Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Supporting Information

Elucidating Absolute Configuration of Unsaturated Alcohols Via Enantioselective Acylation Reactions

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General

(*S*)-(−)-4-dimethylaminopyridinyl(pentaphenylcyclopentadienyl)iron, (or (*S*)-C_5Ph_5-DMAP, CAS # 187596-69-6) and (*R*)-(+)-4-dimethylaminopyridinyl (pentaphenylcyclopentadienyl)iron (or (*R*)-C_5Ph_5-DMAP, CAS # 187682-64-0) were purchased from Strem Chemicals, Newburyport MA, 01950 USA. (*S*)-(–)-1-phenylethanol, (*R*)-(+)-1-phenylethanol, (*S*)-(–)-3-butyn-2-ol and (*R*)-(+)-3-butyn-2-ol were purchased from Alfa Aesar. Unless otherwise noted, all other reagents were purchased from Sigma-Aldrich. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz Bruker NMR spectromter. Silica gel chromatography was completed using 70-230 mesh silica gel (Silicyle, G60) and TLC was completed using Silica gel 60 F254 glass plates (EMD). TLC plates were visualized using UV light (254 nm), iodine chamber, and anisaldehyde stain or CAM stain.

Sample experiment (TLC) (depending on selectivity factor of individual compound in different solvents, *t*-amyl alcohol can often be substituted for other solvents such as $CHCl_3$).

1) Clearly label vials as (+) and (−).
2) Sample to be analyzed is divided equally between the two new, clearly labelled vials (6.4 μmol / vial). To the (+) and (−) labelled reactions, *t*-amyl alcohol (100 μL) is added. Sonication and/or gentle heating may be required to aid in dissolution.
3) Triethylamine (100 μL of 0.64 M solution in *t*-amyl alcohol, 64 μmol) is then added to the (+) and (−) labelled vials.
4) (+)-DMAP-C_5Ph_5 or (−)-DMAP-C_5Ph_5 (100 μL of 6.4 mM catalyst, requires heating/sonication to dissolve) are then added to their respective vials, sonicated to ensure dissolution, capped and placed in a chemical refrigerator for 15 minutes.
5) After the elapsed time, acetic anhydride (100 μL of 0.64 M solution) is added to each of the reaction vials and the time is recorded. Each of the samples is then

capped, wrapped with parafilm, sonicated and then returned to the chemical refrigerator.

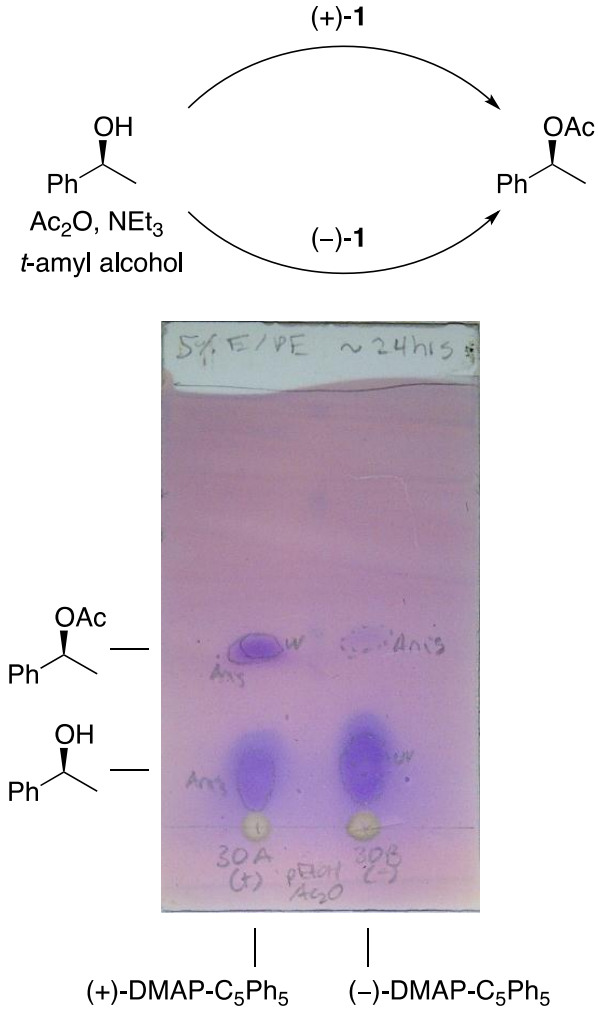
6) A third sample-containing vial can also be used to prepare a standard. It is dissolved in DCM (100 μL) along with acetic anhydride (100 μL of 0.64 M solution in DCM), triethylamine (100 μL of 0.64 M solution in DCM), DMAP (100 μL of 6.4 mM catalyst in DCM) and is then placed into the chemical refrigerator.
7) Identical volumes of sample (typically 10 μL) are removed from each sample for immediate analysis after 0.5, 1, 2, 4, 8, 24 and 48 hours (or as required). It is essential that all samples are handled in an identical fashion.

Analysis

TLC

Reactions to be compared are run beside each other on the same glass-backed TLC plate. The reaction vial containing the achiral DMAP catalyst is used to identify and optimize the Rf of the acetylated product before eluting the (+) and (−) samples. An identical volume of reaction mixture is removed from the reaction vials (10 μL) and spotted directly onto the TLC plate. The use of separate microsyringes is recommended. To minimize the diameter of the spot, a stream of air is used to evaporate *t*-amyl alcohol between individual spots (5 seconds per spot until entire 10 μL volume has been deposited onto TLC plate; this is avoided by use of more volatile solvents such as $CHCl_3$). After elution of the plate using an appropriate solvent system, the TLC plate is allowed to air dry and is then visualized using UV (254 nm) and anisaldehyde stain. Other stains work as well (CAM, Goofy, iodine) but the colors produced by anisaldehyde stain often allow for improved comparison between adjacent spots.

Note that *t*-amyl alcohol stains well with the above stains so removal of the solvent before elution will assist with the comparison.



SI-Figure 1. TLC taken after 25.5 hours of reaction time, Eluent: 5% EtOAc/40-60°C Pet. Ether, Visualization: UV (254 nm) and anisaldehyde stain. The reaction on the left (catalyzed by (+)-DMAP-C_5Ph_5) is proceeding more quickly than the reaction on the right (catalyzed by (–)-DMAP-C_5Ph_5). Note that *t*-amyl alcohol also stains in the TLC staining conditions.

NMR Analysis

Reactions are set up as described above while adjusting the concentrations for a final volume of 800 µL and substituting *t*-amyl alcohol for deuterated solvent (Note: the catalyst selectivity factor differs for different solvents) directly into NMR tubes. All comparisons shown in the manuscript were completed using $CDCl_3$ based on availability and price.

Sample reaction: (*S*)-(−)-1-phenylethanol

1) Clearly label 3 NMR tubes as (+), (−) and DMAP.
2) Sample to be analyzed is dissolved in $CDCl_3$ (300 μL) and divided equally between the three new, clearly labelled tubes (12.8 μmol / tube).
3) Triethylamine (100 μL of 1.28 M solution in $CDCl_3$, 128 μmol) is then added to each tube.
4) (+)-DMAP-C_5Ph_5, (−)-DMAP-C_5Ph_5 or DMAP (1.28 mmol, 100 μL of 12.8 mM, catalyst solution in $CDCl_3$) are then added to their respective vessels, sonicated to ensure dissolution, capped and placed in a chemical refrigerator for 15 minutes.
5) After the elapsed time, acetic anhydride (100 μL of 1.28 M solution) is added to each of the NMR tubes and the time is recorded. Each of the samples is then capped, shaken, and then returned to the chemical refrigerator.
6) After 0.5, 1, 2, 4, 8, 24 and 48 hours (or as required), all samples are removed from the refrigerator at the same time, the spectra are immediately recorded, and all samples are again returned to the refrigerator. It is essential that all samples are handled in an identical fashion.

1-Phenylethyl acetate[1]

TLC R_f 0.41 (5% EtOAc/40-60°C petroleum ether); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.38-7.27 (m, 5H), 5.89 (q, J = 6.6 Hz, 1H), 2.07 (s, 3H), 1.53 (d, J = 6.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.3, 141.7, 128.5, 127.9, 126.1, 72.3, 22.2, 21.3.

But-3-yn-2-yl acetate[2]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 5.40 (qd, J = 6.7, 2.1 Hz, 1H), 2.42 (d, , J = 2.1 Hz, 1H), 2.05 (s, 3H), 1.47 (d, J = 6.7 Hz, 3H).

[1] Chen, P.; Qu, J. *J. Org. Chem.* **2011**, *76*, 2994-3004.
[2] Sheppard, G. S. *et al. J. Med. Chem.* **2006**, 49, 3832-3849.

[(2R,6S,2′′S)-2′′-O-Acetyllobeline [(S)-2-[(2S,6R)-1-Methyl-6-(2-oxo-2-phenylethyl) piperidin-2-yl]-1-phenylethyl acetate]][3]

Integrals used to monitor reaction progress: ^{1}H-NMR (400 MHz, $CDCl_3$)

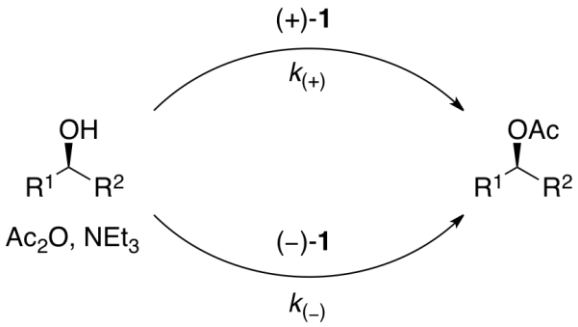
Starting material - 4.84-4.75 (m); Product - 5.77-5.68 (m).

(1*R*,2*S*)-3-((*tert*-butyldimethylsilyl)oxy)-2-(2,2-dichloroacetamido)-1-(4-nitro phenyl)propyl acetate

Integrals used to monitor reaction progress: ^{1}H-NMR (400 MHz, $CDCl_3$)

Starting material 8.16-8.10 (m); Product – 8.24-8.17 (m).

After determining which reaction proceeds more quickly (+ or −), the results are compared to a known model system or to the predictive model outlined in figure 2.



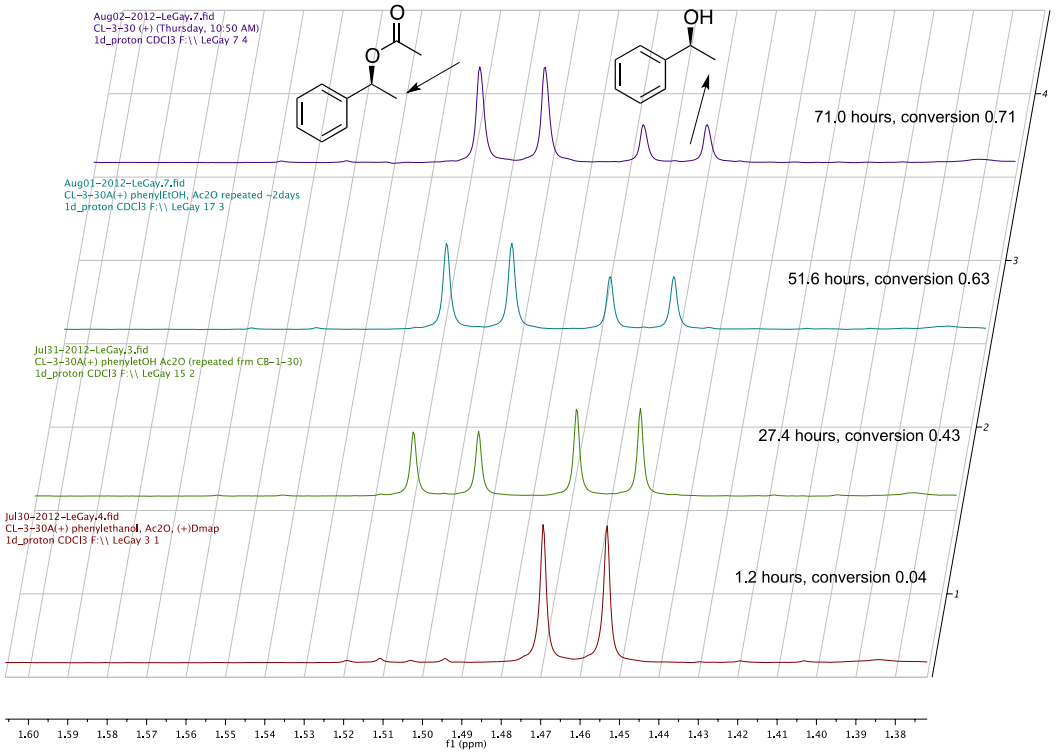
-If $k_{(+)} > k_{(-)}$, R^1 = unsaturated, R^2 = alkyl.

-If $k_{(+)} < k_{(-)}$, R^1 = alkyl, R^2 = unsaturated.

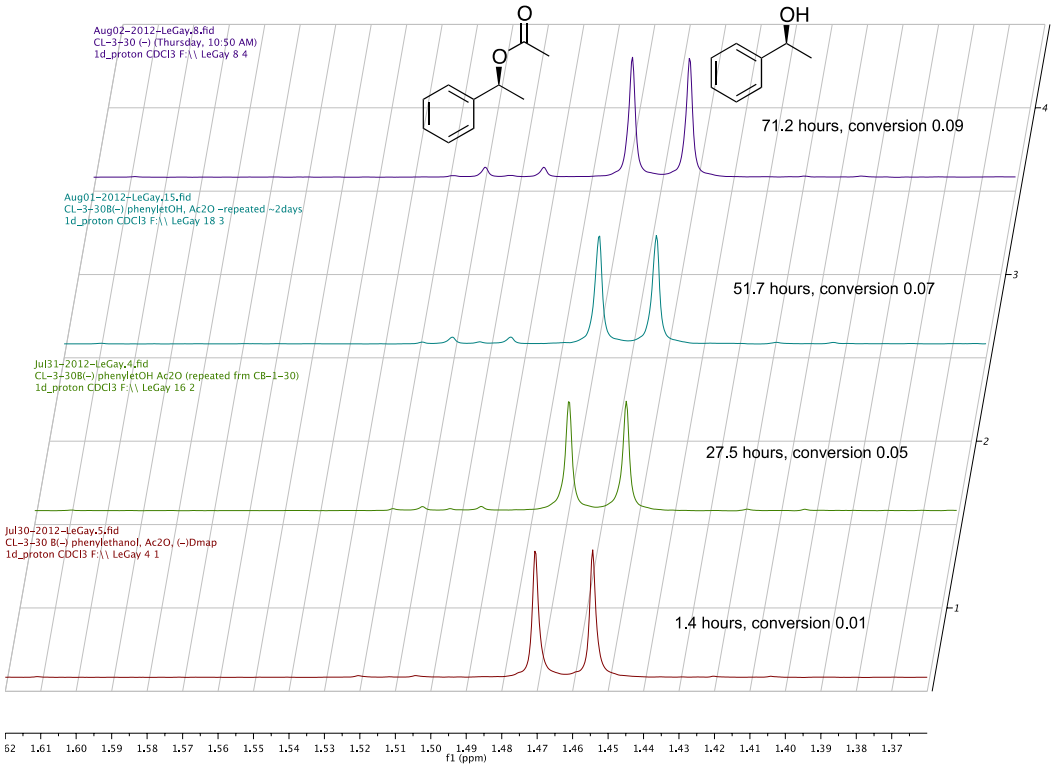
[3] Kesting, J. R.; Tolderlund, I.-L.; Pederson, A. F.; Witt, M.; Jaroszewski, J. W.; Staerk, D. *J. Nat. Prod.* **2009**, *72*, 312.

References:

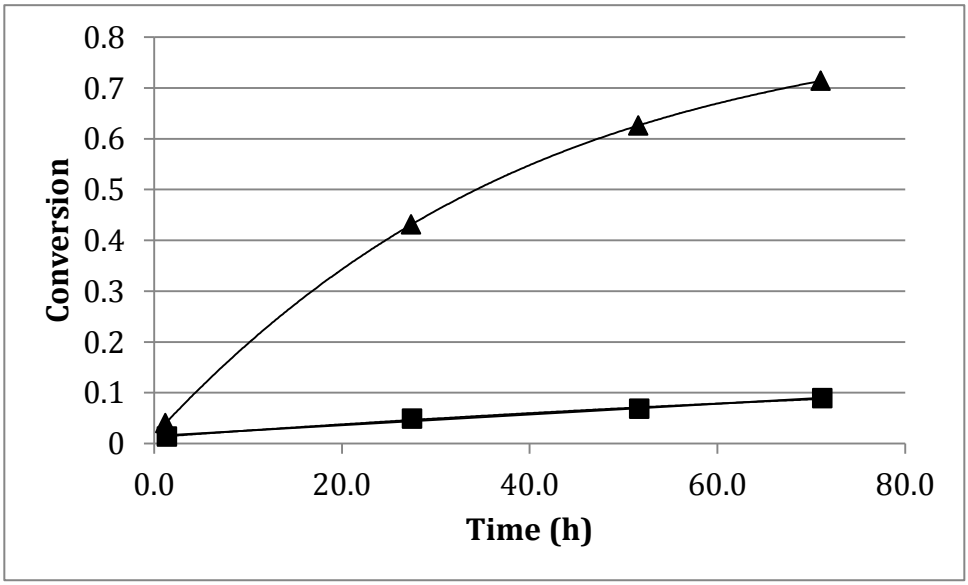
- Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542.
- Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794.
- Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009.
- Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am Chem. Soc.* **1997**, *119*, 1492.



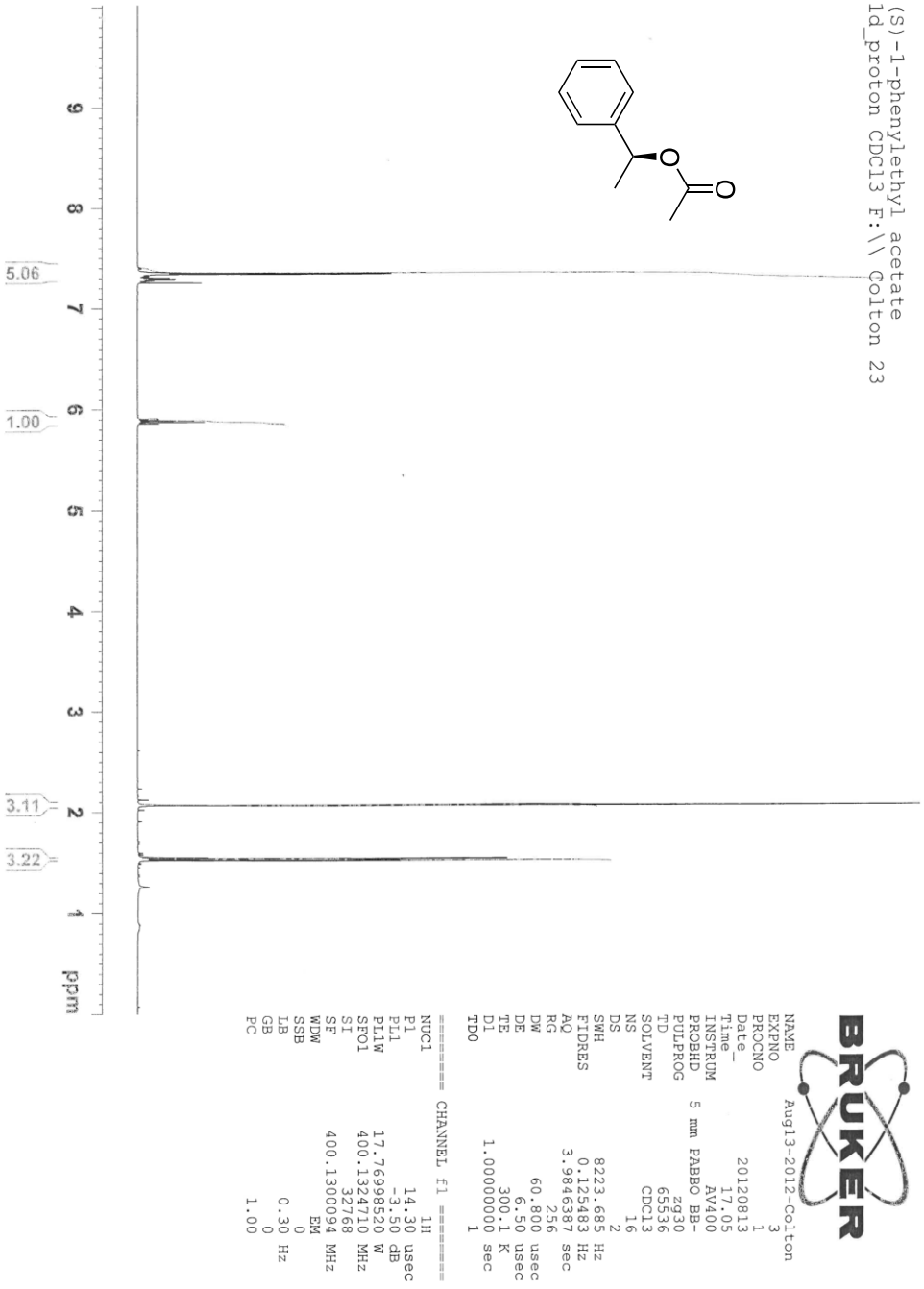
SI-Figure 2. Expansion of NMR spectra of enantioselective acylation of Compound 2 using (+)-DMAP C_5Ph_5 recorded over 71 hours. Indicated methyl protons of starting material (2) occur at 1.46 ppm while indicated methyl protons of acetylated product occur at 1.5 ppm.

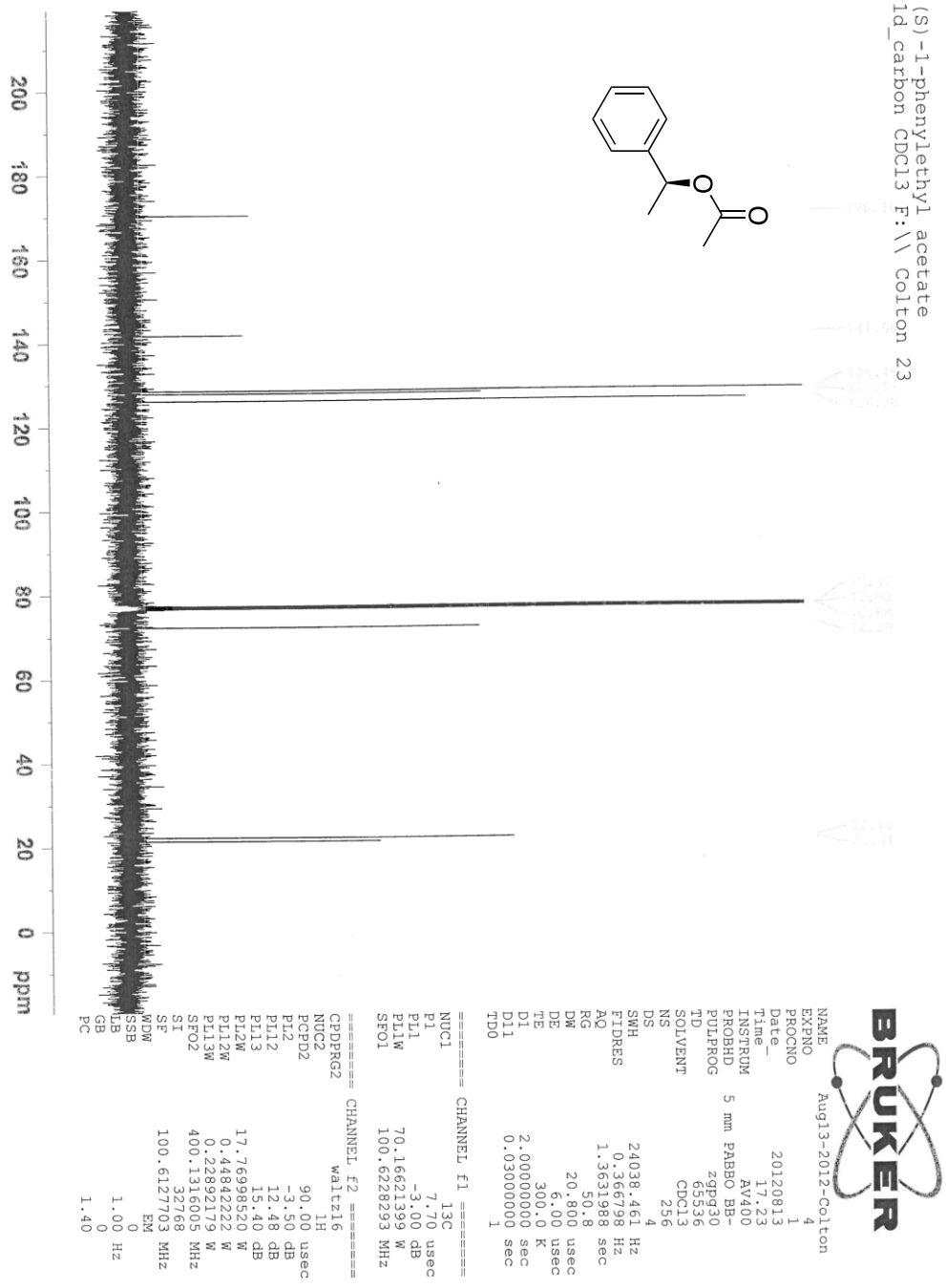


SI-Figure 3. Expansion of NMR spectra of enantioselective acylation of S-(–)-1-phenylethanol using (–)-DMAP C_5Ph_5 recorded over 71 hours. Indicated methyl protons of starting material (2) occur at 1.46 ppm while indicated methyl protons of acetylated product (3) occur at 1.5 ppm.

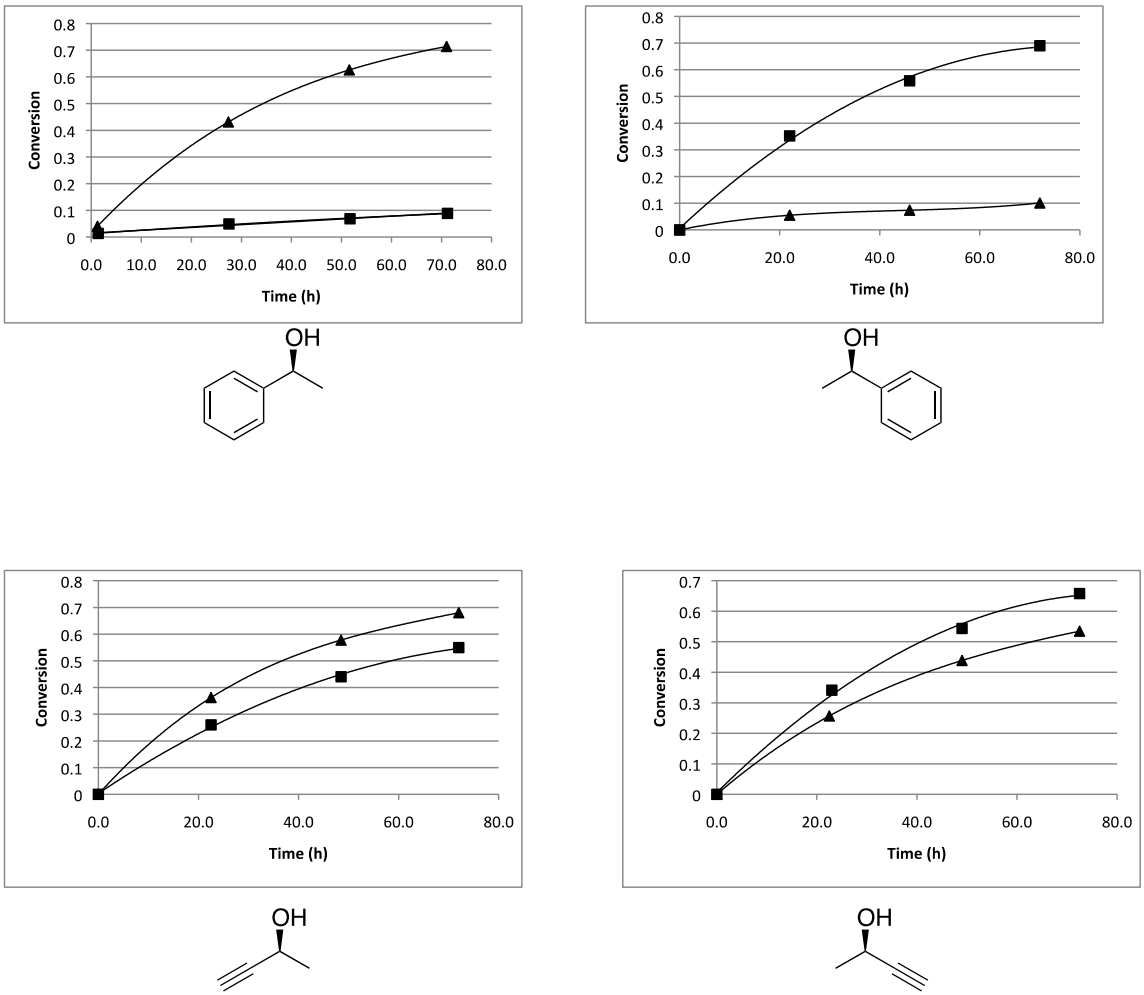


SI-Figure 4. Comparison of conversion from SI-Figures 2 and 3. (+)-DMAP-C_5Ph_5 (triangles) and (-)-DMAP-C_5Ph_5 squares.




(S)-1-phenylethyl acetate
1d_carbon CDCl3 F:\\ Colton 23
BRUKER
200
180
160
140
120
100
80
60
40
20
0
ppm

Comparison of reaction progress in $CDCl_3$ according to page SI-5.
Triangles = (+)-DMAP-C_5Ph_5
Squares = (–)-DMAP- C_5Ph_5



SI-Figure 5. Comparison of reactions progress according to page SI-5. Solvent $CDCl_3$. (+)-DMAP-C_5Ph_5 (triangles) and (-)-DMAP-C_5Ph_5 squares.

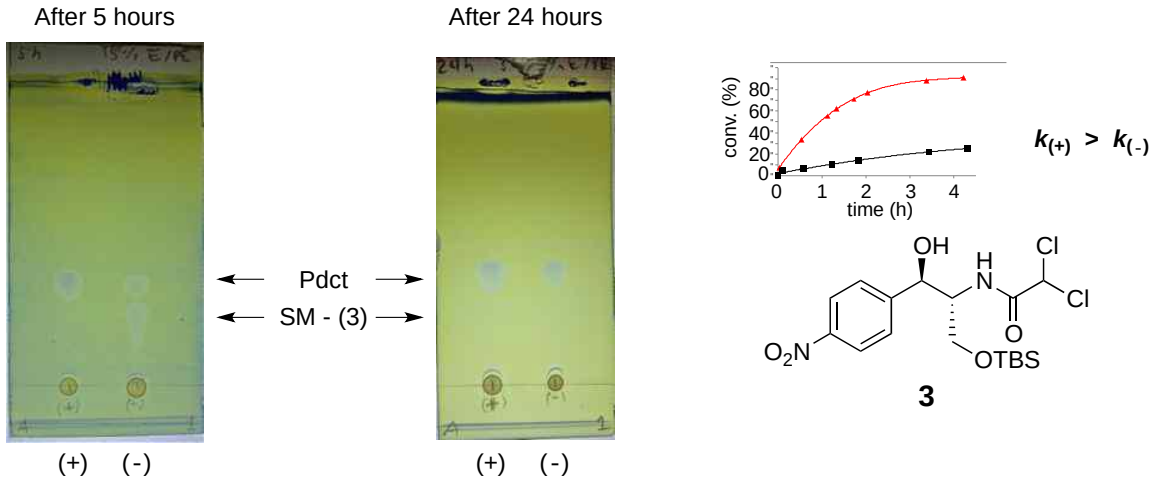


Figure 6. Acylation of TBS-protected chloramphenicol in $CHCl_3$ (3). Left: TLC comparison of (+) and (-) catalyzed reactions after 5 hours (left) and 24 hours(center), ((+) catalyst on left, (-) catalyst on right, Goofy stain). Note that the (+)-catalyzed reaction does not contain starting material after 5 hours. After 24 hours, both reactions have consumed the starting material. TLC plates eluted in 15% EtOAc/40-60 Pet. Ether, eluted 3 times. Right: acylation rates of 3: Conversion vs. time (h)((+)-DMAP-C_5Ph_5 (triangles) and (-)-DMAP-C_5Ph_5 squares).