantitatively extract **3** into the fluorous phase. Quantitative recovery of the tag into the chloroform was achieved under stirring of the biphasic system, by adding ∼200 equiv of THF with respect to **3**. This demonstrates the high efficiency of the phase-switching procedure using such a bis-monopyridyl tag.

The preparation of hydantoin **7** was chosen to evaluate the efficiency of the fluorous phase-switching procedure for synthetic application.[6a,7] It also gave the opportunity to compare the fluorous homogeneous approach to the previously reported nonfluorous homogeneous/heterogeneous method.[4] A limitation of the latter system is associated to the release of the strongly coordinating bipyridine-linker-product moiety from the support. This was achieved by shaking the suspension of the beads for 8 h in the presence of TMEDA ligand (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine). Moreover, the problem of the recovery of the copper−carboxylate resin was not addressed. The hydantoin **7** was prepared by the four-step procedure described in Scheme 3. In the first step, the bis-monopyridyl Wang type tag **3** was acylated in chloroform using a classic amide coupling procedure. After removal of the poorly soluble dicyclohexylurea (DCU) byproduct by filtration, compound **4** was extracted quantitatively in a few minutes into the perfluorodecalin phase containing 2.5 equiv of complex **1** with respect to **3** under stirring of the biphasic system. After decantation (∼30 min), removal of the organic layer, and washing the fluorous phase (three times with chloroform), compound **4** was released almost instantaneously into chloroform by addition of THF (400 equiv with respect to **1**). Both the uptake and release of **4** could be easily monitored by thin-layer chromatography or UV−visible spectroscopy. Evaporation of the chloroform/THF mixture afforded **4** in 98% yield and >95% purity, as evidenced by its ^{1}H NMR spectrum (see Supporting Information). A significant broadening of the ortho and para protons of the pyridine ring was noticed on the ^{1}H NMR spectrum of **4**. This was attributed to the leaching in the chloroform phase of traces of paramagnetic copper(II) ions that should form highly labile

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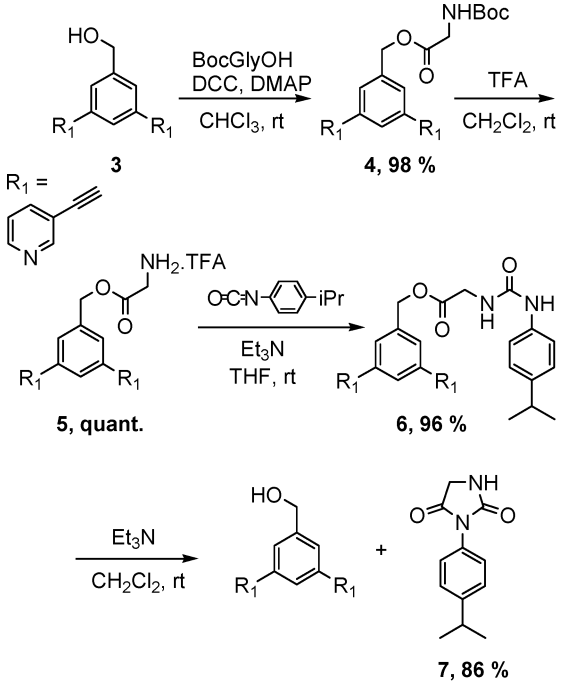
Scheme 3. Synthesis of Hydantoin **7**



coordination bonds with the monodentate pyridyl groups. Notice that the leaching represents a very small amount of copper, as titration of **1** in the fluorous phase monitored by UV−visible spectroscopy after release of **4** revealed no detectable loss. The fluorous phase was reactivated by washing with chloroform to remove the excess THF solubilized in the perfluorodecalin and was then reused in the next steps with the same efficiency. This clearly demonstrates the high recovery of complex **1** in an active form for further pyridyl tag activation. The tris-TFA salt of **5** was obtained quantitatively by treatment of **4** with TFA in dichloromethane and removal of the excess reagent and solvent under reduced pressure. Addition of 4-isopropylphenyl isocyanate (1.1 equiv) to a THF solution of **5** and Et_3N (3 equiv) led to the rapid formation of **6**. After evaporation of the THF and redissolution of the residue in chloroform, the urea derivative **6** was extracted using the copper−fluorous phase recovered from the first step. After washing the fluorous phase, addition of THF (400 equiv), **6** was released into chloroform in 96% yield and >95% purity (Figure 5). As noticed for **4**, a significant broadening of the proton resonances of the pyridines was observed. The urea derivative **6** was then treated with triethylamine in dichloromethane to produce an equimolar mixture of the bis-monopyridyl tag **3** and the expected hydantoin **7**. Removal of the tag was achieved by addition of the perfluorodecalin solution of **1** recovered from the previous step. After phase separation and solvent evaporation followed by washings of the solid residue with pentane, the hydantoin **7** was isolated in 86% yield and purity higher than 95%. The overall yield for the four-step reaction sequence was 81%.

From the results presented above, a set of attractive features emerged that should favor the development of the fluorous phase-switching approach to other synthetic applications: (1) Only two pyridyl groups separated by a rigid spacer was sufficient to ensure a very efficient extraction of rather large and polar molecules into the fluorous phase. (2) By the use of a masked phase tag, reactions were carried out in usual organic solvents. There was no requirement for mixed organic/fluorinated solvent mixture for a reaction to proceed,[6m−o] not for limitation, as could be the case when using solid-supports, to solvents that will favor the swelling of the beads (such as DMF).[4] (3) The advancement of reactions and the phase-switching procedures may be monitored by thin-layer chromatography and/or UV−visible spectroscopy. (4) Both the extraction and release process were shown to occur effectively and rapidly using a small excess of complex **1** with respect to the tag compounds. (5) The purified product was recovered in an organic solvent, not in a perfluorocarbon as it could be the case when employing fluorous tags; moreover, it has been demonstrated that the perfluorocarbon−complex **1** couple can be recovered almost quantitatively in an active form making this approach “fluorous low consuming”.

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Supporting Information Available: Experimental procedures and characterization for all new compounds and ^1H NMR spectra for compounds **4**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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