Cite this: Chem. Commun., 2011, 47, 5286–5288

www.rsc.org/chemcomm

COMMUNICATION

An efficient and recyclable hybrid nanocatalyst to promote enantioselective radical cascade rearrangements of enediynes[†]

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Received 27th January 2011, Accepted 11th March 2011 DOI: 10.1039/c1cc10551e

Mesoporous silica grafted with a tertiary amine was used as a basic nanocatalyst to promote in confined medium the enantioselective cascade rearrangement of enediynes based on the phenomenon of memory of chirality; the multi-substrates recyclable catalytic reagent could easily be recovered by simple filtration, and reused without any decrease in activity even when changing the solvent.

One of the most important goals nowadays is the development of environmentally friendly processes. Cascade reactions are continuously growing in popularity and many new sequences have been published.¹ The benefits of cascade reactions are well established, they include atom and time economy, and low waste generation.² Therefore, cascade reactions can be considered to fall under the banner of "green chemistry". We have recently reported the enantioselective cascade rearrangement of enediynes leading to heterocycles bearing a quaternary stereogenic center.³ These reactions proceed with memory of chirality.⁴

Over the recent past years, there has been a dramatic rise in the number of reports dealing with the preparation, characterisation and use of hybrid materials based on mesoporous silica of a tunable pore size.⁵ Supported heterogeneous catalysts with chemically designed surfaces have received much attention,⁶ not only as recoverable reagents, immobilized in mesoporous silicas,⁷ but also as multifunctional surface materials. Many examples dealing with enantioselective catalysis with chiral ligands have been reported.⁸ The improvements compared to homogeneous processes were ascribed to confinement effects.

There are very few examples dealing with cascade reactions in confined media,⁹ as well as very few reports dealing with the influence of confinement on radical processes (most examples are concerned with photochemical processes).^{10,11}

We describe herein a polar/radical crossover cascade rearrangement of enediynes bearing a sulfone moiety as a precursor of an intermediate enyne-allene.¹² These rearrangements were promoted by recyclable nanocatalysts,

i.e., hybrid materials bearing a tertiary amino group prepared from mesoporous silica according to grafting protocols. In our previous procedure, we used 5 to 10 equivalents of basic Al₂O₃ to induce the formation of the allene moiety from an aryl propargyl sulfone. Alumina could not be recycled; moreover, it was shown to retain part of the reaction products, and, as a consequence, to be responsible for a loss in yield. We disclose herein a new protocol based on mesoporous silicas grafted with a tertiary amine which allowed the generalisation of the rearrangement to alkyl propargyl sulfone based substrates. As exemplified in Scheme 1 with the rearrangement of 1a-b, the cascade involves a 1,3-proton shift leading to A. The latter undergoes a spontaneous Saito-Myers¹³ cyclisation to give biradical **B**. Subsequent 1,5-hydrogen atom transfer¹⁴ leads to biradical (C) which, owing to the conformational requirements imposed by the atom transfer step, is generated in a chiral conformation at the capto-dative reactive center. This chirality is preserved during the intramolecular coupling of biradical (C), which affords diastereomeric mixtures of 2a-b and 3a-b in good yields, together with side-products 4a-b (Fig. 1) resulting from a dismutation process.

Mesoporous silicas with different pore diameters were prepared from tetraethyl orthosilicate (TEOS) in the presence



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Filestration of hybrid materials and new compounds, and analysis by chiral HPLC. See DOI: 10.1039/c1cc10551e



Fig. 1 Structures of substrates and catalysts.

of cetyl-ammonium bromide (CTAB) or pluronic P123 as templates. They were then submitted to post synthesis-grafting with diethylaminopropyltrimethoxysilane (DEAP) (Fig. 1). These materials were analysed by N₂ adsorption/desorption (average pore diameters of 2, and 5 nm were determined for **GA**-MCM41 and **GA**-SBA15, respectively). **GA**-Si2000 was prepared by grafting commercially available Si2000 (200 nm pore diameter). The presence of the organic moiety was confirmed by ¹³C and ²⁹Si solid-state NMR spectroscopy. The small-angle X-ray diffraction (XRD) indicated highly ordered structures with d_{100} values of 3.9 nm and 10.7 nm for **GA**-MCM41 and **GA**-SBA15, respectively. Thermogravimetric analysis showed a ratio close to 1.5 mmol of amine per gram of silica.

We next examined the ability of these mesoporous silicas to promote the cycloaromatisation reaction. The results obtained from the rearrangements of 1a and 1b in benzene at 80 °C are summarized in Table 1. Basic alumina gave a poor conversion in the cyclization of **1a** even when increasing the time of reaction up to 20 h. As expected, ungrafted silica (control reaction) did not afford any rearranged product. In the presence of GA-Si2000 (entry 3), the rearrangement of 1a (88% ee) proceeded with 67% conversion to afford (3S,4S)-2a and (3S,4R)-3a with 68% and 72% ee's, respectively. This means that the reaction proceeded with a high degree of memory of chirality. Product 4a was also isolated. Under the same conditions, GA-MCM41 afforded 2a and 3a (93% conversion) with the same ee's, and identical products ratio (entry 4). Similar results were obtained when using GA-SBA15 used as prepared, or after passivation, (entries 5 and 6). Mesoporous silica has a regular cylindrical shape.

Table 1 Cyclisation of 1a (88% ee) leading to 2a and 3a with variousbases^a

Entry	Base (2 eq.)	Time/ h	$\operatorname{Conv}^{c}(\%)$	$\% 2^d (ee\%)^b$	$\%3^{d} (ee\%)^{b}$	% 4 ^d
1	Al ₂ O ₃	20	20	6	9	4
2	Silica	6	0	_	_	_
3	GA-Si2000	6	67	20 (72)	31 (68)	16
4	GA-MCM41	6	93	28 (71)	45 (69)	20
5	GA-SBA15	6	94	29 (72)	45 (68)	20
6	GA-SBA15 ^e	6	93	29 (73)	45 (70)	19
7	GA-SBA15	10	100	$29^{f}(72)$	$45^{f}(68)$	20 ^f

^{*a*} Reaction conditions: **1a** (0.02 mmol), Benzene (1 mL), base (0.04 mmol), 80 °C. ^{*b*} Determined by chiral HPLC. ^{*c*} Conversion determined by NMR based on consumed substrate. ^{*d*} NMR ratio. ^{*e*} Passivated before grafting. ^{*f*} Isolated yield on 0.26 mmol scale.

The high surface area of the materials concentrates a great density of functional groups. The smaller the pore size, the higher the probability of efficient collisions between the catalyst and the substrate is. A confinement effect explains the lower activity of **GA-Si2000** compared to that of **GA-MCM41** and **GA-SBA15**.

GA-SBA15 was selected to continue our study by screening different substrates. Under these conditions, **2a** (72% ee) and **3a** (68% ee) were isolated in 29% and 45% yields, respectively, from **1a** (88% ee). The dismutation product **4a** was isolated in 20% yield (entry 7). Whereas the influence of the catalyst on the rate of the reaction was obvious, no significant effect of confinement was observed on the diastereoselectivity or on the enantioselectivity.¹⁵

The recycling of the catalyst is of prime importance in a heterogeneous reaction. Therefore, we have investigated the reusability of **GA-SBA15** nanocatalyst. As shown in Table 2, the grafted silica could be reused at least five times in benzene in the rearrangement of **1b** with no loss of activity. The cyclisation of **1b** (97% ee) afforded 30% of **2b** (81% ee); and 39% of **3b** (79% ee); again the dismutation product **4b** was isolated (entry 7). Thus the consecutive uses of the same catalyst allowed the complete conversion of this substrate with enantiomeric excesses very close to those observed in the first run. An additional cycle carried out after changing the solvent from benzene to acetonitrile did not affect either the activity, or the diastereomeric ratio, and the ee's.

The multi-substrates recycling of the same catalyst was extended to other substrates. It was first carried out with oxazolidinone **5a** (Scheme 2) to afford (R,S)-**6a** (21%) and (S,S)-**7a** (62%) with 93% and 84% ee's, respectively (entry 1, Table 3).

Because of the acidity of the proton in position α relative to the ethylsulfonyl group, the stereogenic center linked to sulfur undergoes epimerisation into the thermodynamically most stable product, *i.e.*, (*S*,*S*)-**7a** as the major diastereoisomer, as already evidenced in previous work.³

When submitted to the same conditions, **5b** afforded (*R*,*S*)-**6b** (58%) and (*S*,*S*)-**7b** (29%) with 96% and 72% ee's, respectively (entry 2, Table 3). These results are comparable to those observed in the procedure using alumina,³ except that the yield was higher under the new conditions. Pyroglutamic derivative **5c** (entry 3, Table 3) led to a mixture of (*S*,*S*)-**6c** and (*R*,*S*)-**7c** that were isolated in 35% and 53% yields, with 94% and 87% ee's, respectively. The tosylated analogue **5d** (entry 4) gave very similar results.

Table 2 Recycling of the grafted catalyst in the cascade rearrangement of $1b (97\% \text{ ee})^a$

Cycle	Solvent	Time/h	$\operatorname{Conv}^b(\%)$	ee of $\mathbf{2b}^{c}$ (%)	ee of 3b ^c (%)
1st	Benzene	3	100	82	81
2nd	Benzene	3	100	81	80.5
3rd	Benzene	3	100	82	80.5
4th	Benzene	3	100	82	80
5th	Benzene	3	100	82	80
6th	Acetonitrile	3	100	81	79
7th	Benzene	3	100	$81 (30\%)^d$	79 $(39\%)^d$

^{*a*} Reaction conditions: **1b** (0.035 mmol), Benzene (2 mL), **GA-SBA15** (0.07 mmol), 80 °C. ^{*b*} Conversion determined by NMR based on consumed substrate. ^{*c*} Determined by chiral HPLC. ^{*d*} Number in parentheses give the isolated yield on 0.2 mmol scale.



Table 3Multi-substrates recycling in the rearrangement of enediynes $5a-d^{\alpha}$

Entry	Substrate (ee) ^b	Time/h	$\%6^{c} (ee\%)^{b}$	$\%7^{c} (ee\%)^{b}$
1	5a (99)	4	21 (93)	62 (84)
2	5b (99)	2	58 (96)	29 (72)
3	5c (97)	2.5	35 (94)	53 (87)
4	5d (99)	2	36 (93)	50 (88)

^{*a*} Reaction conditions: **5** (0.34 mmol), Benzene (10 mL), GA-SBA15 (0.7 mmol), 80 °C. ^{*b*} Determined by chiral HPLC. ^{*c*} Isolated yield.

Finally, the cascade rearrangement was achieved using 20 mol% loading of **GA-SBA15**. Under these conditions, only the reaction time was changed, neither the diastereoselectivity nor the enantioselectivity were affected (Table 4). Time needed for completion was 13.5 h instead of 10 h for the cyclo-aromatisation of **1a** (entry 1), which indicated that the procedure was still very efficient. Substrate **1b** afforded **2b** (33%, 81% ee), **3b** (42%, 80% ee) and **4b** (21%) after 8 h (entry 2).

In contrast to the stoichiometric reaction, in the case of 5a, the catalytic procedure led to 6a as the major diastereomer (60%) and 7a was isolated in 30% yield as the minor diastereoisomer (entry 3). This could be explained by the slowing down of the rate of epimerisation under catalytic conditions (entry 1, Table 3). Due to the faster epimerisation of the product, the cyclization of 5b gave almost the same results as the stoichiometric process (entry 4). Similar observations apply to the rearrangement of pyroglutamic derivatives 5c and 5d. By the way, we did succeed in performing a catalytic process with yields as high as those obtained with 2 equivalents of base without any loss of the enantioselectivity.

In conclusion, mesoporous silica grafted with a tertiary amino group is very efficient to promote in confined medium the enantioselective cascade rearrangement of enediynes, in

Table 4 Rearrangement of enediynes 1 and 5 using 20 mol % of**GA-SBA15**^a

Entry	Substrate $(ee)^b$	Time/h	6 ^{<i>c</i>} or 2 % (ee%) ^{<i>b</i>}	7^{c} or 3% (ee%) ^t
1	$1a^{d}$ (88)	13.5	30 (73)	44 (70)
2	$1b^{d}$ (97)	8	33 (81)	42 (80)
3	5a (99)	13	60 (92)	30 (63)
4	5b (99)	5	61 (95)	31 (70)
5	5c (97)	13	34 (94)	56 (86)
6	5d (99)	5	$40^{e}(92)$	60 ^e (90)

^a Reaction conditions: 1 or 5 (0.184 mmol), benzene (4 mL),
 GA-SBA15 (0.037 mmol, 20%), 80 °C. ^b Determined by chiral HPLC. ^c Isolated yield. ^d 21% of 4 was also isolated after cyclization.
 ^e NMR ratio, completed reaction was performed on 0.033 mmol.

catalytic or in stoichiometric amount. This nanoreactor is easy to recover by simple filtration and washing. It can be reused, with no loss in yield or enantioselectivity. Current efforts to induce additional confinement effects will be reported in due course.

We are grateful for the financial support from the ANR-10-JCJC-0710-MOCER2.

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