Intramolecular vinylation of aryl rings by vinyl cations

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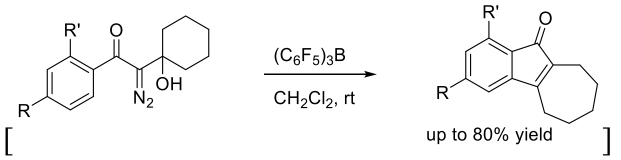
Supporting Information Placeholder

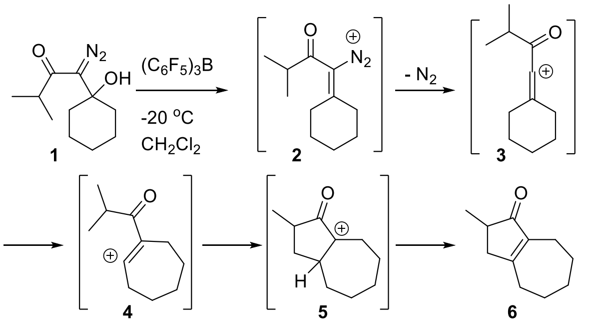


ABSTRACT: A Lewis acid mediated intramolecular electrophilic vinylation of aryl rings by vinyl cations is reported. This reaction takes advantage of β-hydroxy-α-diazo ketones as vinyl cation precursors and provides good yields of tricyclic 1-indenones that contain a 7-membered ring. Extending the alkane chain that tethers the vinyl cation to the aromatic ring leads to 2-napthol and 2-indenone products.

Electrophilic aromatic substitution is a one of the most important and frequently used methods for preparing functionalized aromatic rings.[1] A wide variety of strong electrophiles can be used in these reactions with carbon-based electrophiles giving the well known Friedel-Crafts reactions[2] that were first reported over 140 years ago and are still frequently used.[3] While trisubstituted cations are common electrophiles in Friedel-Crafts reactions, vinyl cations, which would lead to styrenyl products, have not received the same attention from the synthetic community. Historically, this has been due to the fact that vinyl cations are more difficult to prepare then their trisubstituted counterparts. Adding electrophiles to alkynes is a useful method to prepare vinyl cations, but although examples of applying this tactic in Friedel-Crafts sequences exist,[4] this approach suffers from regioselectivity issues, and the initial styrenyl products can react further to give polyaromatic alkanes.[5] Metal catalyzed hydroarylations and carboarylations have been developed to mitigate these selectivity issues, but these approaches are generally limited to acyclic alkynes, or large rings that are able to accommodate the linear alkyne motif.[6] Heterolysis of vinyl triflates and related perfluorosulfonate esters provides an alternative route to vinyl cations.[7] However, these reactions tend to be more facile in polar protic solvents, which lead to the formation of solvolysis products. Nevertheless, Stang and Anderson have reported that several vinyl triflates, including a few cyclic examples, react at high temperature in aromatic solvents to give styrenyl products, and they provide compelling evidence for the intermediacy of vinyl cations in these reactions.[8] Nelson and coworkers recently reported a milder variant of this reaction in which the vinyl triflate leaving group is activated with a silylium ion.[9] In this case, the silane also acts as a reductant leading to aryl-alkane rather than styrenyl products.

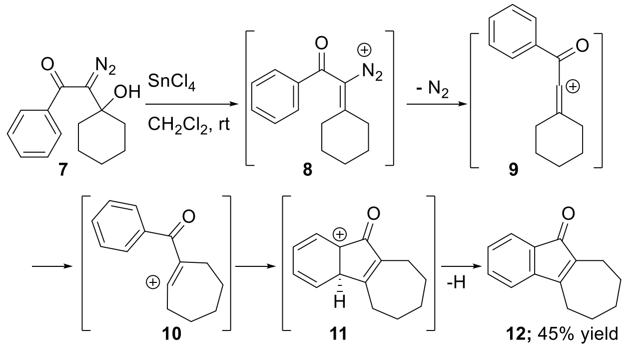
We have recently reported that β-hydroxy-α-diazo ketones react with Lewis acids to generate cyclopentenone products via the C-H insertion of a vinyl cation intermediate.[10,11] We propose that this transformation occurs by the sequence shown in Scheme 1. Lewis acid mediated elimination of the tertiary hydroxide would give vinyl diazonium ion **2**, which would lose nitrogen to give vinyl cation **3**. The cation, which is destabilized by the inductively withdrawing carbonyl, would undergo a 1,2-shift across the alkene to give the ring expanded cyclic vinyl cation **4**.[12] Remote C-H insertion of the vinyl cation into a non-activated pendent methyl C-H bond would provide tertiary cation **5**, and subsequent loss of a proton would give the cyclopentenone product (**6**). In an effort to further expand the use of vinyl cations in synthesis, we have been exploring alternative intramolecular reactions that take advantage of vinyl cations derived from β-hydroxy-α-diazo carbonyls. In this paper, we describe our studies on the intramolecular electrophilic vinylation of aryl rings by vinyl cations that lead to tricyclic indenone products. Indenone and indanone derivatives are important motifs that are present in a number of biologically active compounds.[13]

Scheme 1. Use of β-hydroxy-α-diazo ketone in a C-H insertion reaction.



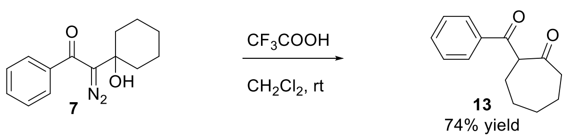
We initiated these studies by preparing β-hydroxy-α-diazo ketone **7** (Scheme 2) via the aldol-type addition of lithiated diazoacetophenone to cyclohexanone. Treating diazo **7** with 1 equivalent of $SnCl_4$ in CH_2Cl_2 at room temperature returned indenone **12** in 45% yield. This reaction presumably occurs by the mechanism shown in Scheme 2. The Lewis acid would facilitate elimination of the β-hydroxyl to generate vinyl diazonium **8**, which would lose molecular nitrogen to give linear vinyl cation **9**. This destabilized cation would rearrange to give ring expanded cyclic vinyl cation **10**,[12] which would react via intramolecular electrophilic aromatic substitution to give indenone **12**.

Scheme 2. Indenone formation via aromatic vinylation of a vinyl cation



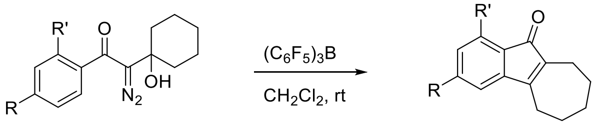
In our prior vinyl cation studies,[10] we observed that changing the Lewis acid can have a dramatic effect on the efficiency of the reaction. With that in mind, we screened several Lewis acids to see how they affected the reaction yield. Aluminium trichloride, aluminium triflate, and scandium triflate were each competent Lewis acids, but provided the product in decreased yields (24%, 26% and 60% respectively). Treating diazo **7** with trifluoroacetic acid did not give any desired product, but instead returned 2-benzoylcycloheptan-1-one (**13**) in 74% yield (Scheme 3). The Lewis acid of choice for facilitating C-H insertion was tris-pentafluorophenyl borane (BCF), which does not have a ligand that can easily trap the cationic intermediates. We were pleased to find that treating diazo **7** with BCF returned indenone **12** in 80% yield at room temperature (Scheme 4). Adding $MgSO_4$ to the reaction mixture did not further improve the outcome.

Scheme 3. TFA mediated ring expansion



With better defined reaction conditions in hand, we were interested to see how substituents on the aromatic ring would affect the outcome of the reaction. To this end, we prepared the β-hydroxy-α-diazo carbonyls shown in Scheme 4 by the addition of aryl-substituted diazoacetophenone derivatives to cyclohexanone. Methyl (**14**) and methoxy (**16**) substituents at the para position returned indenones **15** and **17** in 72% and 68% yields respectively, while incorporating a chlorine at the para-position (**18**) gave indenone **19** in 77% yield. This trend is surprising at first glance since the electron releasing groups should increase the nucleophilicity of the aromatic ring and promote the EAS reaction with the vinyl cation. However, a more electron rich aryl ring would also make the carbonyl group less electron withdrawing, and thus the initially formed vinyl cation (e.g. **9**, Scheme 2) should be more stable and less prone to rearranging to the EAS precursor (e.g. **10**). If the initially formed vinyl cation has a longer lifetime, then it may engage in undesired reactions. In this case, we observed some product derived from trapping the initially formed vinyl cation with a pentafluorophenyl group, which is presumably transferred from the hydroxy(triaryl)borate derivative of the Lewis acid.

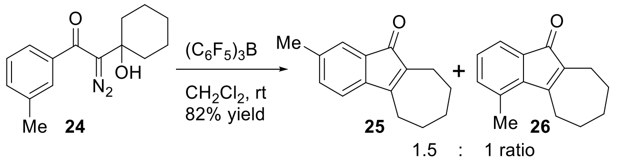
Scheme 4. Inden-1-one formation by intramolecular vinylation of aryl rings



7; R = H, R' = H	**12**; 80%
14; R = Me, R' = H	**15**; 72%
16; R = OMe, R' = H	**17**; 68%
18; R = Cl, R' = H	**19**; 77%
20; R = H, R' = Cl	**21**; 32%
22; R = NO_2, R' = H	**23**; 8%

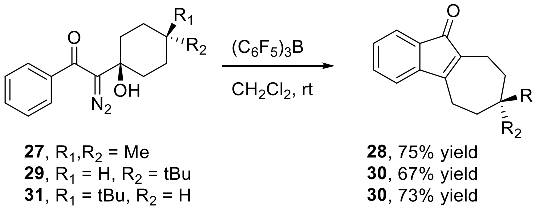
Positioning the chlorine substituent ortho to the ketone (**20**) resulted in a substantial decrease in indenone yield (32%), which may be due to the fact that there is one fewer reactive site available on the aryl ring, resulting in a slower ring closure and an increase in undesired side reactions. Incorporating a strongly electron-withdrawing nitro group on the aryl ring inhibited the reaction substantially; diazo **22** returned indenone **23** in only 8% yield. In view of the low reactivity of nitro aryls in Friedel-Crafts reactions, and the fact that this aryl ring is doubly deactivated, it is surprising that this reaction returned any product.[14] Including a methyl substituent meta to the carbonyl leads to the formation of two regioisomeric indenones (**25** and **26**; Scheme 5) in a 1.5 to 1 ratio in 82% yield. Not surprisingly, the major product in this case results from a reaction at the less sterically hindered position of the aromatic ring.

Scheme 5. Meta substitution leads to a mixture of regioisomers

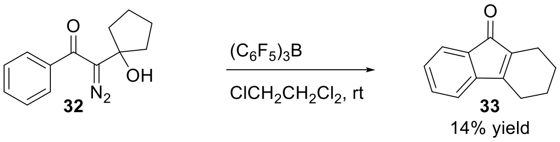


To determine how modifications to the cycloalkane portion of the molecule affect the reaction, we prepared the gem-dimethyl (**27**) and tert-butyl (**29** and **31**) cyclohexane analogs of **7** (Scheme 6), as well as cyclopentane derivative **32** (Scheme 7). The gem-dimethyl species (**27**) reacted smoothly with BCF to give indenone **28** in 75% yield. Aldol addition of lithiated diazoacetophenone to 4-tert-butylcyclohexanone gave two diastereomeric addition products. These diastereomers (**29** and **31**) were separable by column chromatography, and each diastereomer was subjected to the Lewis acid reaction conditions. In this case, the relative stereochemistry of the diazo alcohol had no influence on the reaction outcome, and both diastereomers gave the expected product (**30**) in comparable yield. Changing the cyclohexane ring to a cyclopentane had a dramatic negative affect on the product yield. Diazo **32** reacted under the standard conditions to give 1,2,3,4-tetrahydro-9H-fluoren-9-one (**33**) as a mixture with a chloro-trapped product. In this case, the chloride must be transferred from the dichloromethane solvent. Switching to dichloroethane prevented the formation of the unwanted side product, but still returned fluorenone (**33**) in only 14% yield. This low yield is a reflection of the instability of cyclohexenyl cations due to the strain associated with constraining the vinyl cation into a 6-membered ring.[15] The rearrangement of the initially formed linear cation to the endocyclic vinyl cation is less favorable, which results in diminished product yield.

Scheme 6. Effect of substitution on aliphatic ring

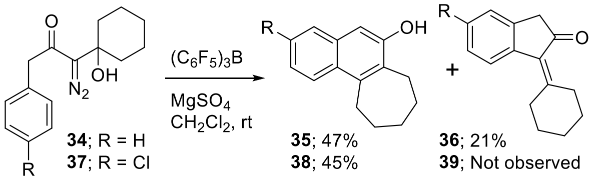


Scheme 7. Formation of 1,2,3,4-tetrahydro-9H-fluoren-9-one



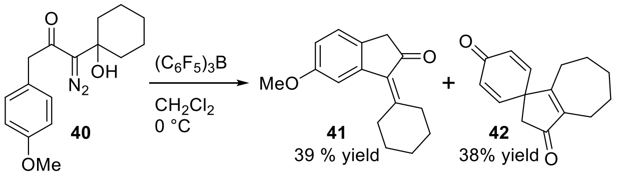
To assess whether this reaction sequence could be used to prepare other ring systems, we prepared diazo ketone **34** (Scheme 8), which includes an additional methylene unit between the aryl ring and the carbonyl. In this case, the initially formed cyclohexanone product would be expected to tautomerize to give a 3,4-disubstituted 2-napthol derivative.[16] In the event, treating diazo **34** with BCF at room temperature gave cycloheptane substituted 2-napthol **35** in 42% yield. In addition, indene-2-one **36** was recovered in 35% yield. This latter product undoubtedly stems from reaction of the aryl ring with the initially formed vinyl cation. Lowering the reaction temperature led to diminished yields of both products, and changing the Lewis acid to $SnCl_4$ or $AlCl_3$ gave little to no desired reaction. The best outcome was achieved by treating diazo **34** with 1 equivalent of BCF at room temperature in the presence of 1 equivalent of $MgSO_4$. In this case, 2-napthol **35** was recovered in 47% yield, with an additional 21% yield of indene-2-one **36**. We thought it might be possible to minimize the formation of the indene-2-one side product by decreasing the nucleophilicity of the aryl ring, thus slowing the rate of the ring closure onto the initially formed vinyl cation. To this end, we prepared the 4-chloroaryl derivative **37** and subjected it to the optimized reaction conditions. In this case, the corresponding indene-2-one was not formed, but the yield of the desired 2-napthol (**38**) did not improve.

Scheme 8. Change in tether length provides 2-napthol product



A more electron rich aryl ring, on the other hand, should promote the formation of the indene-2-one product. Indeed, the 4-methoxyaryl derivative (**40**. Scheme 9) reacted to give indene-2-one **41** in 39% yield along with spiro[4.5]decane **42** in 38% yield. The formation of the spirocycle is consistent with Haack and Beck's results on the Friedel-Craft's acylation of terminal alkynes with methoxyphenylacetyl chloride.[17]

Scheme 9. Spirocycle formation



In conclusion, reacting β-hydroxy-α-diazo ketones with Lewis acids is a convenient method to form vinyl cations that can engage in intramolecular electrophilic aromatic substitution reactions. Depending on the length of the tether connecting the aryl ring to the cation, 1-indenone, 2-indenone, or 2-napthol products are formed in moderate to high yields. While a strongly deactivating nitro group inhibited the electrophilic aromatic substitution, this reaction tolerates electron rich and moderately electron poor aryl rings. Overall, this process offers a unique way to prepare indenones and further highlights the utility of vinyl cations in synthesis.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

General experimental details, experimental procedures, compound characterization data, and copies of ^1H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was financially supported by the NSF (Award Number CHE-1665113). Mass spectrometry data was acquired by Bruce O'Rourke on instruments purchased through instrumentation grants provided by the National Institutes of Health (NIH) (S10 OD018126).

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