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ARTICLE

Enantiopure Isothiourea@Carbon-Based Support: Stacking Interactions for Recycling a Lewis Base in Asymmetric Catalysis

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Yu-Chao Yuan,^{a,b,†} Mariam Abd El Sater,^{a,c} Mohamed Mellah,^a Nada Jaber,^c Olivier R. P. David^{*b} and Emmanuelle Schulz^{*a}

Dedicated to Dr. Christian Bruneau for his outstanding contribution to catalysis

New procedures dedicated to the efficient reuse of chiral organic catalysts are currently in great demand. Indeed, and even if toxicity issues are less problematic than with organometallic catalysts, their easy recovery and recycling allow an overall saving of material, which is of utmost importance when valuable enantiopure catalysts are concerned. We describe here the synthesis of a chiral isothiurea (hyperBTM) functionalized by a pyrene moiety via click chemistry. This new enantiopure Lewis base is used as supported catalyst thanks to its immobilization on reduced graphene oxide via strong π - π interactions between the polyaromatic core and the carbon support. The synthesis of scalemic oxazolidin-4-ones from oxaziridines and arylacetic anhydrides is chosen as a test reaction to assess the validity of the process, this transformation having never been carried out under recycling conditions. Optimization of the reaction conditions led to the synthesis of the targeted products in high yields and good to excellent enantioselectivity values with the supported catalyst. Recovery of the active species occurred by simple filtration, the immobilized catalyst was then successfully reengaged in seven consecutive cycles while maintaining its efficiency. The robustness of this chiral organic isothiurea was also demonstrated in an original multi-substrate procedure.

Introduction

The use of enantiopure catalysts in synthesis is nowadays obvious for the preparation of valuable scalemic substrates. For cost and environmental motivations, these precious promoters must be readily available and exhibit high activity at low catalytic loading. In this context, their easy recovery for an efficient reuse is also of great value. Numerous procedures have already reported the heterogenization of chiral catalysts involving either covalent or non-covalent binding to many supports.¹ As highly stable, ideally porous and mechanically resistant supports, carbon materials have been used extensively in catalysis.² They can indeed be modified by covalent bindings³ or be involved in π - π interactions.⁴ In the first case, a covalent link of the chiral catalyst on the support ensures robustness and decreases any risk of leaching, but it can lead to a tedious synthesis for the necessary modification

of both the ligand and the support. On the contrary, immobilization by non-covalent interactions often means simpler processes and easy recovery of the support, when the catalyst is deactivated. A possible catalyst release must however be taken under consideration.⁵ The chemical modification of carbon supports has already been described for the subsequent covalent grafting of enantiopure organometallic catalysts,⁶ but very few examples have proposed immobilization by non-covalent bonds.⁷ They include the deposit of chiral phosphine-containing catalysts on CNT^{7a} or their assembly onto rGO^{7d} to realize Rh-promoted asymmetric hydrogenation. Our group described the immobilization of copper bis(oxazoline) complexes on various carbon supports for the enantioselective formation of C-C bonds.^{7b} More recently, the non-covalent immobilization of Rh complexes was reported for the asymmetric hydroformylation and implemented in a flow mode.^{7c} This year, imidazolium salts have also been immobilized by π -stacking interactions onto carbon materials and these organocatalysts were efficiently reused in the cycloaddition of epoxides with CO₂.⁸ Worth mentioning is, in each case, the functionalization of the ligand by a pyrene group as a demonstration of its high affinity with the carbon surface by very stable π - π -interactions. However, and as far as we know, there are no examples dealing with the immobilization of an enantiopure organocatalyst on carbon supports by such reversible interactions.

^a Université Paris Saclay, CNRS, Institut de Chimie Moléculaire et des Matériaux d'Orsay, 91405 Orsay, France, emmanuelle.schulz@universite-paris-saclay.fr

^b Institut Lavoisier, UMR 8180, Université de Versailles Saint-Quentin-en-Yvelines, Université Paris Saclay, 45 avenue des Etats-Unis, 78035 Versailles, France, olivier.david@uvsq.fr

^c Laboratoire de Chimie Médicinale et des Produits Naturels, Université Libanaise, Faculté des Sciences (I) and PRASE-EDST, Hadath, Beyrouth, Lebanon

[†] Present address: Jiangsu Key Laboratory of New Drug Research and Clinical Pharmacy, School of Pharmacy, Xuzhou Medical University, Xuzhou 221004, China. Electronic Supplementary Information (ESI) available: [Experimental procedures, spectroscopic characterization data, copy of NMR and HPLC spectra]. See DOI: 10.1039/x0xx00000x

Chiral isothioureas (ITUs)⁹ are enantiopure Lewis bases active to promote numerous asymmetric catalytic processes.^{10,11} These catalysts were already immobilized mostly on organic polymeric supports by covalent grafting; they were stable in many efficient batches and even flow processes.¹² In this context, we describe here the first immobilization of an enantiopure ITU organocatalyst (hyperBTM) on reduced graphene oxide (rGO) as carbon support through π - π non-covalent interactions. We selected the enantioselective formal [3+2] cycloaddition of ammonium enolates with oxaziridines described by the group of Smith,¹³ to test our procedure. This reaction indeed leads to the synthesis of oxazolidin-4-ones, valuable scaffolds present in natural products such as lipoxazolidinones A–C¹⁴ or simply precursors of chiral α -hydroxyacids. While this reaction has never been described under recycling conditions, we report here our efforts to achieve it under heterogeneous conditions on a carbonaceous support, and to evaluate the robustness of the chiral organic catalyst to recovery.

Results and discussion

We targeted the synthesis of *pyr*-hyperBTM for its immobilization on rGO (see Scheme 1). The synthesis of **3** was realized following the procedure described by the group of Smith, starting from benzaldehyde **1**.¹⁵ The introduction of the stereogenic centers occurred via the use of (*S*)-proline leading to the formyl-carbamate **2** (see Supporting Information for details). The anchoring point for the pyrene ring is chosen far from the active center of the organocatalyst, on the phenyl ring of the benzotetramisole. This strategy has already been illustrated by the immobilization of the enantiomer of compound **3** on a Merrifield-type resin, dedicated to the acylative kinetic resolution of alcohols.^{12c} To this aim, compound **3** is functionalized by a propargyl group after demethylation, to give **4** in 42% yield. On the other side,

commercially available pyren-1-yl-methanol is transformed via two consecutive nucleophilic substitutions into the azido derivative **7**, possessing a four methylene spacer. A copper(I)-promoted azide-alkyne cycloaddition between ITU-alkyne **4** and pyrene-azide **7** afforded the desired functionalized *pyr*-hyperBTM. This pyrene-modified organocatalyst was prepared at the gram scale with an overall yield of 4.1 % from benzaldehyde (see Supporting Information for the detailed complete procedure and characterization).

Immobilization of the pyrene-tagged hyperBTM onto the rGO surface was achieved by impregnation of the carbon suspension with a solution of *pyr*-hyperBTM in DCM with a mass ratio of 4/1.¹⁶ After sonication for a few minutes and 24 h of stirring at room temperature, the solid was filtered off, washed with DCM and vacuum-dried. The efficiency of the immobilization was monitored by UV-Vis analyses (see Figure 1 and Supporting Information for details). The comparison with a calibration curve indicated that the entire complex was totally deposited, which was further confirmed by differential weighing. The organocatalyst dispersed as a fine black powder was therefore tested as heterogeneous catalyst.

The catalytic efficiency and the recyclability of *pyr*-hyperBTM@rGO was tested on the asymmetric formal [3+2] cycloaddition of 2-phenylacetic anhydride and *rac*-3-phenyl-2-tosyl-1,2-oxaziridine.¹³ *Pyr*-hyperBTM was firstly engaged under homogeneous conditions to assess its efficiency against the published values of its unmodified analogue. The reaction is indeed described to deliver the oxazolidin-4-ones *anti*-**10a** and *syn*-**10a** from racemic **9** and Cs₂CO₃ as base, in high yield, with excellent enantiocontrol but a poor diastereoselectivity when hyperBTM is used (Table 1, entry 1, ref 13). We explored the activity of the *pyr*-hyperBTM precursor **3** under the same conditions, to evaluate the changes induced by the presence of a methoxy substituent on the phenyl ring of the organocatalyst (entry 2).

Scheme 1. *pyr*-hyperBTM synthesis procedure

Figure 1.

Immobilization of *pyr*-hyperBTM on rGO monitored by UV-Vis analyses (blue curve: UV-Vis spectrum for *pyr*-hyperBTM in DCM. Orange curve: UV-Vis spectrum for *pyr*-hyperBTM/rGO 1/4 wt/wt in DCM, after 24 h stirring).

Table 1. Reaction tests in homogeneous and heterogeneous conditions

Entry	Cat	Base	Yield ^a	d.r. anti/syn ^b	ee anti/syn ^b
1 ^c		Cs ₂ CO ₃	83	57 / 43	97 / 97
2		Cs ₂ CO ₃	81	57 / 43	85 / 81
3	<i>pyr</i> -hyperBTM	Cs ₂ CO ₃	74	61 / 39	96 / 98
4	<i>pyr</i> -hyperBTM	<i>i</i> Pr ₂ NEt	92	55 / 45	89 / 89
5	<i>pyr</i> -hyperBTM@rGO	Cs ₂ CO ₃	64	69 / 31	87 / 81
6	<i>pyr</i> -hyperBTM@rGO	<i>i</i> Pr ₂ NEt	75	59 / 41	88 / 92

^aisolated yield of *anti*-10 + *syn*-10. ^bdetermined by HPLC or SFC analysis with a chiral stationary phase (see Supporting Information).

This species delivered the target products with similar values in terms of yield and diastereoselectivity but a reduction of the enantioselectivity was observed. Fortunately, high selectivity values were again obtained when *pyr*-hyperBTM was tested as catalyst in the presence of Cs₂CO₃ as base, although both oxazolidin-4-ones were synthesized in only 74% yield (entry 3). The use of an organic base, the Hünig base, was then investigated as soluble species in the medium for limiting mass transfer in the context of the subsequent heterogeneous catalysis. These operating conditions led to an improved activity (92 % yield, entry 4) to the detriment of selectivity values. In this last case, both diastereoisomers *anti*-10a and *syn*-10a were recovered but contaminated by a slight amount

of *N*-tosylbenzylimine, as by-product presumably arising from oxidation of the organic base.

The reaction was finally performed under heterogeneous conditions, with *pyr*-hyperBTM@rGO as supported catalyst in the presence of both bases and successful enantioselective catalysis still occurred. The yields were recorded at the same reaction time as under homogeneous conditions, revealing a small decrease in activity as is often observed with supported catalysts. The catalyst deposit on rGO slightly improved the diastereoselectivity, but decreased the enantioselectivity value, specifically when Cs₂CO₃ was concerned (entries 5-6).

The quantity of organocatalyst introduced to carry out this catalytic transformation is not negligible (10 mol %) and we therefore explored the possibility of its recycling to artificially increase the TON. Both the use of the organic or the inorganic base was evaluated for the recovery process and the detailed results are summarized in the Supporting Information (see tables, ESI S14). In all cases, and after the first run, the suspension was left to settle, the supernatant solution was removed by filtration and the remaining solid was washed with DCM, the reaction solvent. A second run was performed after drying the immobilized catalyst under vacuum and addition of new substrates. For instance, Cs₂CO₃ possesses the advantage to avoid the formation of the by-product, but as an insoluble species, it is recovered together with the immobilized catalyst. The second run conducted under these conditions and without addition of supplementary base, delivered the desired mixture of diastereoisomers 10a, rid of *N*-tosylbenzylimine but in only 20 % yield. Addition of Cs₂CO₃ before a third use of the catalyst unfortunately did not result in any formation of the targets. A new batch of *pyr*-hyperBTM@rGO was prepared and a second attempt was completed with the inorganic base, but the work-up implied a washing with a mixture of H₂O/acetone to eliminate all salts. A significant decrease in yield was also observed in this case (2nd run, 40 % yield) but the products

were still isolated in 23% yield after the third cycle. Nevertheless, the decrease in the enantioselectivity values along with recycling is too important under these conditions and the recycling procedure was thus renewed by using the soluble Hünig base. Both acetone and DCM were tested as solvents to wash the recycled supported catalyst leading to better results. Although a slight decrease in activity could not be avoided, the preservation of the enantioselectivity values was noticeable. Unfortunately, however, the mixture of both diastereoisomers remained contaminated with slight amount of inseparable *N*-tosylbenzylimine, as by-product.

The procedure implying several washings of the solid catalyst with DCM as reaction solvent and using *i*Pr₂NEt as base was thus chosen to carry the reaction with *pyr*-hyperBTM@rGO in heterogeneous, recycling conditions (Table 2).

Table 2. Recycling tests with *pyr*-hyperBTM@rGO and *i*Pr₂NEt as a base.

	Yield ^a	d.r. ^b <i>anti</i> / <i>syn</i>	ee ^b <i>anti</i> / <i>syn</i>
1 st run	74	57/43	92/96
2 nd run	66	64/36	90/93
3 rd run	56	62/38	87/92
4 th run	40	66/34	85/87
5 th run	29	63/37	83/95
6 th run	20	68/32	74/89
7 th run ^c	51	67/33	91/93

^aisolated yield of *anti*-**10a** + *syn*-**10a**. ^bdetermined by HPLC analysis with a chiral stationary phase. ^c2 mg of *pyr*-hyperBTM added to the spent supported catalyst before performing the 7th run.

The recycling tests were performed at the 0.1 mmol scale, and the supported catalyst *pyr*-hyperBTM@rGO was engaged seven successive times in reaction. The continuous formation of the target products is observed with each recycling, even if their quantity decreases; after the 2nd run, the imine side product appears as traces together with the expected oxazolidinones. It is important to note that the enantioselectivity values are maintained at a high level, at least until the 5th use of the catalyst. Finally, and before performing the 7th cycle, a small amount (1/5 of the quantity initially introduced) of fresh *pyr*-hyperBTM was added on the supported catalyst in reuse. This notably led to a renewed increase in both the yield and also the selectivity of the reaction. Although some performance instability during recycling was observed, possibly due to catalyst degradation over the process by some hydrolysis,¹⁷ this procedure made it possible to carry out seven runs with notable selectivity, which is unprecedented for this formal [3 + 2] cycloaddition. A hot filtration test was performed to check if the decrease in yield was not due to a partial leaching of the catalyst from its support. The substrates and the base were added to the

supernatant under the usual catalysis conditions and no transformation towards the target product was detected. This test does confirm that the catalysis takes place under heterogeneous conditions.

Finally, *pyr*-hyperBTM@rGO was used in a similar transformation under these optimized conditions, but different arylacetic anhydrides possessing various structures were successively engaged in the reaction, at each recycling, in a challenging multi-substrate procedure, to widen the scope of the methodology and to further test the stability of the supported catalyst.

Table 3. Homoanhydride substrate scope and recycling tests with *pyr*-hyperBTM@rGO in a multi-substrate procedure.

Entry	Run	Cat	Substrate	Yield ^a	d.r. ^b <i>anti</i> / <i>syn</i>	ee ^b <i>anti</i> / <i>syn</i>
1	-	pyr - hyper BTM	8a	92	55/45	89/89
2	-		8b	85	58/42	79/53
3	-		8c	82	63/37	85/60
4	-		8d	90	44/56	76/88
5	1 st	pyr - hyper BTM @rGO	8a	75	62/38	96/91
6	2 nd		8b	65	80/20	86/69
7	3 rd		8c	60	44/56	72/6 ^c
8 ^d	4 th		8d	30	81/19	87/64

^aisolated yield of *anti*-**10** + *syn*-**10**. ^bdetermined by HPLC or SFC analysis with a chiral stationary phase. ^c**10c** contaminated with an impurity preventing an accurate *ee* determination of *syn*-**10c**. ^dCS₂CO₃ is used as base.

The three new arylacetic anhydrides were first subjected separately to the homogeneous asymmetric reaction in the presence of *pyr*-hyperBTM as organocatalyst and yield as selectivity values were determined for comparison (Table 3, entries 2-4). The transformation of these substrates was productive as the target aryl-substituted oxazolidinones were in each case isolated with good to high yields, using Hünig's base. The diastereoselectivity of these reactions are in agreement with published results but the enantioselectivity values turned out to be much weaker than the results reported in the presence of Cs₂CO₃.¹³ The ability of *pyr*-hyperBTM@rGO to catalyze these enantioselective formal cycloadditions by changing the structure of the ammonium enolates at each reuse was finally investigated. After preparation of *anti*-**10a** and *syn*-**10a** in good isolated yield with high enantioselectivity values, the supported catalyst was washed with DCM and reused for the reaction with 2-(naphthalen-1-yl)acetic anhydride, **8b**. *Anti*-**10b** and *syn*-**10b** were easily recovered in their enantioenriched forms, with 65 % yield, importantly free of any trace of oxazolidinones prepared in the previous cycle. A third recycling of this batch of *pyr*-hyperBTM@rGO led to the oxazolidinones from the reaction with **8c**, however affected by a reduction of the expected values. A final reuse,

carried out in the presence of Cs_2CO_3 as base with **8d** anhydride bearing an electron donor substituent, still made it possible to isolate the targeted products *anti*-**10d** and *syn*-**10d** with high enantioselectivity values.

Conclusions

The functionalization of hyperBTM by a pyrene group therefore allowed the proposal of a new method for its recycling, which involves the formation of non-covalent bonds with rGO. These π -stacking interactions advantageously make it possible to avoid any modification of the support. We have here discussed the fine-tuning of the procedure allowing for the formation of various oxazolidinones from a racemic oxaziridine with arylacetic anhydrides. Two bases were evaluated: the Hünig's base led to high yield and enantioselectivity values in the target products; the use of Cs_2CO_3 , which is insoluble and accumulates during the recycling of the heterogeneous catalyst made it possible, on the other hand, to avoid the formation of the secondary product, the *N*-tosylbenzylimine. The catalytic reaction is nevertheless carried out under operating conditions matching those used in the homogeneous phase while maintaining high activity and selectivity. The recovery of the catalyst before its re-engagement in a new reaction is simply carried out by its filtration and further washing with the reaction solvent. Its effectiveness has been demonstrated by its reuse in 7 successive cycles of catalysis and also in a multi-substrate procedure (4 cycles) during which the structure of the anhydride reagent was changed at each recycling. Although a decrease in the activity and selectivity values of the spent catalyst could not be avoided, this is the first demonstration of its reuse in this formal cycloaddition reaction. To our knowledge, this study is also the first use of a chiral organic catalyst under these conditions, among the very few reports which deal with non-covalent immobilization by π -stacking of asymmetric organometallic catalysts. This study paves the way for the application of this procedure to promote other catalytic reactivities by these chiral isothiourea species, immobilized alone, or with other catalysts, towards asymmetric multicatalysis.

Conflicts of interest

There are no conflicts to declare.

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