

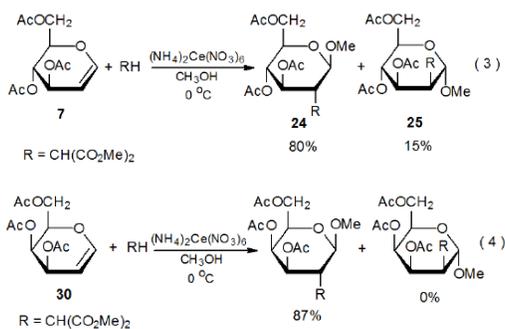
III. Ammonium Cerium(IV) Nitrate

A. Addition of CH-Acidic Compounds to D-Glycals

1. Dimethyl Malonate

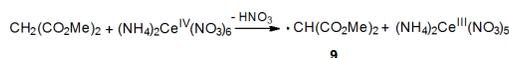
a. Regioselectivity

In a manner similar to manganese(III) acetate reaction, ammonium cerium(IV) nitrate promotes regioselective addition of CH-acidic compounds to carbohydrates with electron-rich double bonds.^{6-9,15,16,19-22} Examples of such reactions are given in equations 3 and 4, and a mechanism for the addition process is proposed in Scheme 7.⁶⁻⁹ Reactions of glycals with $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ (eq 3 and eq 4) can be conducted at lower temperatures than those with $\text{Mn}(\text{OAc})_3$ (eq 1 and eq 2). These milder conditions completely suppress formation of the Ferrier rearrangement product **8**, a compound formed in the reaction given in eq 1 but absent in that shown in eq 3.

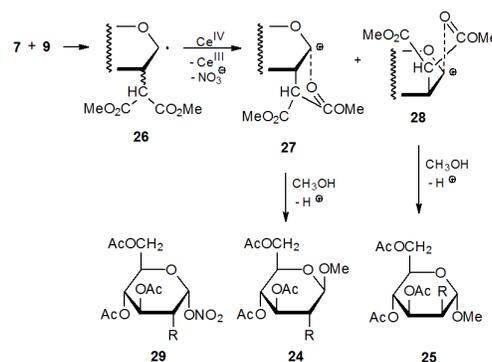


Scheme 7

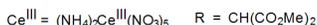
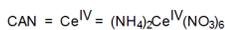
radical formation



radical reaction

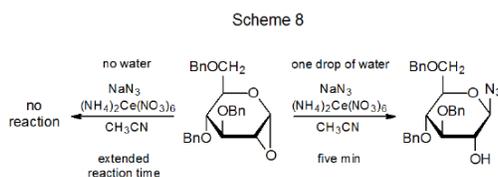


CAN (dried)	0%	80%	15%
CAN (not dried)	16%	62%	14%
CAN (water added)	34%	41%	12%



If water is present, even in small amounts, a new compound (**29**) is produced in the reaction shown in Scheme 7.²² How is this compound formed? Direct reaction between the cation **27** and the nitrate anion is one possibility, but if this pathway is the correct one, addition of sodium nitrate to the reaction mixture should increase the yield of **29**. It does not.⁷ Ligand transfer from $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ to the radical **26** also is possible,^{6,7} but it is difficult to see why such a process should be dependent on the amount of water present in the reaction mixture. Both of these possibilities [reaction of **27** with NaNO_3 or ligand transfer from $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$] appear more likely to produce the anomer of **29** rather than **29** itself. The data in Scheme 7 do show that formation of the nitrate **29** comes at the expense of the β -glycoside **24**. Conversion of **24** into **29** could result from reaction of **24**

with the nitric acid produced by interaction of $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ with water. This possibility is supported by the reaction shown in Scheme 8, where a drop of water apparently reacts with $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ to create the nitric acid needed for an acid-catalyzed ring opening.²³



b. Stereoselectivity

Reaction stereoselectivity improves when $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ replaces $\text{Mn}(\text{OAc})_3$ in the addition of dimethyl malonate to 3,4,6-tri-*O*-acetyl-D-glucal (**7**). The ratio of α -face to β -face addition at C-2 by the malonyl radical changes from 52:14 (eq 1, Scheme 4)⁶ to 80:15 (eq 3, Scheme 7).²² The difference in the temperature of these reactions [95 °C (eq 1) to 0 °C (eq 3)] is a likely cause for this increase in stereoselectivity.

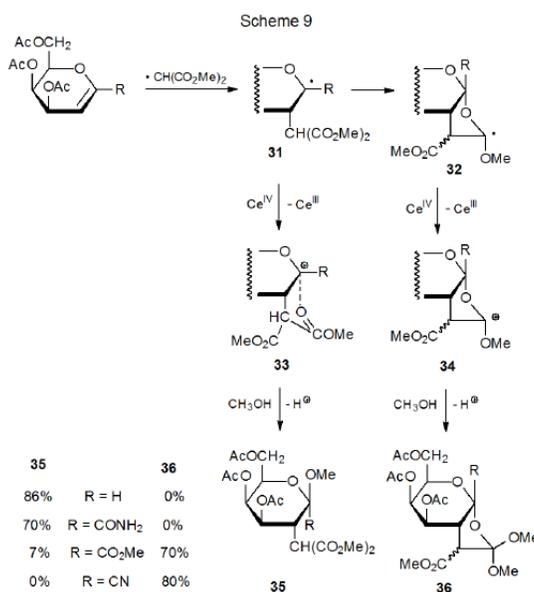
A second, stereoselective step in the reactions shown in Schemes 3 and 7 occurs during solvent capture by intermediate cations. Methanol reacts with the cations **27** and **28** exclusively from the face of the ring opposite to the malonyl group and produces a single stereoisomer in each case (Scheme 7). The capture of acetic acid pictured in Scheme 3 also is stereoselective but less so because each intermediate cation reacts to give a mixture of stereoisomers. Once again, greater reaction stereoselectivity correlates with lower reaction temperature.

Stereoselectivity in malonyl-radical addition also increases when approach to one face of a ring becomes more difficult due to a change in substrate structure. Such a change occurs when 3,4,6-tri-*O*-acetyl-D-glucal (**7**) (eq 3) is replaced by 3,4,6-tri-*O*-acetyl-D-galactal (**30**) (eq 4).⁷ Projection of the C-4 acetoxy group onto the β face of the pyranoid ring in **30** makes this face more congested than the β face of the pyranoid ring in **7**.

c. Reactivity

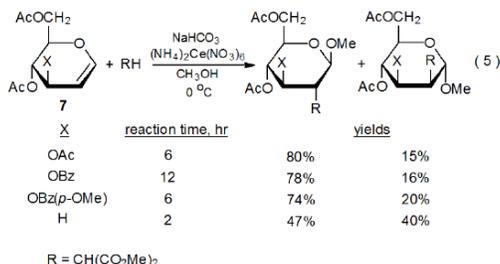
(1). Effect of C-1 Substituents on Glycal Reactivity Ortho-Ester Formation

The products formed from addition of the malonyl radical **9** to C-1 substituted glycals depend on the structure of the C-1 substituents (Scheme 9).²⁴ When R is H or C(=O)NH₂, the glycoside **35** forms, but when R is CO₂Me or CN, the products are the orthoesters **36**. An explanation for this difference in reactivity is that when R is highly electron-withdrawing (e.g., CN or CO₂Me), the oxidation potential of the radical **31** is high enough that its conversion to the cation **33** by reaction with $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ is suppressed (Scheme 9).^{24,25} When this suppression occurs, cyclization of **31** produces **32**, a radical that now can be oxidized easily to the corresponding cation (**34**). Reaction of this cation with methanol then gives the orthoesters **36**.



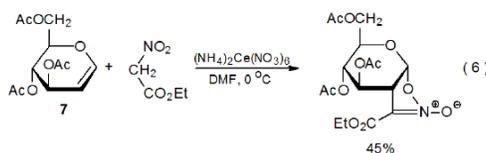
(2). Effect of a C-3 Substituent of Glycol Reactivity

The importance of electron-withdrawing substituents to glycol reactivity also is apparent when different substituents are attached to C-3 (eq 5).²⁵ The reactions shown in eq 5 confirm the previously mentioned findings (Sections III.A.1.a and III.A.1.b) about regioselectivity (the malonyl radical **9** adds exclusively to C-2) and stereoselectivity (**9** adds preferentially to the face of the pyranoid ring opposite to that containing the C-3 substituent). These reactions also demonstrate the effect of the electron-withdrawing character of a C-3 substituent on reaction rate (eq 5). Since the reactions involve the electrophilic malonyl radical adding to an electron-rich double bond, increasing the electron-withdrawing character of the R group decreases the reaction rate by reducing the electron density in the double bond; thus, an *O*-benzoyl group, which is more electron-withdrawing than an *O*-acetyl group, causes a slower rate of reaction. The reaction rate of an *O*-benzoyl-substituted glycol can be increased by placing an electron-donating methoxy group in the benzene ring. Reaction can be made even faster by eliminating any electron-withdrawing group from C-3 (eq 5).



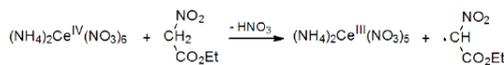
2. Ethyl Nitroacetate

When ethyl nitroacetate reacts with (NH₄)₂Ce(NO₃)₆ in the presence of the D-glucal **7** (eq 6),²⁰ a transformation takes place that is similar in its early stages to the dimethyl malonate reaction shown in □ eq 3. These two processes follow different pathways once the adduct radical has been oxidized to a cation. In the ethyl nitroacetate reaction, cyclization occurs (Scheme 10) rather than the solvent capture that characterizes reaction with dimethyl malonate (□ Scheme 7).

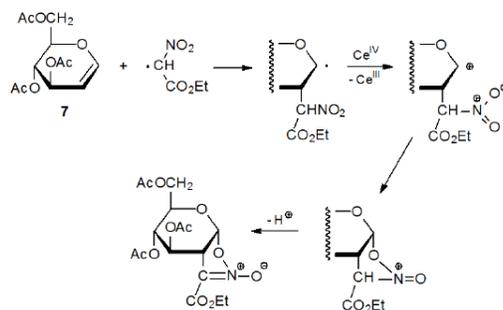


Scheme 10

radical formation



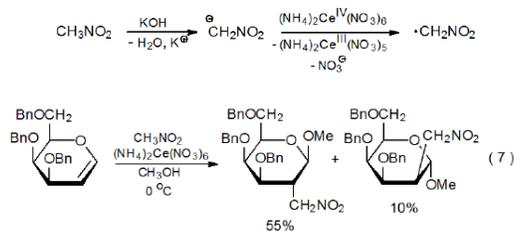
radical reaction



3. Nitromethane

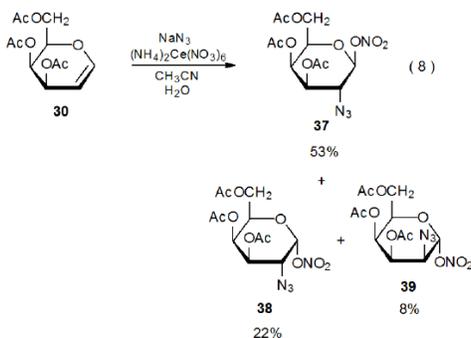
Nitromethane is a CH-acidic compound that reacts with potassium hydroxide to form a nitronate anion. Oxidation of this anion with ammonium cerium(IV) nitrate produces the electrophilic radical $\cdot\text{CH}_2\text{NO}_2$ (Scheme 11). If a compound with an electron-rich double bond is present in the reaction mixture, radical addition takes place (eq 7).²⁶

Scheme 11

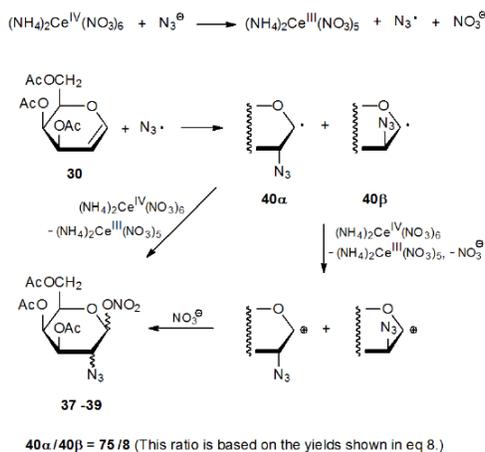


B. Addition of the Azide Radical to a D-Glycal

Reaction of ammonium cerium(IV) nitrate with sodium azide in the presence of the D-galactal **30** produces the diastereomeric azido nitrates **37-39** (eq 8).²⁷ There is convincing evidence that $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ oxidizes NaN_3 to produce the azide radical (Scheme 12).²⁸ Highly stereoselective addition of this radical to **30** gives adduct radicals **40 α** and **40 β** in a ratio of 75:8. The azido nitrates **37-39** then form either indirectly by reaction of nitrate ion with the cations produced by oxidation of **40 α** and **40 β** or directly by ligand transfer from $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ to these radicals.²⁹ (Section II.B.2 of Chapter 15 contains more information on azidonitration and additional references to this reaction.)

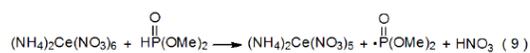


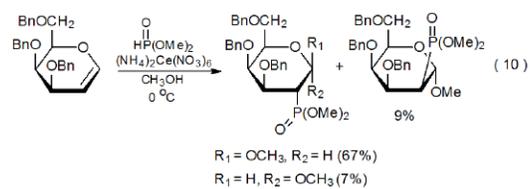
Scheme 12



C. Addition of a Phosphonyl Radical to a D-Glycal

Dimethyl phosphite reacts with $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ to produce the phosphorous-centered radical **41** (eq 9).³⁰ This radical then adds to D-glycals in a regiospecific, highly stereoselective manner (eq 10).





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