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Aryl Annulation of Cyclic Ketones via a Magnesium Carbometalation−6-π-Electrocyclization Protocol
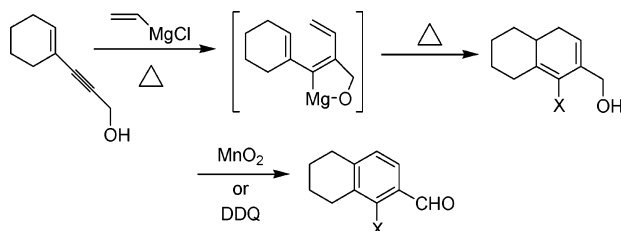
Pierre E. Tessier,[†] Natalie Nguyen, Matthew D. Clay, and Alex G. Fallis*

Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada K1N 6N5

afallis@science.uottawa.ca

ABSTRACT

A new strategy for the aryl annulation of cyclic ketones is described. Palladium(0) coupling of a propargyl alcohol with the enol triflate of a ketone and addition of vinylmagnesium chloride generates a triene as a magnesium chelate that may be quenched with an electrophile. In some cases, the triene cyclizes under the reaction conditions. Aromatization is accomplished by exposure to manganese dioxide or dichlorodicyanoquinone (DDQ).

We have previously described some of the attributes and versatility of the magnesium-mediated carbometalation of propargyl alcohols to assemble several diverse compounds generated in a single reaction, for a variety of objectives.[1] These reactions have included the regio- and stereoselective generation of diene-halides, diene-diols, enediynes, furans, furanones, taxoid intermediates and palladium(0) cross-couplings for dienes, and the stereospecific synthesis of (Z)-Tamoxifen.[2]

The common feature of this chemistry is the reaction of a propargyl alcohol either directly or in situ with a Grignard reagent, subsequent generation of the magnesium chelate, followed by reaction with an appropriate electrophile.

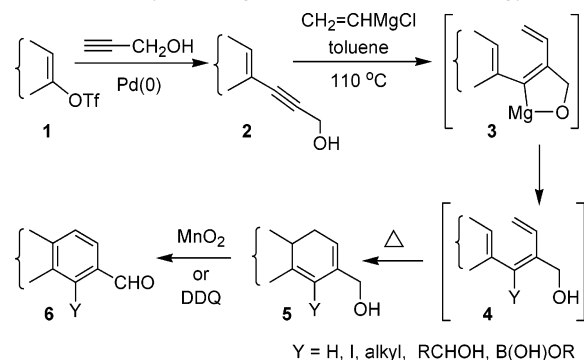We report a new annulation procedure to attach substituted benzene rings to cyclic ketones. This aryl annulation strategy involves a regio- and stereospecific magnesium-mediated carbometalation followed by 6-π-electrocyclic ring closure of the resulting triene and oxidation as illustrated in Scheme 1. This method employs a vinyl triflate **1** derived from an appropriate cyclic ketone, which is coupled in the presence of palladium(0) with propargyl alcohol to give **2**. Addition of vinylmagnesium chloride generates the magnesium chelate **3**, and an in situ reaction with an electrophile such as iodide (Y = I) affords a triene of type **4**. In the case of some bicyclic ketones, this triene undergoes spontaneous electrocyclic cyclization to **5** in the same reaction vessel; otherwise, additional heating is required. Oxidation with MnO$_2$ or DDQ affords an iodo-benzaldehyde **6**. However, various substitu-

† Present address: Methyl Gene, Inc., 7220 Frederick Banting, Montreal, Québec, Canada, H4S 2A1.

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(2) (a) Wong, T.; Tjepkema, M. W.; Audrain, H.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **1996**, *37*, 755. (b) Forgione P.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 11. (c) Forgione, P.; Wilson, P. D.; Fallis, A. G. *Tetrahedron Lett.* **2000**, *41*, 17. (d) Forgione P.; Wilson, P. D.; Yap, G. P. A.; Fallis, A. G. *Synthesis* **2000**, 921. (e) Tessier, P. J.; Penwell, A. J.; Souza, F. E. S.; Fallis A. G. *Org. Lett.* **2003**, *5*, 2989. (f) Villava-Serin, N. P.; Laurent, A. Fallis, A. G. *Synlett* **2003**, 1263. (g) Smil, D. V.; Laurent, A.; Villava-Serin, N. P.; Forgione, P.; Wilson, P. D.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 215. (h) Smil, D. V.; Laurent, A.; Villava-Serin, N. P.; F. Souza, F. E. S.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 227.

Scheme 1. Aryl Annulation via a Carbometalation−6-π-Electrocyclic Ring Closure Oxidation Strategy

CH₂=CHMgCl toluene 110 °C

MnO₂ or DDQ

Y = H, I, alkyl, RCHOH, B(OH)OR

1 2 3 4 5 6

Table 1. Bicyclic Ketones: Synthesis of Triflates, Propargyl Alcohols, and Cyclized Dienes/Trienes

(iPr)₂NH
nBuLi
PhN(Tf)₂
-78 °C to rt

Pd(PPh₃)₂Cl₂ (5 mol%)
CuI (10 mol%)
≡—CH₂OH
THF:DEA (1:1)
reflux, 16 h

a) PhMe or C₆H₁₂
CH₂=CHMgCl
reflux, 16 h
b) NH₄Cl, rt

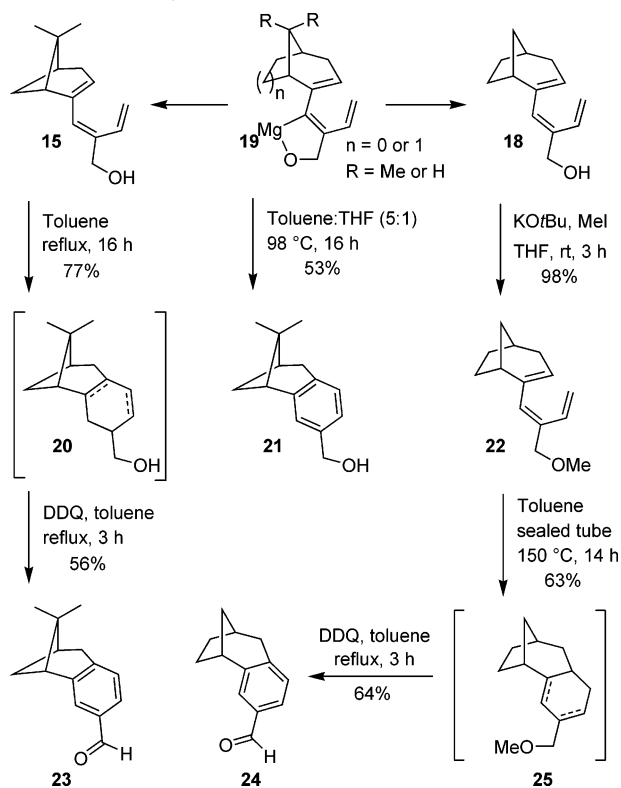| Entry	Vinyl Triflate	Propargyl Alcohol	Triene/Cyclized Diene
a	59% **7**[3]	60% **8**	43% **9**
b	89% **10**[4]	97% **11**	81% **12**
c	54% **13**	89% **14**	77% **15**
d	87% **16**	65% **17**	64% **18**

tion patterns may be generated for different objectives as outlined below.
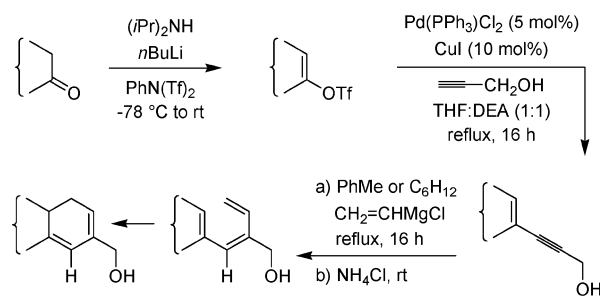
The triflates were prepared from the corresponding ketones upon treatment with LDA in THF at −78 °C followed by exposure to *N*-phenyl-trifluoromethanesulfonimide. In addition to the bicyclic systems **7**[3] and **10**[4] the triflates **39**[5] and **421**[6] (Table 2) have been prepared previously.

The trienes generated from bridged ring bicycle[2.2.1]-heptanones display a propensity to undergo the electrocyclization in situ, in contrast to other more conformationally mobile ring systems. This behavior is ascribed to the limited flexibility of the pendant vinyl group in the cyclic chelates

derived from the norbornene (entry a) and bornene (entry b) skeletons. The product distribution for entries c and d could be varied depending upon the reaction conditions (Scheme 2).

Our trienes cyclized over a temperature range that was consistent with literature precedent. The energy requirement for 6-π-electrocyclic ring closure varies significantly. Lithium enolates with adjacent electron-withdrawing groups (esters) proceeded below room temperature.[7] Less activated trienes also with an ester substituent required temperatures from 100 to 215 °C depending on the substitution pattern.[8]

Scheme 2. Bridged Ring Systems: Representative Cyclizations and Aromatizations

R R
( )n
n = 0 or 1
R = Me or H

15 **19** **18**

Toluene reflux, 16 h 77%

Toluene:THF (5:1) 98 °C, 16 h 53%

KOtBu, MeI THF, rt, 3 h 98%

20 **21** **22**

DDQ, toluene reflux, 3 h 56%

Toluene sealed tube 150 °C, 14 h 63%

DDQ, toluene reflux, 3 h 64%

23 **24** **25**

(3) Bentz, H.; Subramananian, L. R.; Hanack, M.; Martinez, G. A.; Marin, M. G.; Perez-Gssorio, R. *Tetrahedron Lett.* **1977**, 9.
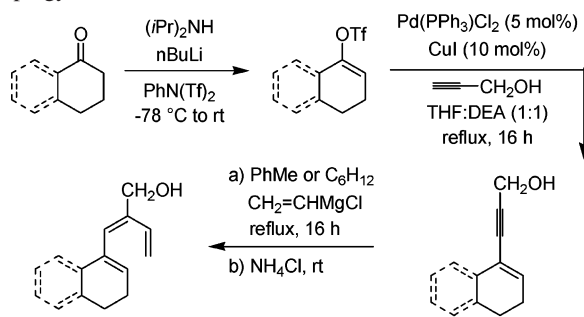(4) McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, 979.
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(6) Stang, P. J.; Warren, T. *Synthesis* **1980**, 283
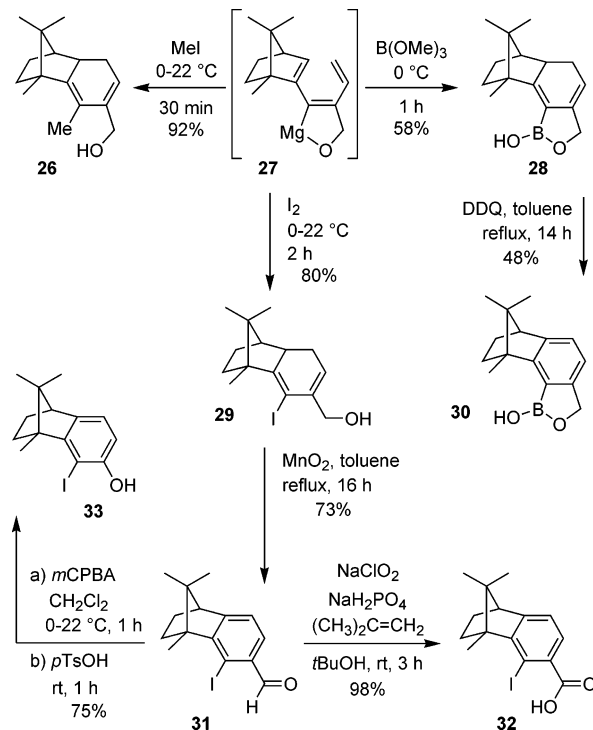(7) Magomedov, N. A.; Ruggiero, P. L.; Tang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 1624.

Table 2. Fused Ring Ketones: Synthesis of Triflates, Propargyl Alcohols, and Trienes

Entry	Vinyl Triflate	Propargyl Alcohol	Trienes
a	82% **34**	53% **35**	**36a** R = H, 78% **36b** R = Me, 99%
b	82% **37**	53% **38**	**39a** R = H, 77% **39b** R = Me, 87%
c	55% **40**[6]	64% **41**	**42a** R = H, 90% **42b** R = Me, 99%

Scheme 3. Reaction of the "Camphor Chelate" with Different Electrophiles

Upon treatment of the pinene triene **15** in a sealed tube at 150 °C in toluene, an inseparable mixture of regioisomeric cyclohexadiene isomers of type **20** was produced (Scheme 2). Additional exposure to toluene (110 °C) containing DDQ afforded the aldehyde **23**. In a similar manner, the chelate of type **19** was converted directly to the benzyl alcohol **21** after 16 h of heating in toluene/THF (5:1). In some cases, it was preferable to protect the alcohol in order to minimize decomposition. Consequently, alcohol **18** was protected as the methyl ether **22**. The methyl ether acts as a transient protecting group due to its removal by DDQ in the next step. A related pattern of inseparable diene isomers **25** was observed when **22** was heated in a sealed tube (toluene, 150

°C). Consistent with the behavior of **20**, further heating of **25** in the presence of DDQ afforded the aldehyde **24**.

This protocol is not limited to a proton quench. The intermediate chelate can be reacted with other electrophiles such as methyl iodide, iodine, or boron to generate the compounds in Scheme 3.

The intermediate chelate **27** derived from the camphor propargylic alcohol **11** was reacted with different electrophiles for the construction of variably substituted dienes and aromatic ring systems. Treatment with methyl iodide afforded the methyl substituted diene **26** in 92% yield. An analogous reaction in which the quenching agent was trimethyl borate provided the borinic acid **28**, while the parallel treatment with iodine gave the iodo-alcohol **29** in 73% yield. To prepare the aromatic compound **30**, the diene **28** was treated with DDQ in refluxing toluene. The iodo-benzaldehyde **31** was generated from **29** in 86% yield after treatment with excess manganese dioxide in refluxing toluene.

Peracid oxidation (*m*-CPBA) of aldehyde **31** led, via the formate (hydrolyzed directly with TsOH), to the iodo-phenol **33**, and oxidation in buffered sodium chlorite afforded the iodobenzoic acid **32**. We attempted to convert this *ortho*-iodobenzoic acid into organic solvent soluble IBX and Dess−Martin periodinanes (not illustrated) for the potential kinetic oxidative resolution of alcohols and asymmetric oxidation of sulfides. Unfortunately, despite considerable effort, the solubility inherent in these molecules precluded their successful conversion to the periodinanes. Another factor may be the potential nonbonded interaction that develops between the periodinane and the adjacent bridgehead methyl group in the desired product.

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Scheme 4. Fused Ring Systems: Representative Cyclizations and Aromatizations
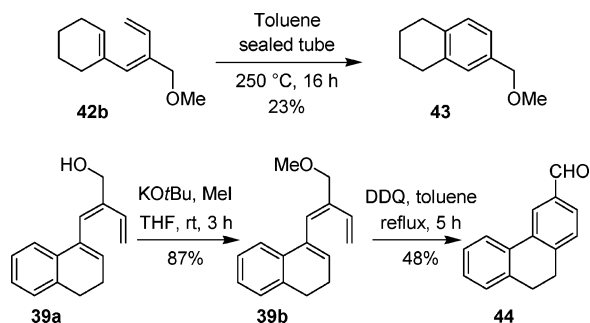
The potential of our annulation strategy for attachment of an aryl ring to cyclohexanones was also examined. These examples all stopped at the triene stage (Table 2) and required further heating to effect the electrocyclizations. The cyclohexanone-derived triene **42b** required rather forcing conditions in a sealed tube in toluene at 250 °C for 16 h to achieve a 23% yield of **43**. In parallel with the observations for the bridged ring examples, more rigid compounds such as **39b** cyclized readily in refluxing toluene with DDQ. This series afforded the aldehyde **44** directly due to methyl ether cleavage and concomitant oxidation, as illustrated in Scheme 4.

In summary, we have developed a versatile aryl annulation procedure from the enol triflates of various cyclic ketones via vinylmagnesium chloride addition to the derived propargyl alcohol, followed by 6-π-electrocyclization to generate the substituted benzene ring after oxidation. In several cases, if a benzaldehyde is the objective, the complete carbometalation−annulation−oxidation sequence may be conducted in one reaction flask.

Supporting Information Available: Experimental details and spectral characterization for these compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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