Radical Stabilization Algorithm as a Predictive Tool for Novel and Reported Non-Canonical Thiele’s Acid Analogues

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General Experimental Methods

All reactions were performed in single-neck, flame-dried, round-bottom flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Liquid reagents were transferred via glass microsyringe. Solvents were transferred via syringe with a stainless steel needle. Organic solutions were concentrated at 40 °C by rotary evaporation under vacuum. Analytical thin-layer chromatography (TLC) was performed using aluminum plates pre-coated with silica gel (0.20 mm, 60 Å pore-size, 230-400 mesh, Macherey-Nagel) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light. Flash-column chromatography was employed over silica gel (60 Å, 40-63 µM, SiliaFlash® F60).

Materials

Commercial solvents and reagents were used as received with the following exceptions. Tetrahydrofuran was dried by distillation over sodium and benzophenone.

Instrumentation

Proton nuclear magnetic resonance spectra (\(^1\)H NMR) were recorded at 300 MHz or 500 MHz at ambient temperature. Proton chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane, and are referenced to residual protium in the NMR solvent (CDCl\(_3\), δ 7.26; MeOD δ 3.31). Data are represented as follows: chemical shift, multiplicity (s = singlet; d = doublet; t = triplet; dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, ddt = doublet of doublet of triplets, td = triplet of doublets, m = multiplet, br = broad)), coupling constant in Hertz, and integration. Carbon nuclear magnetic resonance spectra (\(^13\)C NMR) were recorded at 75 MHz or 125 MHz at ambient temperature. Carbon chemical shifts are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl\(_3\), δ 77.16; MeOD δ 49.00). Phosphorus nuclear magnetic resonance spectra (\(^31\)P NMR) were recorded at 202 MHz at ambient temperature, and are uncalibrated. Infrared (IR) spectra were obtained using an ATR-IR spectrometer. Data are represented as follows: frequency of absorption (cm\(^{-1}\)). Accurate masses were obtained using an orbitrap mass spectrometer.
Synthesis of 7a

A flame dried round bottom flask under argon atmosphere was charged with diphenylphosphinic chloride (236 mg, 1 mmol) and THF (3 mL). To this solution was added sodium cyclopentadienylide (2M in THF, 1 mmol) at 0°C with stirring. After 30 minutes, the reaction was quenched by water, extracted with DCM and dried over MgSO₄. After the removal of solvent, the neat mixture was heated to 50°C overnight. The resulting deep purple mixture was loaded onto a silica gel column and eluted with DCM/MeOH (20:1 to 10:1) to give 7a as a brown oil (159 mg, 60%).

\[ \text{1H NMR (500 MHz, CDCl}_3 \] \( \delta \) 7.80-7.84 (m, 2H), 7.71-7.77 (m, 2H), 7.47-7.59 (m, 7H), 7.33-7.47 (m, 7H), 7.29 (td, J = 7.7, 2.7 Hz, 2H), 6.19-6.24 (m, 2H), 5.38 (dd, J = 10.5, 2.0 Hz, 1H), 3.91-3.97 (m, 1H), 3.06-3.10 (m, 1H), 2.97-3.03 (m, 1H), 2.50 (ddd, J = 17.6, 10.4, 1.7 Hz, 1H), 1.69 (d, J = 17.6 Hz, 1H), 1.85 (dd, J = 8.7, 1.7 Hz, 1H), 1.68 (d, J = 8.7 Hz, 1H); \[ \text{13C NMR (125 MHz, CDCl}_3 \] \( \delta \) 146.5 (d, J = 12.9 Hz), 140.6 (d, J = 99.5 Hz), 135.4 (d, J = 11.2 Hz), 133.7 (d, J = 4.7 Hz), 132.6 (d, J = 86.6 Hz), 132.2-131.2 (m), 128.6-128.4 (m), 58.1 (d, J = 16.2 Hz), 57.7 (d, J = 87.7 Hz), 52.6, 46.9 (d, J = 13.9 Hz), 43.7 (dd, J = 9.4, 5.6 Hz), 34.7 (d, J = 11.2 Hz); \[ \text{31P NMR (202 MHz, CDCl}_3 \] \( \delta \) 29.9, 23.6; \[ \text{IR (cm}^{-1}, \text{film) 3056, 2929, 1607, 1436, 1176, 1116; HR-ESIMS calculated for [M+Na]^[+] C_{34}H_{30}O_2P_2Na 555.1613 Found 555.1612. \]

Synthesis of 7b

In a glove box, a vial was charged with dimethylphosphinic chloride (56.3 mg, 0.5 mmol) and THF (3 mL). To this solution was added sodium cyclopentadienylide (2M in THF, 0.5 mmol) at room temperature with stirring. After 30 minutes, the reaction mixture was concentrated and the resulting neat oil was heated to 50°C overnight. The reaction mixture was then loaded onto a silica gel column and eluted with DCM/MeOH (10:1 to 5:1) to give 7b as a pale-yellow oil (46 mg, 65%).

\[ \text{1H NMR (500 MHz, MeOD} \] \( \delta \) 6.37 (dd, J = 10.3, 2.0 Hz, 1H), 6.31-6.34 (m, 1H), 6.04 (dd, J = 5.9, 4.0 Hz, 1H), 3.79-3.85 (m, 1H), 3.15-3.23 (m, 2H), 2.50 (ddd, J = 16.9, 9.8, 1.9 Hz, 1H), 2.00 (d, J = 17.2 Hz, 1H), 1.68 (d, J = 8.5 Hz, 1H), 1.59-1.66 (m, 7H), 1.55 (dd, J = 13.3, 2.8 Hz, 6H); \[ \text{13C NMR (75 MHz, MeOD} \] \( \delta \) 144.5 (d, J = 95.4 Hz), 142.3 (d, J = 95.4 Hz), 137.0 (d, J = 10.9 Hz), 133.2 (d, J = 4.5 Hz), 58.2 (d, J = 16.5 Hz), 57.7 (d, J = 85.9 Hz), 52.3, 48.3 (d, J = 14.4 Hz), 45.2 (dd, J = 8.7, 5.2 Hz), 35.2 (d, J = 12.4 Hz), 16.0 (d, J = 73.0 Hz), 14.5 (d, J = 68.5 Hz), 13.6 (d, J = 69.8 Hz); \[ \text{31P NMR (202 MHz, MeOD} \] \( \delta \) 50.6, 36.3; \[ \text{IR (cm}^{-1}, \text{film) 2926, 1645, 1421, 1296, 1129; HR-ESIMS calculated for [M+H]^[+] C_{14}H_{23}O_2P_2 285.1168 Found 285.1165. \]
Figure S1 Assignment of least stabilized radical of 4B, 4C and cyclopentadiene.

2° allylic radical therefore less stable
3° allylic radical further stabilized by adjacent carbonyl therefore more stable
2° allylic radical conjugated to position alpha to carbonyl therefore more stable
2° allylic radical subject to no further stabilization therefore less stable

Symmetric molecule therefore equally stable
Figure S2 Assignment of least stabilized radical of 10A, 10B and 10C.

Figure S3 Assignment of least stabilized radical of 6B and 6C.
Figure S4 Application of radical stabilization logic to possible combination of 6B and 6C. (Electronically favoured combinations are in blue boxes)
Figure S5 Application of radical stabilization logic to possible combination of 10A, 10B and 10C (R = Ph). (Electronically favoured combinations are in boxes)

Analysis:

Pairings 10A\textsubscript{DIENE} + 10C\textsubscript{DIENOPHILE} and 10B\textsubscript{DIENE} + 10C\textsubscript{DIENOPHILE} (in red boxes) will lead to products with two adjacent quaternary centres. Thus, both of them can be rejected on steric grounds.

Pairings 10C\textsubscript{DIENE} + 10B\textsubscript{DIENOPHILE}, 10C\textsubscript{DIENE} + 10A\textsubscript{DIENOPHILE} and 10C\textsubscript{DIENE} + 10C\textsubscript{DIENOPHILE} (in pink boxes) will likewise suffer from obvious steric clashes in their transition states, as shown in Figure S6, below.

Pairings 10A\textsubscript{DIENE} + 10B\textsubscript{DIENOPHILE}, 10B\textsubscript{DIENE} + 10A\textsubscript{DIENOPHILE}, 10A\textsubscript{DIENE} + 10A\textsubscript{DIENOPHILE} and 10B\textsubscript{DIENE} + 10B\textsubscript{DIENOPHILE} (in blue boxes) are discussed in Figure 2 of the paper.
Figure S6 Transition states and steric clashes for pairings \(10C_{\text{DIENE}} + 10B_{\text{DIENOPHILE}}, 10C_{\text{DIENE}} + 10A_{\text{DIENOPHILE}}\) and \(10C_{\text{DIENE}} + 10C_{\text{DIENOPHILE}}\) \((R = \text{Ph})\).

Figure S7 Algorithm for the application of radical stabilization logic to the rationalization of Diels-Alder outcomes.

- Identify (by calculation or spectroscopy) the dienes and/or dienophiles that can participate in the reaction.
- Draw 1,4-diradical resonance structures for both dienes and dienophiles.
- Assign the least stabilized radical for each diradical resonance form.
- Align the two least stabilized radicals of each reaction partner together to identify “allowed” couplings.
- Rule out transition states that are substantially more sterically hindered.
- Identify the remaining likely products.
$^1$H NMR Spectrum for 7a in CDCl$_3$

$^{13}$C NMR Spectrum for 7a in CDCl$_3$
DEPT135 NMR Spectrum for 7a in CDCl₃

³¹P NMR Spectrum for 7a in CDCl₃
$^{31}$P-HMBC Spectrum for 7a in CDCl$_3$

1D-NOE Spectrum for 7a, with Irradiation at 3.95 ppm
1D-NOE Spectrum for 7a, with Irradiation at 1.68 ppm

COSY Spectrum for 7a in CDCl₃
HMOC Spectrum for 7a in CDCl₃
$^1$H NMR Spectrum for Crude 6Ba in CDCl$_3$

$^{31}$P NMR Spectrum for Crude 6Ba in CDCl$_3$
$^{31}$P-HMBC Spectrum for Crude 6Ba in CDCl$_3$
$^1$H NMR Spectrum for 7b in MeOD

$^{13}$C NMR Spectrum for 7b in MeOD
DEPT135 Spectrum for 7b in MeOD

$^{31}$P NMR Spectrum for 7b in MeOD
$^{31}$P-HMBC Spectrum for 7b in MeOD

1D-TOCSY Spectrum 7b, with Irradiation at 6.31–6.42 ppm
1D-NOE Spectrum 7b, with Irradiation at 3.85 ppm