

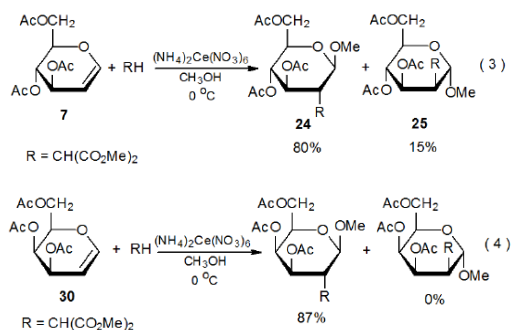
### III. Ammonium Cerium(IV) Nitrate

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

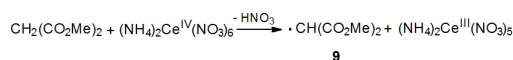
##### 1. Dimethyl Malonate

##### a. Regioselectivity

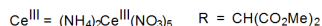
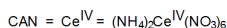
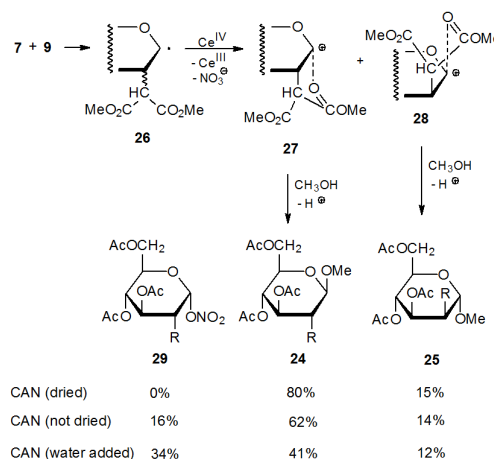
In a manner similar to manganese(III) acetate reaction, ammonium cerium(IV) nitrate promotes regioselective addition of CH-acidic compounds to carbohydrates with electron-rich double bonds.<sup>6-9,15,16,19-22</sup> Examples of such reactions are given in equations 3 and 4, and a mechanism for the addition process is proposed in Scheme 7.<sup>6-9</sup> 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.



radical formation

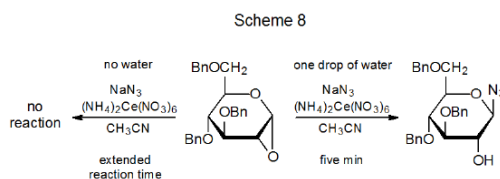


radical reaction



If water is present, even in small amounts, a new compound (**29**) is produced in the reaction shown in Scheme 7.<sup>22</sup> 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.<sup>7</sup> Ligand transfer from  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  to the radical **26** also is possible,<sup>6,7</sup> 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  $\text{NaNO}_3$  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  $\beta$ -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.<sup>23</sup>



## 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  $\alpha$ -face to  $\beta$ -face addition at C-2 by the malonyl radical changes from 52:14 (eq 1, Scheme 4)<sup>6</sup> to 80:15 (eq 3, Scheme 7).<sup>22</sup> 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.

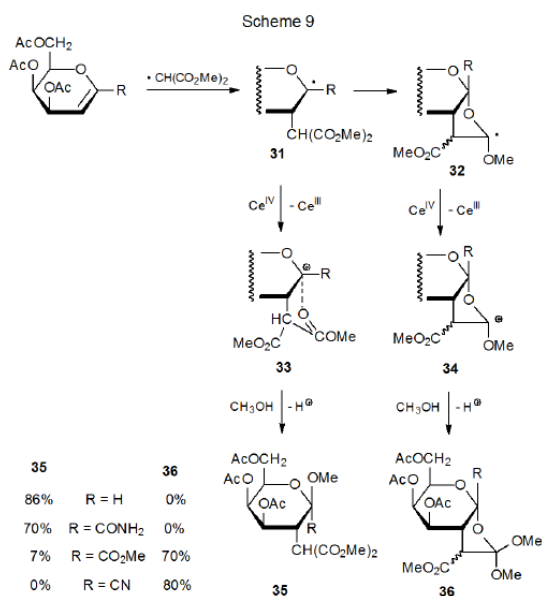
A second, stereoselective step in the reactions shown in Schemes 3 and 7 occurs during solvent capture by intermediate cations. Methanol reacts with the cations **27** and **28** exclusively from the face of the ring opposite to the malonyl group and produces a single stereoisomer in each case (Scheme 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).<sup>7</sup> Projection of the C-4 acetoxy group onto the  $\beta$  face of the pyranoid ring in **30** makes this face more congested than the  $\beta$  face of the pyranoid ring in **7**.

## c. Reactivity

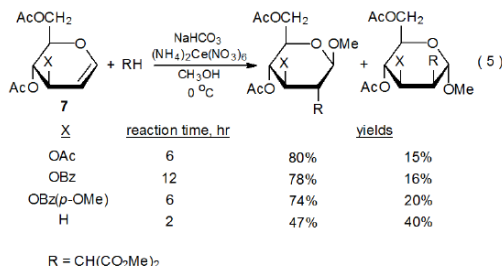
### (1). Effect of C-1 Substituents on Glycal Reactivity Ortho-Ester Formation

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).<sup>24</sup> When R is H or  $\text{C}(=\text{O})\text{NH}_2$ , the glycoside **35** forms, but when R is  $\text{CO}_2\text{Me}$  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  $\text{CO}_2\text{Me}$ ), 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).<sup>24,25</sup> 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**.



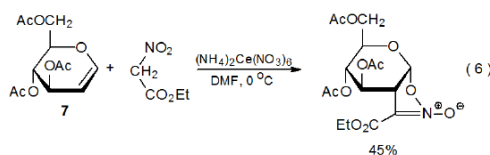
## (2). Effect of a C-3 Substituent of Glycal Reactivity

The importance of electron-withdrawing substituents to glycal reactivity also is apparent when different substituents are attached to C-3 (eq 5).<sup>25</sup> 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 glycal 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).



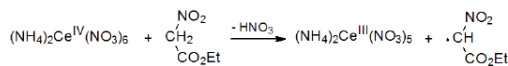
## 2. Ethyl Nitroacetate

When ethyl nitroacetate reacts with (NH<sub>4</sub>)<sub>2</sub>Ce(NO<sub>3</sub>)<sub>6</sub> in the presence of the D-glucal **7** (eq 6),<sup>20</sup> 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).

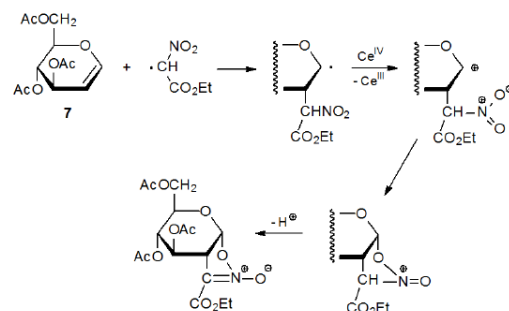


Scheme 10

radical formation



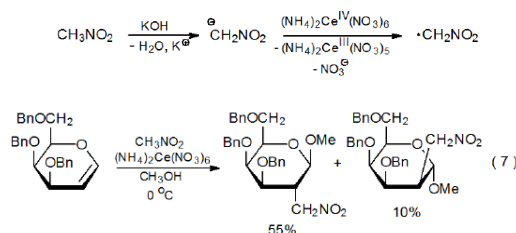
radical reaction



## 3. Nitromethane

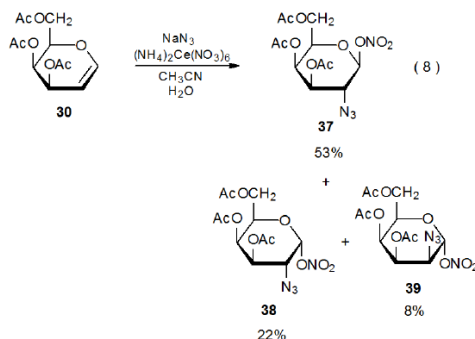
Nitromethane is a CH-acidic compound that reacts with potassium hydroxide to form a nitronate anion. Oxidation of this anion with ammonium cerium(IV) nitrate produces the electrophilic radical  $\cdot\text{CH}_2\text{NO}_2$  (Scheme 11). If a compound with an electron-rich double bond is present in the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

Scheme 11

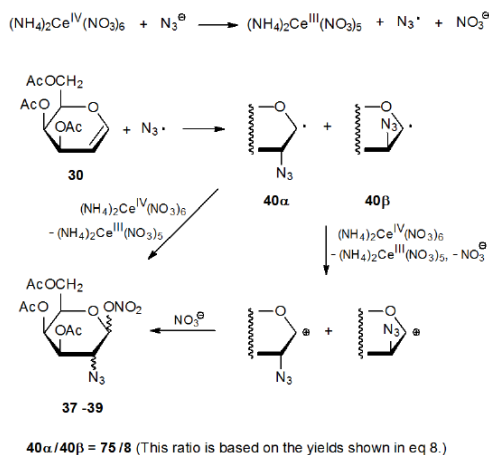


## B. Addition of the Azide Radical to a D-Glycal

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).<sup>27</sup> There is convincing evidence that  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  oxidizes  $\text{NaN}_3$  to produce the azide radical (Scheme 12).<sup>28</sup> Highly stereoselective addition of this radical to **30** gives adduct radicals **40 $\alpha$**  and **40 $\beta$**  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 $\alpha$**  and **40 $\beta$**  or directly by ligand transfer from  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$  to these radicals.<sup>29</sup> (Section II.B.2 of Chapter 15 contains more information on azidonitration and additional references to this reaction.)

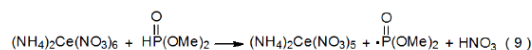


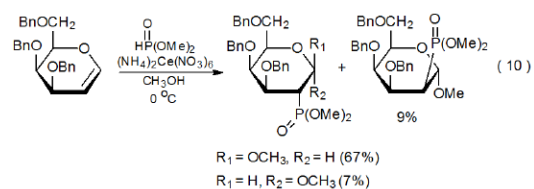
Scheme 12



## 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).<sup>30</sup> This radical then adds to D-glycals in a regiospecific, highly stereoselective manner (eq 10).





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