Supporting Information

Elucidating Absolute Configuration of Unsaturated Alcohols Via Enantioselective Acylation Reactions

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General

(S)-(−)-4-dimethylaminopyridinyl(pentaphenylcyclopentadienyl)iron, (or (S)-C₅Ph₅-DMAP, CAS # 187596-69-6) and (R)-(+)4-dimethylaminopyridinyl (pentaphenylcyclopentadienyl)iron (or (R)-C₅Ph₅-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 ¹³C NMR spectra were recorded on a 400 MHz Bruker NMR spectrometer. Silica gel chromatography was completed using 70-230 mesh silica gel (Silicycle, 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 CHCl₃).

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-C₅Ph₅ or (−)-DMAP-C₅Ph₅ (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 CHCl₃). 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-C₅Ph₅) is proceeding more quickly than the reaction on the right (catalyzed by (−)-DMAP-C₅Ph₅). 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 CDCl₃ based on availability and price.
Sample reaction: \((S)-(\text{--})-1\text{-phenylethanol}\)

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\(_5\)Ph\(_5\), (−)-DMAP-C\(_5\)Ph\(_5\) 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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).


Integrals used to monitor reaction progress: ¹H-NMR (400 MHz, CDCl₃)  
Starting material - 4.84-4.75 (m); Product - 5.77-5.68 (m).

(1R,2S)-3-[(tert-butyldimethylsilyl)oxy]-2-(2,2-dichloroacetamido)-1-(4-nitrophenyl)propyl acetate  
Integrals used to monitor reaction progress: ¹H-NMR (400 MHz, CDCl₃)  
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.

References:

SI-Figure 2. Expansion of NMR spectra of enantioselective acylation of Compound 2 using (+)-DMAP C₅Ph₅ 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 C₅Ph₅ 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-C₅Ph₅ (triangles) and (−)-DMAP-C₅Ph₅ squares.
Comparison of reaction progress in CDCl₃ according to page SI-5.

Triangles = (+)-DMAP-C₅Ph₅
Squares = (−)-DMAP-C₅Ph₅

SI-Figure 5. Comparison of reactions progress according to page SI-5. Solvent CDCl₃. (+)-DMAP-C₅Ph₅ (triangles) and (−)-DMAP-C₅Ph₅ squares.
Figure 6. Acylation of TBS-protected chloramphenicol in CHCl₃ (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-CS₅Ph₅ (triangles) and (-)-DMAP-CS₅Ph₅ squares).