Regiodivergent Isosorbide Acylation by Oxidative NHC-Catalysis in Batch and Continuous-Flow

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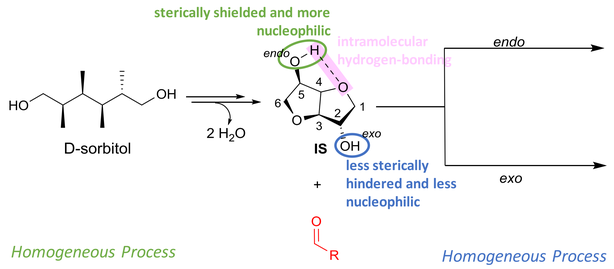
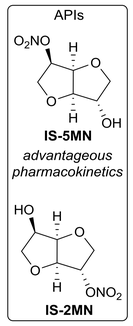
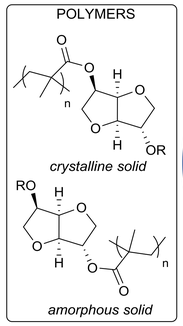






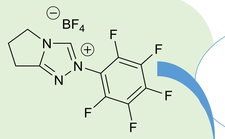
IS is a chiral, rigid, non-toxic diol derived from glucose, which displays a bi-heterocyclic V-shaped backbone made of two fused furan units bearing two secondary non-equivalent hydroxyl groups at C5 and C2 positions in endo and exo configurations, respectively

The regioselective functionalization of the 2- and 5-hydroxyl groups is a thriving strategy to obtain high-added valued IS-based products with different chemical, biological, and physical properties

In this context we describe an unprecedent N-heterocyclic carbene (NHC)-organocatalyzed strategy under oxidative conditions for the fully regiodivergent synthesis of endo and exo monoacyl-isosorbides (MAIs), using aldehydes as mild acylating agents, in homogeneous and heterogeneous phase catalysis processes

Homogeneous Process

EN DO

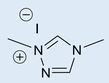


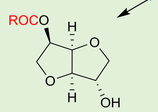
Oxidative Conditions
NHC HX
Base
Oxidant

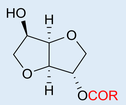
N-heterocyclic carbene (NHC)-catalyzed synthesis of endo and exo monoacyl-isosorbides (MAIs)

Homogeneous Process

EX O

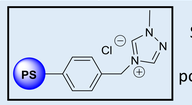




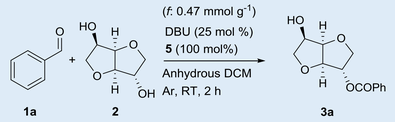


*From Homogeneous Process to **Heterogeneous Process** in **Batch Conditions***

Heterogeneous catalysis in Batch Conditions



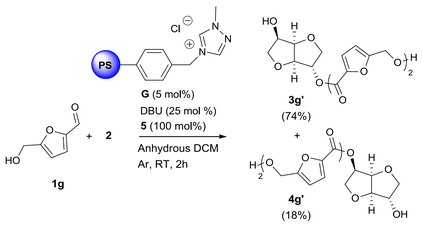
Supported NHC catalyst onto polystyrene matrix



Time (h)	Yield(%) b	exo/endo (%) c
3	80	4.4

[a]**1a** (0.50 mmol), **2** (1.50 mmol), anhydrous solvent (4.0 mL). [b]Detected by ^{1}H NMR of the crude reaction mixture with durene as an internal standard. [c]Selectivity detected by ^{1}H NMR of the crude reaction mixture. [d]Fifth recycle.

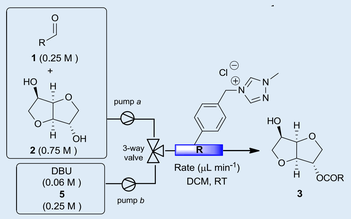
Isosorbide acylation with 5-HMF



Useful applications of Hereogeneous processes in Batch and Continous Flow Conditions

*From Heterogeneous Process in Batch Conditions to **Hereogeneous Process** in **Continous Flow Conditions***

Continuous-flow production of *exo*-MAIs **3**



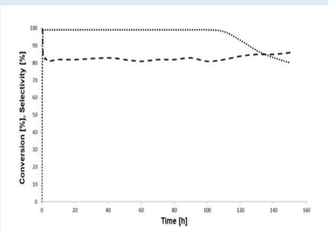
Main features of packed-bed mesoreactor **R**

Loaded G [g][a]	V_G [mL][b]	V_o [mL][c]	Total Porosity [d]	Time [min][e]	Pressure [bar][f]
1.2	1.66	1.29	0.78	26	3

[a]Calculated by difference with catalyst amount in the residual slurry solution. [b]Geometric volume (V_G) of the stainless-steel column. [c]Void volume (V_o) determined by pycnometry. [d]Total porosity ε_{tot}= V_o/V_G. [e]Residence time calculated at 50 µLmin^{-1}. [f]Backpressure measured at 50 µLmin^{-1} (RT, DCM).

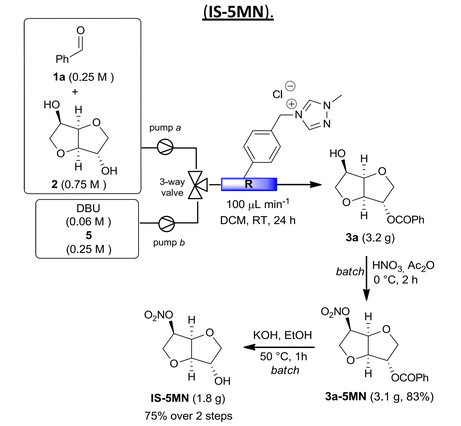
Entry	Exo-MAI 3 (conv. [%])[b]	Rate (µL min^{-1})	Exo/endo (%)[c]	P[d]
1	3a (>95)	100	4.6	1.32
2	3c (>95)	100	4.0	1.32
3	3e (90)	40	4.3	0.48
4	3f (>95)	100	5.3	1.32
5	3h (93)	100	4.3	1.24

[b]Instant conversion in the steady-state regime as determined by ^{1}H NMR analysis. [c]Established by ^{1}H NMR analysis of the collected reaction mixture. [d]Productivities (*P*) are measured in mmol h^{-1} mmol$_{cat}^{-1}$ (see the SI for details)



Long-term stability experiment (**1a**-IS coupling). Conversion [%], dotted line; **3a** selectivity [%], dashed line.

Three-step (flow and batch) synthesis of isosorbide-5-mononitrate **(IS-5MN).**



Entry	Aldehyde	4 (%)[b]	endo:exo[c]
1	1a	4a (75)	5.3
2	1b	4b (73)	4.9
3	1c	4c (75)	4.6
4	1d	4d (71)	3.8
5	1e	4e (73)	4.3
6	1f	4f (45)	3.3
7[d]	1g	4g (60)	4.0
8	1h	4h (76)	4.6

D (5 mol%), NEt_3 (25 mol %), 5 (100 mol%), Anhydrous DMSO, Ar, RT

[a]**1a-h** (0.5 mmol), **2** (1.5 mmol), anhydrous DMSO (4.0 mL). Isolated yields of *exo*-MAIs **3** and diesters **6** are reported in SI. [b]Isolated yield. [c]Selectivity detected by ^{1}H NMR of the crude reaction mixture. [d]**2** (20 equiv., 10.0 mmol).

Entry	Aldehyde	3 (%)[b]	exo:endo[c]
1	1a	3a (72)	4.6
2	1b	3b (70)	4.3
3	1c	3c (71)	4.0
4	1d	3d (68)	3.5
5	1e	3e (74)	4.3
6	1f	3f (74)	5.3
7[d]	1g	3g (65)	4.0
8	1h	3h (76)	4.6

C (5 mol%), DBU (25 mol %), 5 (100 mol%), Anhydrous THF, Ar, RT

[a]**1a-h** (0.5 mmol), **2** (1.5 mmol), anhydrous THF (4.0 mL). Isolated yields of *endo*-MAIs **4** and diesters **6** are reported in the SI. [b]Isolated yield. [c]Selectivity detected by ^{1}H NMR of the crude reaction mixture. [d]**2** (20 equiv., 10.0 mmol).