Electronic Supplementary Information (ESI)

A salt made of 4-N,N-Dimethylaminopyridine (DMAP) and saccharin as an efficient recyclable acylation catalyst: a new bridge between heterogeneous and homogeneous catalysis†

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Experimental Section

General. Gas chromatographic/mass spectrometric data were obtained using an Agilent 6890 Series gas chromatograph with a series 5973 mass selective detector. The GC monitoring employed a HP 6890 GC using a 30 m x 0.250 mm HP-1 capillary column with a 0.25 μm stationary phase film thickness. Infrared spectra were obtained on a Perkin Elmer RX I FT-IR Spectrometer. NMR spectra were recorded on Bruker AM 500 and Joel 200 using 5 mm sample tubes. The residual peaks of D_2O or $CDCl_3$ was used as the reference peaks for ^{1}H or ^{13}C NMR spectra. Elemental Analysis was done by the staff of the National Taiwan University Elemental Analysis Laboratory. The X-ray diffraction data of catalyst **1** were collected at 200 K employing a Bruker (Nonius BV) CCD diffractometer; the structure was solved by successive Fourier maps.

Preparation of catalyst 1

The 100 mL round bottomed flask was charged with 4-(*N,N*-Dimethylamino)pyridine (DMAP; 4.09 mmol, 500 mg) and equimolar of saccharin (4.09 mmol, 500 mg) followed by the addition of 20 mL THF as solvent. Then the reaction mixture was set to react in THF, at *ca* 60 °C for overnight. After the reaction, the solvent was removed by vacuum. The crude product (1.24 g; yield= 99%) was then obtained. Recrystallization proceeded with dissolution of crude product in methanol to form a saturated solution, to which a hexane overlayer (*ca* 10 cm high) was added. Solvent diffusion over a period of a week at room temperature afforded white needle-shaped crystals of catalyst **1**.

Analytical data of catalyst **1**

Analytical data of catalyst **1**: Yield (purified): 95 %, mp: 218 °C.

^{1}H NMR (500 MHz, D_2O) δ 7.90 (d, 2H, *J* = 7.5 Hz, C_5H_4N-), 7.76-7.71 (m, 4H, C_6H_4-; Saccharin H), 6.72 (d, 2H, *J* = 7.59 Hz, C_5H_4N-), 3.12 (s, 6H, CH_3); ^{13}C NMR (126 MHz, D_2O) δ 39.6, 107.0, 142.3, 157.6 (C's on the DMAP) 120.6, 123.9, 132.7, 133.6, 134.1, 138.3, 172.6 (C's on the Saccharin).

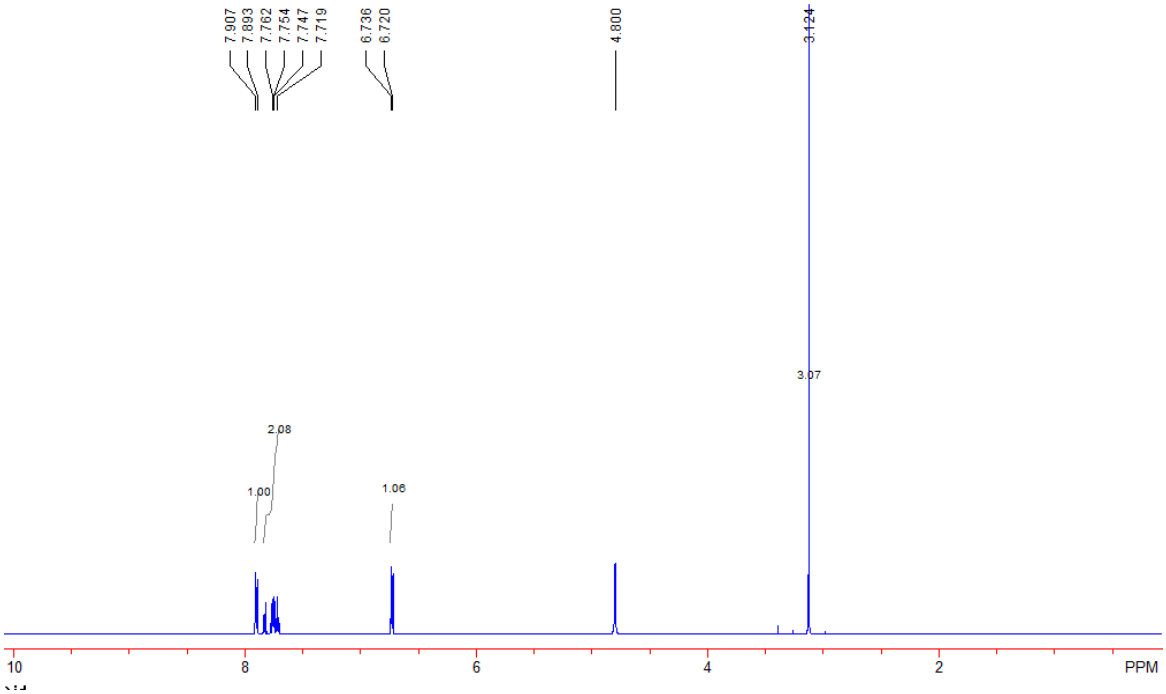
FT-IR ν (cm^{-1}) 3077s (N-H), 1646s (C=O, stretch), 1542, 1443m (pyridine), 1329, 1163, 1130, (R-SO_2-N), 1270s (N-CH_3).

Anal. Found：C 54.50; H 4.85; N 13.50;

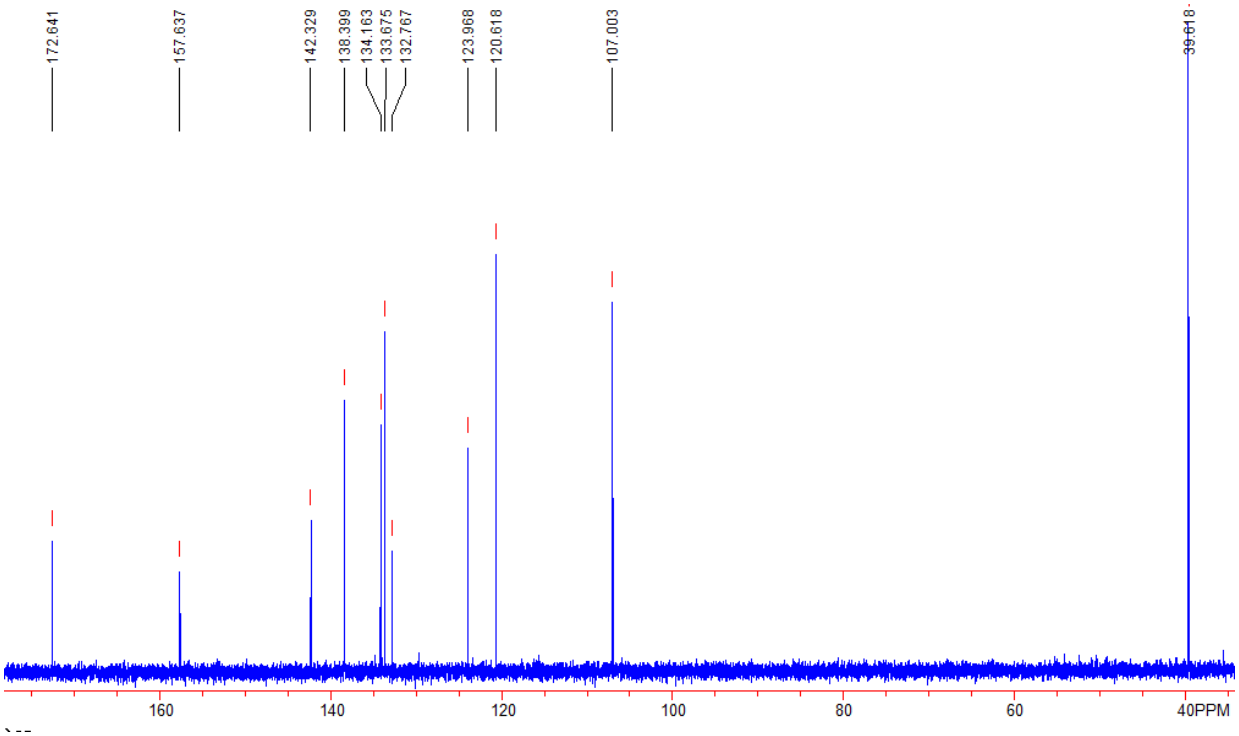
Calcd for $C_{14}H_{15}N_3O_3S$: C 55.07; H 4.95; N 13.76.

NMR spectra of catalyst **1:** (^{1}H NMR and ^{13}C NMR spectra)

^{1}H NMR spectrum



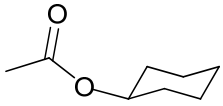
^{13}C NMR spectrum



General procedure for the DMAP.saccharin-catalysed esterification

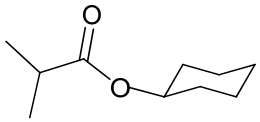
The alcohol (2 mmol) and the anhydride (2.2 mmol) were mixed in a 10 mL test tube and 1 mol% of catalyst **1** (0.02 mmol) was added. The tube was then capped (or under N_2 purge) and the reaction mixture was stirred at room temperature (except for 1-methylcyclopentanol at 60 °C). After a couple of hours the acid effluent was evaporated in vacuum. The residue was then allowed to cool to room temperature and the catalyst was precipitated by adding 2 mL hexane (or toluene). After filtration, catalyst **1** was recovered, and then evaporating solvent from the filtrate afforded the crude ester product. The recovered catalyst **1** was charged with the substrates, and the reaction mixture was then proceeded to the next run. The products were quantified with GC analysis by comparison to NMP as an internal standard. In Table 1, the products from the 1st run were all further purified by the column chromatography, and the isolated yields from all the 1st runs were in good agreement with those from GC/MS data listed in Table 1.

All the **1**-catalyzed esterification products from Table 1 are known compounds. The products (**1, 2, 5, 6** and **8-15**) have been checked by GC/MS, NMR spectrometer and m.p. if the product is a solid. These known compounds that exhibited spectroscopic data identical to those reported in the literature[1-10] are listed below.



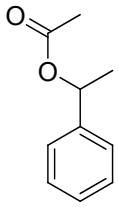
(**a**)[1]

a. Prod. 1: Cyclohexyl acetate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (m, H, OC*H*-), 2.01 (s, 3H, CH_3), 1.87-1.85 (m, 2H, C*H*-), 1.75-1.71 (m, 2H, C*H*-), 1.57-1.54 (m, 2H, CH_2-), 1.45-1.22 (m, 4H, CH_2-).
$C_6H_{11}OC(O)CH_3$, GC/MS (m/z; EI): 142 (M^+), 99 (M^+-C_2H_3O), 83 (M^+-$C_2H_3O_2$), 43 ($C_2H_3O^+$).



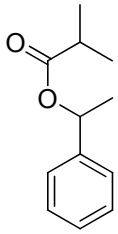
(**b**)[2]

b. Prod. 2: Cyclohexyl isobutyrate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (m, H, OC*H*-), 2.46 (sept, H, *J* = 6.8 Hz, O=CC*H*-), 1.83-1.78 (m, 2H, C*H*-), 1.72-1.68 (m, 2H, C*H*-), 1.53-1.49 (m, 2H, CH_2-), 1.44-1.23 (m, 4H, CH_2-), 1.11 (d, 6H, *J* = 6.8 Hz, CH_3).
$C_6H_{11}OC(O)CH(CH_3)_2$, GC/MS (m/z; EI): 170 (M^+), 127 (M^+-C_3H_7), 99 (M^+-C_4H_7O), 83 (M^+-$C_4H_7O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).



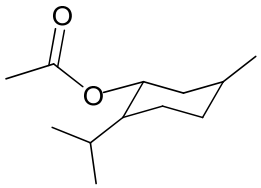
(**c**)[3]

c. Prod. 5: 1-phenylethyl acetate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H, C_6H_5-), 7.27 (m, H, C_6H_5-), 5.88 (q, H, J = 6.8 Hz, OC*H*-), 2.05 (s, 3H, CH_3), 1.53 (d, 3H, J = 6.8 Hz, CH_3).
$PhCH(CH_3)OC(O)CH_3$, GC/MS (m/z; EI): 164 (M^+), 121 (M^+-C_2H_3O), 105 (M^+-$C_2H_3O_2$), 77 (M^+-$C_4H_7O_2$), 43 ($C_2H_3O^+$).



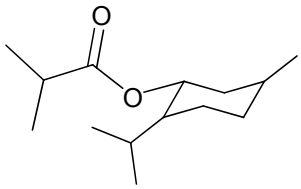
(**d**)[4]

d. Prod. 6: 1-phenylethyl isobutyrate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 4H, C_6H_5-), 7.27 (m, H, C_6H_5-), 5.87 (q, H, J = 6.8 Hz, OC*H*-), 2.57 (sept, H, J = 6.8 Hz, O=CC*H*-), 1.53 (d, 3H, J = 6.8 Hz, CH_3), 1.19 (d, 3H, J = 7.1 Hz, CH_3), 1.17 (d, 3H, J = 7.1 Hz, CH_3).
$PhCH(CH_3)OC(O)CH(CH_3)_2$, GC/MS (m/z; EI): 192 ($M^+$), 121 ($M^+$-$C_4H_7O$), 105 ($M^+$-$C_4H_7O_2$), 77 ($M^+$- $C_6H_{11}O_2$), 43 ($C_3H_7^+$).



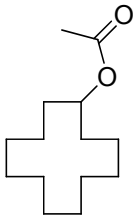
(**e**)[5]

e. Prod. 8: 2-isopropyl-5-methylcyclohexyl acetate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (dt, H, J = 4.3 Hz and 11.1 Hz, OC*H*-), 1.95 (s, 3H, CH_3), 1.92 (d, H, J = 11.9 Hz, C*H*-), 1.79 (dsept, H, J = 2.6 Hz and 6.8 Hz, C*H*-), 1.63-1.57 (m, 2H, CH_2-), 1.44-1.37 (m, H, C*H*-), 1.28 (tt, H, J = 2.6 Hz and 11.1 Hz, C*H*-), 0.99 (dq, H, J = 3.4 Hz and 9.4 Hz, C*H*-), 0.88 (q, H, J = 11.1 Hz, C*H*-), 0.83 (d, 3H, J = 3.4 Hz, CH_3), 0.82 (d, 3H, J = 3.4 Hz, CH_3), 0.81 (m, H, C*H*-), 0.69 (d, 3H, J = 7.7 Hz, CH_3).
2-$CH(CH_3)_2$-5-$CH_3C_6H_9OC(O)CH_3$, GC/MS (m/z; EI): 198 (M^+), 139 (M^+-$C_2H_3O_2$), 124 (M^+-$C_3H_6O_2$), 96 (M^+- $C_5H_{10}O_2$), 81 (M^+-$C_6H_{13}O_2$), 43 ($C_2H_3O^+$).



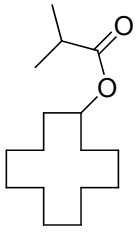
(**f**)[6]

f. Prod. 9: 2-isopropyl-5-methylcyclohexyl isobutyrate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.60 (m, H, OC*H*-), 2.43 (sept, H, *J* = 6.8 Hz, O=CC*H*-), 1.89 (d, H, *J* = 11.9 Hz, C*H*-), 1.81 (dsept, H, *J* = 2.6 Hz and 6.8 Hz, C*H*-), 1.63-1.57 (m, 2H, CH_2-), 1.43-1.39 (m, H, C*H*-), 1.31 (tt, H, *J* = 2.6 Hz and 11.1 Hz, C*H*-), 1.08 (d, 3H, *J* = 3.4 Hz, CH_3), 1.07 (d, 3H, *J* = 3.4 Hz, CH_3), 0.98 (dq, H, *J* = 3.4 Hz and 9.4 Hz, C*H*-), 0.87 (q, H, *J* = 11.1 Hz, C*H*-), 0.83 (d, 3H, *J* = 3.4 Hz, CH_3), 0.81 (d, 3H, *J* = 3.4 Hz, CH_3), 0.75 (m, H, C*H*-), 0.68 (d, 3H, *J* = 6.8 Hz, CH_3).
2-CH$(CH_3)_2$-5-$CH_3C_6H_9$OC(O)CH$(CH_3)_2$, GC/MS (m/z; EI): 226 (M^+), 139 (M^+-$C_4H_7O_2$), 124 (M^+-$C_5H_{10}O_2$), 96 (M^+- $C_7H_{14}O_2$), 81 (M^+-$C_8H_{17}O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).



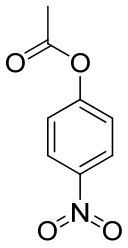
(**g**)[7]

g. Prod. 10: Cyclododecyl acetate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.02 (m, H, OC*H*-), 2.04 (s, 3H, CH_3), 1.72 (hex, 2H, *J* = 6.8 Hz, CH_2-), 1.52 - 1.29 (m, 20H, CH_2-).
$C_{12}H_{23}$OC(O)CH_3, GC/MS (m/z; EI): 226 (M^+), 167 (M^+-$C_2H_3O_2$), 43 ($C_2H_3O^+$).



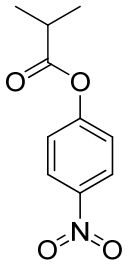
(**h**)[8]

h. Prod. 11: Cyclododecyl isobutyrate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (m, H, OC*H*-), 2.51 (sept, H, *J* = 6.8 Hz, O=CC*H*-), 1.71 ((hex, 2H, *J* = 6.8 Hz, CH_2-), 1.54 -1.28 (m, 20H, CH_2-), 1.16 (d, 6H, *J* = 6.8 Hz, CH_3).
$C_{12}H_{23}$OC(O)CH$(CH_3)_2$, GC/MS (m/z; EI): 254 (M^+), 211 (M^+-C_3H_7), 167 (M^+-$C_4H_7O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).



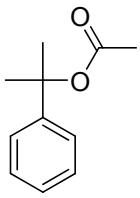
(**i**)[9]

i. Prod. 12. 4-nitrophenyl acetate; pale yellow solid, m.p: 77 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (d, 2H, *J* = 8.7 Hz, C_6H_4-), 7.26 (d, 2H, *J* = 8.7 Hz, C_6H_4-), 2.32 (s, 3H, CH_3).
4-$NO_2PhOC(O)CH_3$, GC/MS (m/z; EI): 181 (M^+), 138 (M^+-C_2H_3O), 122 (M^+-$C_2H_3O_2$), 92 (M^+-$C_2H_3NO_3$), 43 ($C_2H_3O^+$).



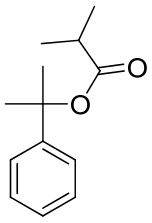
(**j**)[10]

j. Prod. 13: 4-nitrophenyl isobutyrate; pale yellow solid, m.p: 39.4 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 2H, *J* = 8.6 Hz, C_6H_4-), 7.25 (d, 2H, *J* = 8.6 Hz, C_6H_4-), 2.81 (sept, H, *J* = 6.8 Hz, O=CC*H*-), 1.30 (d, 6H, *J* = 6.8 Hz, CH_3).
4-$NO_2PhOC(O)CH(CH_3)_2$, GC/MS (m/z; EI): 209 (M^+), 138 (M^+-C_4H_7O), 122 (M^+-$C_4H_7O_2$), 92 (M^+-$C_2H_3NO_3$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).



(**k**)[10]

k. Prod. 14: dimethylbenzyl acetate; colorless liquid
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 4H, C_6H_5-), 7.28 (t, H, *J* = 6.8Hz, C_6H_5-), 2.07 (s, 3H, CH_3), 1.82 (s, 6H, CH_3).
$PhCH(CH_3)_2OC(O)CH_3$, GC/MS (m/z; EI): 178 (M^+), 135 (M^+-C_2H_3O), 119 (M^+-$C_2H_3O_2$), 91 (M^+-$C_4H_7O_2$),77 (M^+-$C_5H_9O_2$), 43 ($C_2H_3O^+$).



(**l**)[10]

l. Prod. 15: dimethylbenzyl isobutyrate; pale yellow solid, m.p: 72.4 °C
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 4H, C_6H_5-), 7.27 (t, H, J = 6.8Hz, C_6H_5-), 2.57 (sept, H, J = 6.8Hz, O=CC*H*-), 1.81 (s, 6H, CH_3), 1.20 (d, 6H, J = 6.8 Hz, CH_3).
$PhCH(CH_3)_2OC(O)CH(CH_3)_2$, GC/MS (m/z; EI): 206 ($M^+$), 135 ($M^+$-$C_4H_7O$), 119 ($M^+$-$C_4H_7O_2$), 91 ($M^+$- $C_6H_{11}O_2$), 71 ($C_4H_7O^+$), 43 ($C_3H_7^+$).

Table A

We also compared our results with those from Ishihara *et al.* who used DMAP as a catalyst reported in 2007 JACS paper.[10] These comparisons are shown in Table A. (The entries 4 and 5 from their Table 1 are quoted and listed below in the entries 10 and 11, respectively):

Table A. Comparison of DMAP.saccharin-catalysed and DMAP-catalysed acylation.

entry[i]	Catalyst loading	substrate	anhydride (R=)	Time (h)	Yield (%)
8	1% (DMAP.saccharin)	*l*-menthol	Me	8	97
9	1% (DMAP.saccharin)	*l*-menthol	iPr	8	98
10[ii]	0.5% DMAP	*l*-menthol	Me	9	84
11[ii]	0.5% DMAP	*l*-menthol	iPr	9	98

[i]The same entry numbers used here as those in the manuscript; [ii]We also repeated the same reactions (DMAP-catalysed acylations), and the outcomes were almost the same as those reported by Ishihara *et al.*

From Table A above, we can easily see that the results from either DMAP-catalysed or DMAP.sacchain-catalysed acylations are similar. Taken the catalyst loading into consideration, then the results from DMAP-catalysed acylation are only slightly better than those reported by us. Because the rate-determining step[11] of esterification of this type is the reaction of the N-acylpyridinium carboxylate with the alcohol, neither DMAP nor the auxiliary base (e.g. NEt_3) enters the kinetic equation. Thus, although the generation of some free DMAP in the reaction system is important for the catalytic activity, it is not DMAP itself, but the N-acylpyridinium carboxylate[11] directly participating the rate determining step.

X-ray Study (The CIF data of catalyst **1** are uploaded separately.)

X-Ray crystallographic data of catalyst **1** (CCDC 817088): C14H15N3O3S, Mr 305.35, P 21/c, a= 7.1258(2) b= 14.8941(5) c= 13.4114(5) Å, α= 90 β= 92.103(2) γ= 90°, V 1422.43(8) Å^3, Z 4, T= 200 K, No of refln. 2423, GoF 1.181, R 0.0924, [I > 2s(I)], Rw 0.2651.

The reaction of saccharin with pyridine, aliphatic diimine, and bipyridine derivatives have been reported,[12,13] where one 7-membered, robust synthon **1** with simultaneous N^+-H…O(=C) and C-H…N^- interactions was found specific, as shown in Fig. A.

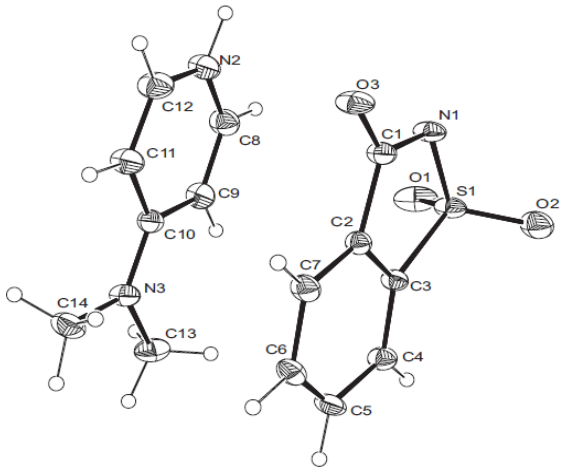
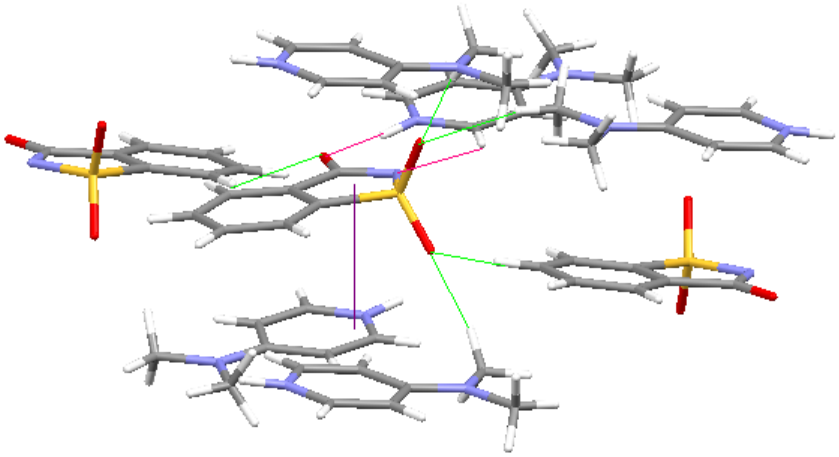


Fig. A. The X-ray structure of the salt made of DMAP and saccharin; the short ionic N1-S1 bond [1.619(5) Å] is noticed.[12]

As shown in Figure B below, forming 7-membered, robust synthon is the primary stabilizing force for the DMAP.saccharin adduct. The partial π-π stacking interactions of the aromatic ring systems from the DMAP and the saccharin also contribute to the stabilization of the DMAP.saccharin salt. Furthermore, the secondary stabilizing forces are several weak C–H…O(=S) H-bonding interactions, which includes the three H-bondings formed by the interactions of two O atoms from SO_2 group with the three methyl H atoms from the three different -NMe_2 groups in the neighborhood, and the one H-bonding formed by the interaction of the aromatic H from the phenyl ring with one O atom of SO_2 group. [Interaction distance: three C–H…O(=S) H-bondings 2.48(1), 2.48(1) and 2.66(1) Å; one aromatic C–H…O(=S) H-bonding 2.62(1) Å.]

Additionally, the carbonyl O atom mainly participates in the synthon formation, and also forms the weak H-bond [distance: 2.48(1) Å] with the phenyl H atom from another saccharin molecule nearby.



[Note: Pink lines indicating the synthon; purple line indicating the partial π-π interaction; green lines indicating the weak H-bond interactions. (O: orange, N: blue, S: yellow, C: grey, H: white)]

Fig. B The drawing of the crystal of DMAP.saccharin to show the hydrogen bonding interactions.

Table B

The acylation of 1-cyclohexanol with acetic anhydride was demonstrated for the recovery and reuse. (More than 99% of catalyst was recycled after each cycle for total 8 times.)

Table B. The recovery studies of the catalyst **1** after reuse.

Entry	Recovered catalyst **1** [g; %]	Yield (%)	Entry	Recovered catalyst **1** [g; %]	Yield (%)
1	0.151 ; 99.3	>99	5	0.144; 98.6	>99
2	0.150; 99.3	>99	6	0.142; 98.6	>99
3	0.148; 98.7	>99	7	0.140; 98.6	>99
4	0.146; 98.6	>99	8	0.138; 98.6	>99

Reaction conditions: 1-cyclohexanol (50 mmol; 200.3 mg), 1 mol % catalyst **1** (152.7 mg), neat reaction at 25 °C.

Kinetic Studies (Figure C; conversion as a function of time.)

The 1 mol% of catalyst **1** (or saccharin or no catalyst) was used for acylation of 1-cyclohexanol (50 mmol; 200.3 mg) with acetic anhydride (*ca* 50 mmol). The resulting acylation reaction of acetic anhydride was monitored at 25 °C for the set time intervals - by taking out small (negligible) amounts of the reaction mixture for GC/MS analysis at the set intervals. The conversion was calculated from the GC/MS results using NMP as the internal standard.

Furthermore, the kinetic plot of the esterification of 1-cyclohexanol with acetic anhydride has been studied and shown in Fig. C below. When catalyst **1** was used, the esterification was completed within 2 hours. In contrast, almost no reaction was happening without catalyst **1**. The saccharin is a weak acid, so the saccaharin-catalysed esterification of 1-cyclohexanol was also studied.

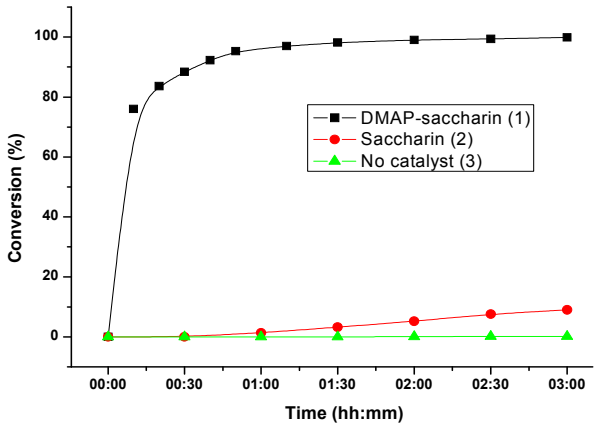


Fig. C Kinetic plot of the esterification of 1-cyclohexanol with acetic anhydride using the catalyst (1,■) DMAP.saccharin, (2,●) saccharin or (3,▲) no catalyst.

Alternative procedures of recovering the catalytic system (the referee's suggestions and general comments: the catalyst precipitates from hexane or toluene; could the authors give more information about the possibility to employ other solvents to recover the catalyst, when the solubility profiles of the products are similar to the DMAP.saccharin adduct ?)

Response: The DMAP.saccharin adduct (salt) is soluble in polar solvents- e.g. methanol, water and so on. This salt is insoluble in non-polar solvents. Thus, besides hexane and toluene, one can also add pentane or heptane to make the catalyst precipitate. When the solubility profiles of the products are similar to the catalyst adduct, we'll suggest to use the water. Because most of organic products are not water soluble, the water will be a good solvent to dissolve the DMAP.saccharin salt and then the organic products and the aqueous solution can be easily separated in this way. After drying the salt by removing the water, the recovered catalyst can then be used for the following runs.

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