Green Chemistry

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DOI: 10.1039/C4GC01990C

Cite this: DOI: 10.1039/c0xx00000x

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COMMUNICATIONS

Simple metal salts supported on Montmorillonite as recyclable catalysts for intramolecular hydroalkoxylation of double bonds in conventional and VOC exempt solvents

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Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X
DOI: 10.1039/b000000x

We describe herein an efficient and particularly sustainable catalytic system for the intramolecular hydroalkoxylation of double bonds. A heteregenous catalyst based on the impregnation of benign metals such as iron and bismuth on Montmorillonite was used for a highly atom-economical transformation in DMC, a non-VOC solvant. The transformation allowed the formation of a large range of cyclic ethers from the corresponding unsaturated alcohols and the catalyst could be recycled several times.

Intramolecular hydroalkoxylation of olefins is the most straightforward and atom-economical route to cyclic ethers. The reaction can be promoted or catalysed by a large variety of Bronsted or Lewis acids in homogeneous conditions[1,2] heterogeneous catalysts such as zeolites.[3,4] The methodology has proven its utility in the synthesis of fine chemicals including bioactives[5-7] and fragrant molecules,[8,9] for example (Fig. 1).

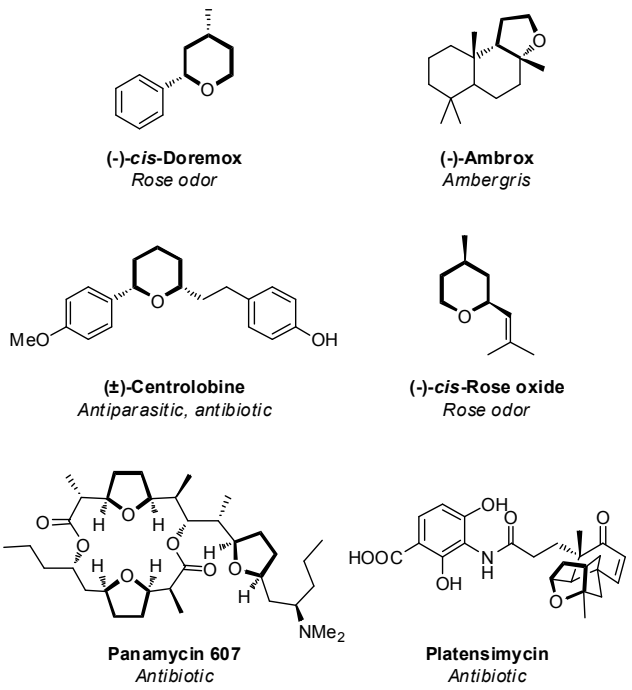

Fig. 1. Fine chemicals featuring cyclic ether frameworks obtained by intramolecular double bonds hydroalkoxylation.

To go beyond the laboratory towards large-scale applications, the ideal catalyst should however not only by efficient in terms of yields and selectivity, but also offer recycling capabilities. To achieve this goal, various stategies have been developped including for example the use of solid acid catalysts[10] such as zeolites[11-14] or acidic resins (Amberlyst, nafion),[15,16] attachment of metal complexes or salts to a solid support such as silica[17,18] or nafion[19] by physisorption, or by covalent linkage of one or more ligand.[20] The non-covalent linkage of catalysts onto solid supports has been developped with success through "catch and release" strategies.[21] Recently, supported metal nanoparticles (e.g. gold nanoparticles) have appeared in the litterature as efficient catalysts in various chemical processes.[22-26]

We have been looking for a cheap and readily available unprocessed solid material to support simple metal salts and use these supported metals as catalysts for the intramolecular hydroalkoxylation of double bonds. In this regards, Montmorillonite (MMT) appeared very appealing to us to provide supported metal catalysts with limited footprints among other advantages as supporting material.[27,28] We previously reported the use of MMT-supported gallium species as catalyst for 1,6-enynes cycloisomerisation.[29]

The catalysts were prepared by impregnation of solutions of sustainable metals salts such as $BiCl_3$, $FeCl_3$, and $CuCl_2$ in MeOH. Under an inert atmosphere, 10 mmol of anhydrous precursor was added to 10 g of pre-lyophilised MMT and 50 mL of MeOH. The mixture was stirred vigorously for 4 hours, filtered and then triturated in a minimum of methanol. The material was dried under vacuum for 24 h and stored under inert atmosphere. Characterisation of the catalysts involved ICP-MS titration of the metal contents, indicating 4.87% w/w for Bi@MMT, 2.67% w/w for Fe@MMT, and 2.04% w/w for Cu@MMT. Small angle XRD analysis confirmed the insertion of metal cations in the MMT interlayers. In the case of Bi-MMT, signals attributed to crystals of BiOCl, presumably formed upon hydrolysis within the MMT, could be observed. Those cations are under their most stable oxidation state (Bi^{3+}, Fe^{3+}/Fe^{2+} (53/47) and Cu^{2+}) as witnessed by XPS analysis (See Electronic Supplementary Information).

We started our study with a screening of the reaction conditions and solvents including conventional and VOC exempt solvents

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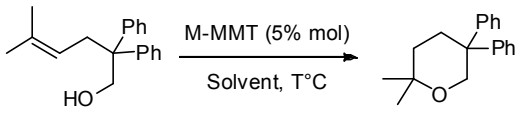
such as dimethyl carbonate (DMC) and 2-methyltetrahydrofuran (Table 1). DMC is particularly attractive since it is considered non-VOC thanks to its low vapour pressure (2400 Pa, to be compared to 2340 for water and 29000 for toluene), and have good solvent properties (bp=90 °C, δ=3.1, μ=0.91 D).[30]

DMC and nitromethane appeared as the most suitable solvents for the model reaction of olefinic alcohol **1a** converted with total Markovnikov regioselectivity to cyclic ether **1b**. With Bi-MMT, yields beyond 75% in 5 hours at 80 °C were obtained (entries 1,2). Reaction in acetonitrile needed prolonged reaction times (24 h, entry 3) to proceed efficiently, while the other tested solvents gave moderate results within the same reaction time (30-70%, entries 4-7).



1a **1b**

Table 1. Solvents and conditions screening[a]

Entry	M	Solvent	T (°C)	Time (hr)	GC Yield[b]
1	Bi	DMC	80	5	76%
2	Bi	CH_3NO_2	80	5	77%
3	Bi	CH_3CN	80	24	76%
4	Bi	$CH_3(CO)CH_3$	80	24	70%
5	Bi	2-Me-THF	80	24	20%
6	Bi	AcOEt	80	24	45%
7	Bi	DCE	80	24	60%
8	**Fe**	**DMC**	**80**	**7**	**86%**
9	Fe	CH_3NO_2	80	24	83%
10	Cu	DMC	80	24	36%
11	Cu	CH_3NO_2	80	24	81%
12	Bi	CH_3NO_2	30	24	77%
13	Fe	CH_3NO_2	30	4	80%
14	Cu	CH_3NO_2	30	24	7%
15	MMT	CH_3NO_2	80	7	0%
16	-	CH_3NO_2	80	24	0%

[a] Reaction conditions: substrate (0.25 mmol), anhydrous and degassed solvent (1 mL) and catalyst (5 mol% metal/substrate ratio). [b] Determined by GC-TCD by external calibration. Trace of hydroarylation product **1b'** resulting from the 6-*endo*-trig addition of one phenyl group across the double bond could be observed.

We only focused on DMC and nitromethane for further catalysts testing and obtained again very good isolated yields of cyclic ether with Fe-MMT (entries 8,9). With Cu-MMT, the reaction proceeded poorly in DMC with a low 31% yield, while in nitromethane 81% yield was obtained (entries 10,11). In a last set of experiments, the temparature was lowered to 30°C and the reaction conducted in nitromethane. Bi-MMT yielded 77% of product after 24 hrs (entry 12), but Fe-MMT was the most efficent catalyst in these conditions with 80% isolated yield after only 4 hrs (entry 13). Cu-MMT did not allow to reach 10% yield at this temperature (entry 14). Control experiments without metal (MMT alone) and without additives were performed and showed no background reaction (entries 15,16). The performance of these supported catalysts was compared with their homogeneous counterparts. Thus, the reaction of **1a** was performed with 5 mol% $FeCl_3$ and $BiCl_3$ in DMC at 80 °C. After 7 hrs, cyclic product **1b** was formed in 76% yield with $FeCl_3$, along with 5% of Friedel-Crafts product **1b'**. With $BiCl_3$, substrate **1a** was recovered unchanged, indicating the presence of the active Bi species in the heterogeneous reaction within the solid catalyst and not in solution phase after leaching from the support. Thus, supported catalysts Fe-MMT and Bi-MMT were equal or superior to their homogeneous equivalents in terms of both activity and selectivity.

Fe-MMT being identified as the most potent catalyst, we further performed a recycling study in our optimised conditions in DMC (Fig. 2). Satisfyingly, the Fe-MMT catalyst could be recycled 4 times and at the 5th cycle still allowed to reach 80% yield of cyclised product **1b** upon total conversion of **1a**. This result suggested that the possible leaching of iron species was not significant in DMC at 80 °C. It is interesting to note that the recycling capacities in CH_3NO_2 were found to be lower (ESI page S13).

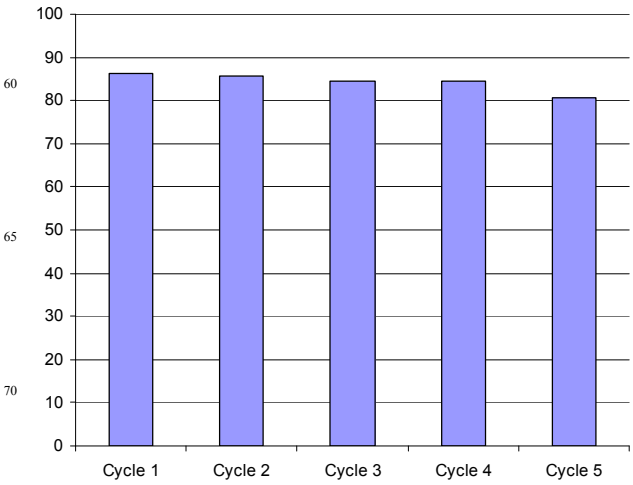


Fig. 2. Recycling studies. Yields of **1b** in % obtained after 7 hrs at 80 °C in DMC with recycled Fe-MMT.

To further estimate the possibility of leaching in these systems, kinetic plots of reactions of Fe-MMT and Bi-MMT in DMC were recorded and a hot filtration test was performed after 75 mins reaction time.[31] After removal of the catalyst, the concentration of cyclised product **1b** in the filtrate did not change over a period of 220 mins, ruling out the possibility of hidden homogeneous catalysis (ESI page S13).

With this sustainable catalytic system in hand, we next turned our attention to the reaction substrate scope (Table 2). Unsaturated secondary alcohols such **2a** and **3a** reacted readily in the presence of 5 mol% Fe-MMT in DMC at 80°C to yield regioselectively the corresponding 6-membered cyclic ethers **2b** and **3b** in excellent yields (entry 1, 2). The introduction of an aryl substituent in geminal position with the hydroxyl group as in **4a** was detrimental to the intramolecular hydroalkoxylation and the cyclic ether **4b** was formed in a modest 38%, together with 12% of styryl derivative obtained upon the dehydration of **4a** (entry 3). The high mass loss observed was presumably due to polymerisation reaction. Substrate **5a** however, with the phenyl substituent one ethylene away from the alcohol function, could efficiently cyclise to **5b** with 89% yield under the same conditions (entry 4). With *ortho*-prenylated phenol **6a**, the conversion was 81% in the same conditions, and the expected cyclic ether **6b** was formed in 63% yield (entry 5). Bis-hydroxylated substrate **7a** was prepared from biosourced glycerol and afforded a mixture of 5 and 6-membered cyclic ketals **7c** and

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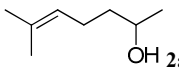
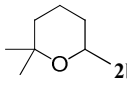
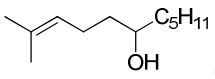
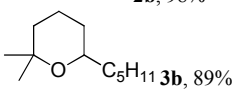
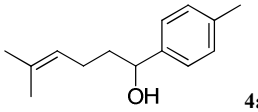
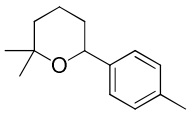
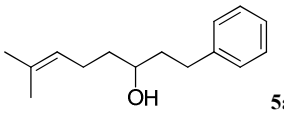
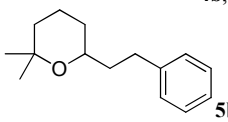
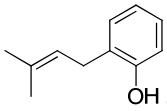
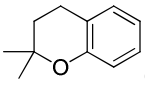
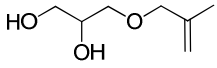
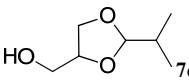
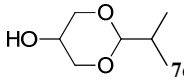
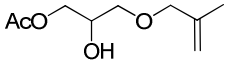
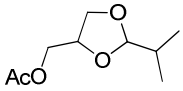
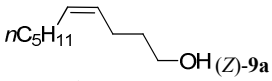
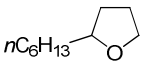
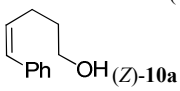
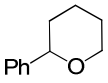
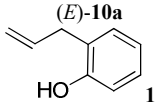
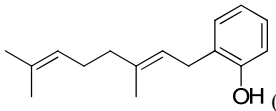
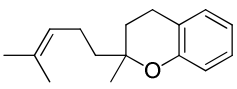
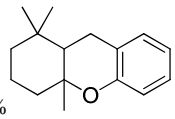
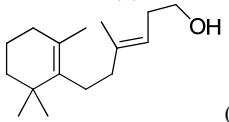
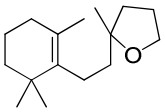
7d in 51 and 31% yield, respectively (entry 6). The reaction presumably proceeded by isomerisation/cyclisation, involving the formation of an enol ether intermediate, in a process already described with α-methallyloxy carboxylic acids in the presence of $Cu(OTf)_2$ as the catalyst.[32] Both products were formed as equimolar mixtures of diastereomers. After conversion of the primary alcohol function into its acetate, the reaction proceeded selectively towards the formation of the 5-membered ring **8c** (2 dias 1:1) in 59% yield (entry 7). TBDMS protecting group was not stable in our conditions (not shown). With a linear substrate such as **9a**, featuring an internal disubstituted double bond, the reaction required both high temperature and longer reaction time in CH_3NO_2 to reach 89% conversion and to deliver regioselectively the product **9b** in 62% yield (entry 8).

Table 2. Substrate scope[a]

Entry	Substrate	M	Solvent	T (°C)	Time (hr)	Products, Isolated Yield
1	 **2a**	Fe	DMC	80	7	 **2b**, 98%[b]
2	 **3a**	Fe	DMC	80	7	 **3b**, 89%
3	 **4a**	Fe	DMC	80	7	 **4b**, 38%[c]
4	 **5a**	Fe	DMC	80	7	 **5b**, 89%
5	 **6a**	Fe	DMC	80	7	 **6b**, 63%[d]
6	 **7a**	Fe	DMC	80	24	 **7c** (2 dias 1:1), 51%  **7d** (2 dias 1:1), 31%
7	 **8a**	Fe	DMC	80	20	 **8c** (2 dias 1:1), 59%
8	 (*Z*)-**9a**	Fe	CH_3NO_2	100	72	 **9b**, 62%[e]
9	 (*Z*)-**10a**	Fe	CH_3NO_2	100	2.5	 **10b**, Quant.
10	(*E*)-**10a**	Fe	CH_3NO_2	100	24	**10b**, Quant.
11	 **11a**	Fe	DMC	80	48	-[f]
12	**11a**	Bi	DMC	80	48	-[f]
13	 (*E*)-**12a**	Fe	DMC	80	5	 **12b**, 40%  **12b'** (*trans*/*cis* 2:1), 39%
14	(*E*)-**12a**	Bi	DMC	80	24	**12b**, 32% + **12b'** (*trans*/*cis* 2:1), 42%
15	(*E*)-**12a**	Fe	CH_3NO_2	80	5	**12b**, 21% + **12b'** (*trans*/*cis* 4:1), 79%
16	(*E*)-**12a**	Bi	CH_3NO_2	80	24	**12b'** (*trans*/*cis* 2:1), 96%
17	(*E*)-**12a**	Bi	DCE	80	24	**12b'** (*trans*/*cis* 2:1), 92%
18	 (*E*)-**13a**	Fe	DMC	80	24	 **13b**, 56%[g]
19	(*E*)-**13a**	Fe	CH_3NO_2	80	21	**13b**, 71%
20	(*E*)-**13a**	Bi	CH_3NO_2	80	21	Mixture

[a] Reaction conditions: substrate (1 mmol), anhydrous and degassed solvent (2 mL) and catalyst (5 mol% metal/substrate ratio). [b] Reaction performed in DMC-d6 using benzene as internal standard. [c] Along with 12% of dehydration product. [d] Conversion 81%. [e] Conversion 89%. Traces of 6-membered ring product were observed (~5%). [f] No conversion, quantitative recovery of the starting material. [g] Conversion 63%.

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DOI: 10.1039/C4GC01990C

Cite this: DOI: 10.1039/c0xx00000x

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Substrate (*Z*)-**10a** afforded an example of internal disubstituted double bond reacting efficiently towards the formation of the 6-membered ring **10b** obtained in an excellent 99% yield but required heating in CH_3NO_2 at 100 °C (entry 9). The presence of the phenyl substituent allowed both a perfect regiocontrol of the nucleophilic attack of the hydroxyl group and a sufficient stability of the reactive intermediates. Its stereoisomer (*E*)-**10a** reacted similarly, ableit in longer reaction time (entry 10). Substrate **11a** featuring a monosubstituted double bond did not react neither in the presence of Fe-MMT or Bi-MMT at 80 °C in DMC and was quantitatively recovered unchanged after 48 hrs (entry 11,12). Homogeneous versions of the reaction with this substrate and analogs have been previously reported to require the dual action of an aluminium-based catalyst and high temperatures (250 °C)[33] or the combination of $FeCl_3$ and silver triflate[34] as additive to proceed efficiently.

With this system in hand, we evaluated the possiblity to catalyse tandem reaction involving the formation of C-C and C-O bonds with polyunsaturated alcohols. Firstly, the *ortho*-geranylated phenol (*E*)-**12a** was reacted in the presence of 5 mol% Fe-MMT or Bi-MMT in DMC at 80°C, and a mixture of the tricyclic product **12b'** (in the form of a 2:1 diastereomeric mixture in favor of the *trans*-fused ring system), resulting from the double cyclisation of **12a**, and the monocyclic ether **12b** were obtained unselectively (entries 13,14). With Fe-MMT in CH_3NO_2, the selectivity in favour of **12b'** was increased to 79% (entry 15). Interestingly, the tricyclic product **12b'** was the sole product obtained in 96 and 92% isolated yields when the reaction was run with Bi-MMT in CH_3NO_2 and DCE, respectively (entries 16, 17). In an effort to obtain the commercial odorant Ambrox®, we tested our system for a tandem reaction with substrate (*E*)-**13a**. However, in contrast with the case of substrate (*E*)-**12a**, only one single cyclisation was observed to yield the tetrahydrofuran derivative **13b** in 56-71% yield (entries 18, 19). The use of Bi-MMT resulted in the formation of a mixture of isomerised products in the same reaction conditions, but no tandem product (entry 20).

To proceed, the tandem reaction requires the initial activation of the terminal double bond followed by an ene-reaction with the internal double bond, the resulting carbenium ion being trapped intramolecularly by the hydroxyl group. In the reaction of (*E*)-**12a**, Bi-MMT, featuring a large cation (ionic radius[35] for Bi^{3+}=0.96-1.17 Å) could only activate the terminal double bond and favour the selective formation of the tandem product, while Fe-MMT, featuring smaller cations (0.49-0.78 Å), could interact with both double bonds and led unselectively to a mixture of products. With (*E*)-**13a**, the remote double bond is too hindered, and only the internal double bond is activated by the catalyst followed by the nucleophilic attack of the hydroxyl group leading to the tetrahydrofuranic product.

Conclusions

In summary, we have developped and described herein an efficient and particularly sustainable catalytic system based on the use of benign metals such as iron and bismuth supported on a natural inorganic material to allow for an highly atom-economical transformation in DMC, a non-VOC solvant. The transformation allowed the formation of a large range of cyclic ethers from the corresponding unsaturated alcohols by intramolecular hydroalkoxylation and the catalyst could be recycled several times.

Acknowledgements

This work was supported by the University Nice Sophia Antipolis, the CNRS, and the ANR program CD2I (Nanocausys project, grant number 12-CDII-0010-02). We are grateful to Dr Charles Fehr (Firmenich, CH) for a kind gift of compound (*E*)-**13a** and Dr Cyril Aymonier and Baptiste Giroire from ICMCB (Bordeaux, France) for material analyses.

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† Electronic Supplementary Information (ESI) available: Procedures and full spectral data of products and catalysts. See DOI: 10.1039/b000000x/

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