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Efficient and recyclable rare earth-based catalysts for Friedel–Crafts acylations under microwave heating: dendrimers show the way[†]

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The catalytic system involving $Sc(OTf)_3$ and a dendritic terpyridine ligand is able to promote the Friedel–Crafts acylation of a wide range of aromatics under microwave irradiation. The expected products are obtained in high yields after short reaction times and the nano-sized catalyst can be recovered and successfully used in 12 consecutive runs.

Lewis acid (LA) catalysis provides access to unique reactivity and selectivity under mild conditions. Although various types of Lewis acids have been developed and used in industry, most of the reported systems require strictly anhydrous conditions and/or stoichiometric amounts.¹ Therefore, the search for more robust Lewis acids attracted much attention and in these lines,² rare earth triflates ($RE(OTf)_3$) revealed appealing candidates.³ Indeed, RE(OTf)₃ are air- and moisture-stable and can be used in catalytic amounts in various reactions.³ Noteworthy, although the development of recyclable catalysts appears as one of the most exciting challenges for chemists, the recycling of RE(OTf)₃ has only been scarcely studied. The few methodologies published so far, generally displaying low recycling capabilities, involve the extraction of RE(OTf)₃ in water (with removing of water between two runs under harsh conditions: 190 °C/vacuum),⁴ their encapsulation in ionic liquids⁵ or their immobilization on solid supports.^{6,7} Besides, we and others demonstrated that dendritic supports generally offer the possibility to recover and reuse catalysts.^{8,9} Beyond this advantage, dendritic ligands may strongly enhance the catalytic activity of the metal ('dendritic effect').8,9g,10 We also recently reported their surprising ability to dramatically decrease palladium leaching in Suzuki couplings.^{9k} Moreover, terpyridines constitute attractive ligands of a wide range of metals due to their strong π -acceptor character¹¹ and their thermal stability¹² and the corresponding complexes are able to promote a wide

We focused on Friedel-Crafts (FC) arene acylation [eqn (1)], one of the most efficient methods for functionalizing aromatic compounds which affords access to targets or key intermediates in the pharmaceutical and agrochemical industries.¹⁶ Although these reactions are of great value in both academic and industrial contexts, more than stoichiometric amounts of Lewis acids such as AlCl₃ have to be used because of the coordination of the latter to the aromatic ketones produced.^{1a,16} Moreover, the reaction has to be guenched under acidic conditions, creating large volumes of corrosive acidic wastes.¹⁷ Other catalysts involving solid Lewis acids (zeolites, clays, and metal oxides),¹⁸ methanesulfonic or trifluoroacetic anhydrides,¹⁹ indium complexes,²⁰ gallium²¹ or bismuth triflates²² have been developed but except for the last two cases, the use of stoichiometric amounts, of high quantities of additional explosive LiClO4 or of harsh temperature conditions is required. Surprisingly, despite the obvious advantages of RE (OTf)₃-based Lewis acids, their ability to promote FC acylations has been scarcely studied (<25 publications).^{4a,c,5c,d,6,23} Moreover, to our knowledge, only a few recyclable systems based on $RE(OTf)_3$ for FC acylations have been reported so far and they involve ionic liquids, $5^{c,d}$ a large excess of LiClO₄ as the cocatalyst,^{4a,c} stoichiometric amounts of RE(OTf)₃^{6c} or high temperature (160 °C).6b,7a,f

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intermediates and targets in pharmaceutical and agrochemical industries

(1)

variety of reactions.¹³ To our knowledge, although terpyridines are known to coordinate RE,¹⁴ only one example reported the use of a terpyridine–RE complex in a catalytic reaction.¹⁵ We thus planned to prepare dendritic terpyridines and to use them as ligands for RE(OTf)₃. The nanometric size of the expected resulting complexes should enable their separation from the reaction mixture and recovery by precipitation.

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Herein we report a highly stable and recyclable LA based on $Sc(OTf)_3$ and dendritic terpyridines which is able to catalytically and efficiently promote the FC acylation of aromatics with various electrophiles. Moreover, microwave (MW) activation allowed to improve the yields of aromatic ketones and to widen the substrate scope. This corresponds to the first application of dendritic terpyridines in the field of catalysis,²⁴ to the first use of terpyridine–RE complexes for FC acylation and to the second use of such complexes in catalysis. This is also the first example of a recyclable dendritic catalyst based on RE in catalysis²⁵ and the first time that MW activation is applied with dendritic catalysts.

New dendrimers **2-Gn** (n = 1, 2, 3, 4) were prepared from dendrimers **1-Gn** bearing respectively 6, 12, 24 and 48 P(S)Cl₂ end groups^{26a,b} and 4'-(4-hydroxyphenyl)-2,2':6',2''-terpyridine **3**^{26c} in the presence of cesium carbonate (Fig. 1, ESI[†]). Monomeric terpyridine **M** functionalized with a 4-methoxyphenyl substituent and mimicking the end groups of dendrimer branches was also prepared according to the literature.^{26c}

The FC acylation of anisole **4a** with acetic anhydride **5a** was first performed in acetonitrile in the presence of $Sc(OTf)_3$ (Scheme 1). In the absence of a ligand, the corresponding ketone **6a** was obtained in 60% yield. The latter decreased to 47% when using monomeric terpyridine **M** as the ligand (Sc/**M** ratio = 1 : 1). Moreover, the activity conferred on Sc by dendritic terpyridines was improved when the dendrimer generation increased (55% for **2-G**₁, 59% for **2-G**₂, 66% for **2-G**₃), the best performances being obtained with 2-G₄ for which a significant enhancement of the activity was observed (80% against 60% without ligand). Noteworthy, in all cases, the amount of ligand was calculated to reach a Sc/terpyridine moiety ratio of 1:1. Moreover, other RE(OTf)₃ tested were less efficient under the same conditions and the best performances were obtained in CH₃CN.²⁷ The observed positive dendritic effect might be due to the hydrophobic interiors of phosphorus dendrimers which are known to act as nanosponges for hydrophobic molecules.²⁸ Dendritic ligand skeletons could therefore favor the concentration of hydrophobic arenes to be acylated, thus creating a high local concentration of substrates next to the catalytic sites. The size of dendrimer interiors increasing from the first generation to the fourth one, this could contribute to explaining the increasing performances of the resulting catalyst moving from $2-G_1$ to $2-G_4$.

The conditions were then applied to other substrates and 1,3-dimethoxybenzene, 1,2-dimethoxybenzene as well as 1,3,5trimethoxybenzene could be quantitatively converted into the corresponding acylated compounds 6b, 6c and 6d (Fig. 2). More challenging substrates such as thioanisole or dimethylaniline could however not be functionalized under the same conditions. Noteworthy, the substrate scope of RE(OTf)₃ without any co-catalyst is known to be limited to strongly electron-donating arenes involving methoxy substituents.²³ⁱ Interestingly, although MWs permit acceleration of a wide range of organic transformations,²⁹ their application to RE(OTf)₃-catalyzed FC acylations has only been scarcely studied and is limited to a very narrow scope of activated substrates.^{5d,30} In the case of anisole, the yield of 6a could be improved from 80 to 99% within only 45 minutes under MW activation (30 W, Fig. 2, c) instead of 16 h under classical heating (the performances were the same in the presence of naked Sc(OTf)₃ after 45 min). Along the same lines, ketones 6b, 6c, and 6d were quantitatively obtained within only 30 minutes instead of 16 h (Fig. 2, c). Use of MWs thus enabled to greatly accelerate reactions of activated substrates. Even more interestingly, it also





Fig. 2 Acylation of different aromatic substrates in the presence of $Sc(OTf)_3$ and **2-G**₄ ^a under classical^b or MW heating^c. ^aConditions: $Sc(OTf)_3$ (0.035 mmol), **2-G**₄ (0.00035 mmol), substrate (0.35 mmol), acetic anhydride (0.70 mmol), CH₃CN (2 mL). GC yields determined by using anisole or 1,3,5-trimethoxybenzene as the standard. ^bReflux, 16 h. ^cMWs 30 W (for the corresponding temperatures: see the general procedure). ^d*para–ortho* (4 : 1).

allowed to extend the application scope of Sc(OTf)₃. Indeed, the MW-assisted acylation of thioanisole could successfully be achieved and ketone 6e, an important pharmaceutical intermediate,^{18,31} was obtained as one regioisomer in 80% yield within 2 h (Fig. 2). The substrate scope could also be extended to dimethylaniline which gave rise to ketone 6f in 95% yield as a mixture of para- and ortho-substituted arenes (para-ortho (4:1)) under the same conditions. Noteworthy, in the literature, only a few methods enable RE(OTf)₃-catalyzed FC acylation of these last two substrates and they all involve high amounts of catalyst (≥20 mol%) and/or a large excess of LiClO₄ believed to enhance the reaction rates (4 to 16 equivalents compared to the aromatic substrate).^{4a,c,23f,i} However, xylene was not functionalized under the same conditions (Fig. 2, 6g). Acylation of such unactivated benzene derivatives is indeed known to require the replacement of triflate counteranions in RE(OTf)₃ by perfluorinated anions associated with high temperatures and long reaction times (180-250 °C, 6-24 h).^{7a,23c,e,g}

The recycling ability of the dendritic catalyst based on 2-G₄ and Sc(OTf)₃ was next tested under classical heating by using 1,3-dimethoxybenzene as the substrate and under MW heating for dimethylaniline (Scheme 2). The recovery procedure was optimized and consisted of the addition of diethyl ether³² at the end of the reaction to enable the precipitation of the catalyst, and a further filtration. In the first case, the catalyst could be successfully reused twice without significant loss of activity (from 99 to 95%) but the yield of 6b decreased to 75% in the 4th run. In contrast, under MWs, the catalytic system was efficient for at least four consecutive runs without loss of activity. Noteworthy, recycling is not possible when using the monomeric terpyridine as the ligand. The superiority of MW activation in terms of recycling efficiency might be rationalized by the shorter reaction times required (2 h instead of 16) which might limit its deactivation. For all these reasons and given the fact that MW-assisted acylations are much faster and thus attractive in the context of green chemistry, we planned to test the robustness of the $Sc(OTf)_3$ -2-G₄ catalyst when changing the substrate at each run. In total, 12 consecutive reaction



Scheme 2 Recycling tests under classic or MW heating. Conditions: see Scheme 1.

cycles were carried out with little loss of activity. This work also aimed at extending the scope of $Sc(OTf)_3$ -2-G₄ to heteroarenes and other electrophiles (Table 1).

Heteroarenes such as furan, thiophene and pyrrole underwent FC acylation in the presence of **5a**, the corresponding ketones **6h**, **6i** and **6j** being quantitatively isolated within only 15 or 30 min in the first three runs (Table 1, runs 1 to 3, yields in bold characters). In the 4th run, ketone **6d** was also obtained in quantitative yield. The catalytic activity did not decrease during the first 4 uses (see yields obtained for single runs given in brackets) which is in accordance with the results obtained when recycling the catalyst in the case of dimethylaniline (Scheme 2).

The first loss of activity was observed for the 5th run, **6b** being obtained in 87% yield (bold characters) instead of the 99% expected (yield in brackets, see also Fig. 2). Nevertheless, from the 5th to the 12th run and despite the loss of activity of the catalyst (from 10 to 20% depending on the substrates), all acylated arenes could be isolated in good to excellent yields. Therefore, ketones **6a** and **6c** could be obtained in 85 and 80% yields respectively from **5a** and anisole or 1,2-dimethoxybenzene respectively (6th and 7th runs).

Moreover, the scope of the catalyst $Sc(OTf)_3$ -2- G_4 could be successfully extended to other electrophiles such as acetyl chloride **5b** (run 8) or benzoic anhydride **5c** (run 9), the corresponding arenes **6b** and **6k** being prepared in good yields (78 and 82 respectively in 1 h). Even after 9 runs, the performances of the catalyst in the case of more challenging substrates such as thioanisole and dimethylaniline were found to be competitive, **6e** and **6f** being obtained in 62 and 75% yields respectively (11th and 12th runs).

Lastly, by increasing the reaction times compared to those used for single runs, it was possible to quantitatively isolate **6f** and **6d** after 6 h and 2 h respectively instead of 2 h and 30 minutes respectively (11th and 12th runs). Such recyclability makes the catalyst $Sc(OTf)_3$ -**2**-**G**₄ one of the most efficient reported to date for FC acylation.^{4a,c,5c,d,6b}

Conclusions

In summary, dendritic terpyridines have been prepared and tested as ligands for $Sc(OTf)_3$ in FC acylation and the fourth generation dendritic ligand $2-G_4$ was found to enhance the catalytic activity of the RE. The corresponding air- and moisture-stable catalytic system is able to promote the acylation of anisole derivatives by acetic anhydride in refluxing acetonitrile and the use of MW irradiation enabled both to greatly accelerate the reactions (from 16 h to 15–45 min) and to enlarge the substrate scope to poorly reactive thioanisole and aniline derivatives. The application field could next be extended to heteroarenes and other acylating agents such as acyl chlorides and less reactive anhydrides. The reported catalyst is very competitive in terms of catalytic performances (high yields, very short reaction times: 15 minutes to 2 h) and recycling abilities (12 successful consecutive runs). Dendritic terpyridine ligands

Table 1 R	ecycling of the catalyst based on	Sc(OTf) ₃ and dendritic terpyridine 2	2-G ₄ by changing the substrate at each run ^a
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	Ar—I or Het—	H O + X T	Sc(OTf) ₃ (10 mol%) 2-G ₄ (0.1 mol%) Ar—C(O)R pryvridine moiety per Sc or CH ₃ CN, MW irradiation Het—C(O)R 6a-k		
	Substrate	RCOX	Product	Time	Yield ^b
Run 1		5a	MeOC 6h	15 min	99 (99)
Run 2	S	5a	MeOC S 6i	15 min	99 (99)
Run 3	NH	5a	MeOC H 6j	30 min	99 (99)
Run 4	MeO OMe	5a	COMe MeO 6d	30 min	99 (99)
Run 5	MeO	5a		30 min	87 (99)
Run 6	MeO	5a		45 min	85 (99)
Run 7	MeO MeO	5a	MeO MeO COMe	30 min	80 (99)
Run 8	MeO	5b	6c MeO 6b COMe	1 h	78 (88)
Run 9	MeO	5c		1 h	82 (90)
Run 10	MeS	5a	MeS 6e COMe	2 h	62 (<i>80</i>)
Run 11	Me ₂ N	5a	Me ₂ N 6f	2 h 6 h	75 ^c (95) 96 ^c (99)
Run 12	MeO	5a	COMe MeO	2 h	98 (99)
	ÓMe		6d OMe		

^{*a*} Acylation of ArH and Het-H (0.35 mmol) with various electrophiles (0.70 mmol) in the presence of Sc(OTf)₃ (0.035 mmol) and 2-G₄ (0.00035 mmol), CH₃CN (2 mL), MWs (30 W). ^{*b*} Isolated yields when recycling the catalyst Sc(OTf)₃-2-G₄ (in bold characters) and GC yields obtained when using the catalyst for a single run in italics and brackets (GC yield determined by using 1,3-dimethoxybenzene or 1,3,5-trimethoxybenzene as the standard). ^{*c*} para-ortho (4:1).

thus allowed us to propose practical answers to specific challenges of RE catalysis and in particular those concerning the crucial need to dispose of $\text{RE}(\text{OTf})_3$ -based catalysts with high recycling capabilities (the few reported examples do generally not allow more than 4 successful reuses).^{4–6} The dendritic system also displays unprecedented recyclability compared to any other system known to promote FC acylations.^{16–22} Additionally, the recovery technique (precipitation/filtration) being convenient to apply on a large scale, the reported

catalytic Lewis acid can dramatically cut the environmental impact of AlCl₃¹⁸ currently still used on the industrial scale for FC acylations. The proposed catalytic system is also very innovative since we report here the first application of dendritic terpyridines to the field of catalysis,²⁴ the first use of terpyridine–RE complexes for FC acylation and the second use of such complexes in catalysis.²⁵ This is also the first example of a recyclable dendritic catalyst based on RE in these reactions and the first time that MW activation is applied with dendritic catalysts. Studies on the nature of catalytic species formed in the FC reactions as well as the extension of the application field of our RE(OTf)₃-based catalytic system to FC acylation of very challenging unactivated benzene derivatives as well as to other reactions are now under way.

Experimental

General procedure for recycling tests under microwaves

A CEM, Discover, SP apparatus was used for all reactions under MW irradiation. A 10 mL reactor equipped with a magnetic stirring bar was charged with $Sc(OTf)_3$ (0.035 mmol, 15.0 mg), 2-G₄ (0.00035 mmol, 18.1 mg) and CH₃CN (2 mL). After 15 minutes stirring at room temperature, arene (0.35 mmol) and an acylating agent (0.70 mmol) were introduced. The tube was closed, stirred, and heated by MWs (30 W) for the required time period. After cooling to room temperature, Et₂O (8 mL) was added and the resulting precipitate filtered and washed twice with Et₂O (5 mL). The filtrate was concentrated under vacuum and the expected product isolated by column chromatography if necessary. The precipitate was directly used for a new catalytic run: CH₃CN (2 mL), arene (0.35 mmol) and an acylating agent (0.70 mmol) were introduced. The flask was closed, stirred and heated by MWs for the required time period.

Note: The maximum temperature reached in the reaction mixtures mainly depends on the reaction time and to a lesser extent on the substrate. The temperature is in the range of 130–140 °C for reactions of less than 45 min and in the range of 150–160 °C for reaction times exceeding one hour (in all cases, the pressure did not exceed 2 bars in the reactor). Noteworthy, the performances of acylations at these temperatures (130–160 °C) under classic heating were the same as those obtained in refluxing CH₃CN.

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