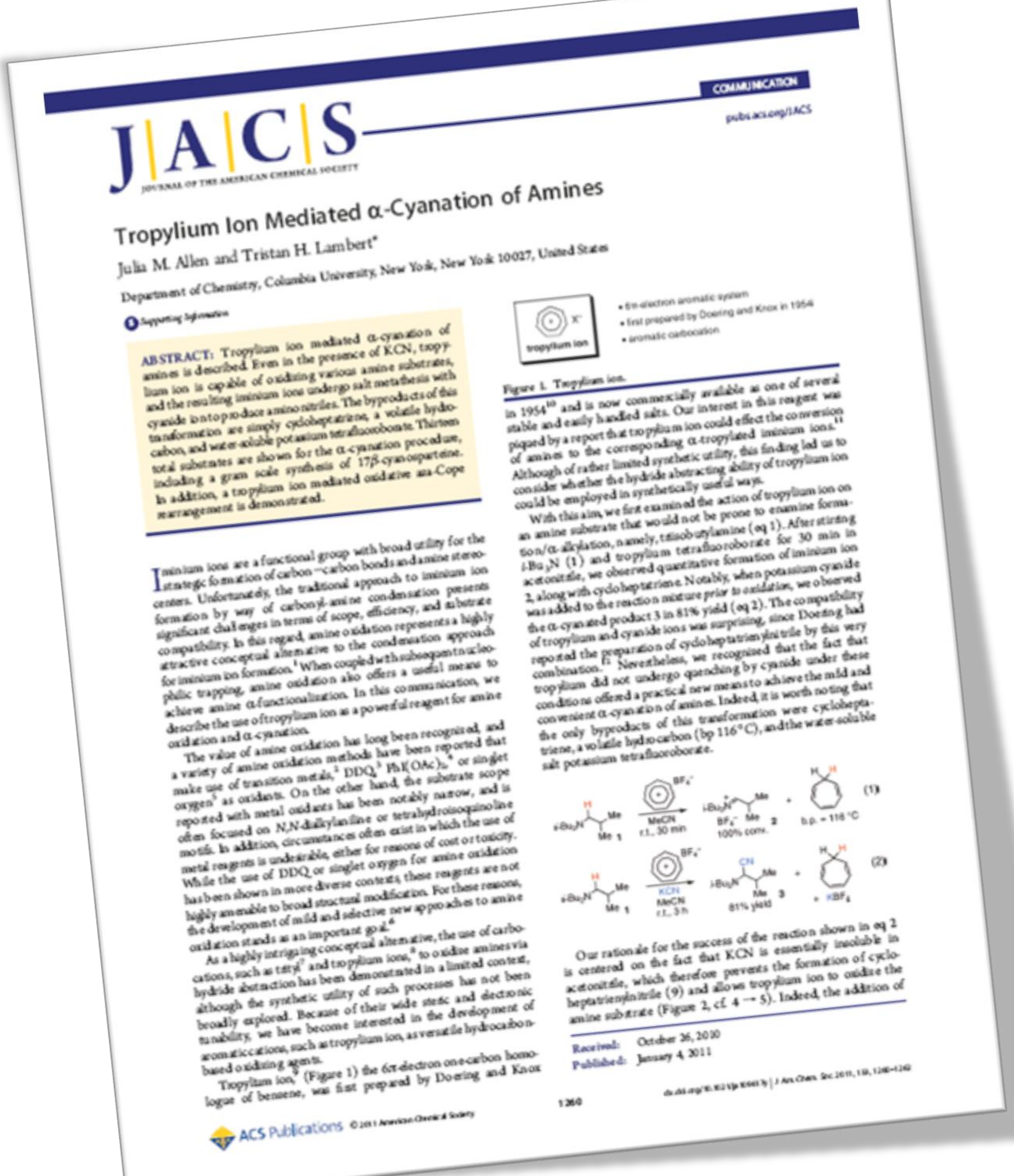

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Tropylium Ion Mediated α-Cyanation of Amines

Julia M. Allen and Tristan H. Lambert*

Department of Chemistry, Columbia University, New York, New York 10027, United States

S Supporting Information

ABSTRACT: Tropylium ion mediated α-cyanation of amines is described. Even in the presence of KCN, tropylium ion is capable of oxidizing various amine substrates, and the resulting iminium ions undergo salt metathesis with cyanide ion to produce amino nitriles. The byproducts of this transformation are simply cycloheptatriene, a volatile hydrocarbon, and water-soluble potassium tetrafluoroborate. Thirteen total substrates are shown for the α-cyanation procedure, including a gram scale synthesis of 17β-cyanosparteine. In addition, a tropylium ion mediated oxidative aza-Cope rearrangement is demonstrated.

Iminium ions are a functional group with broad utility for the strategic formation of carbon−carbon bonds and amine stereocenters. Unfortunately, the traditional approach to iminium ion formation by way of carbonyl-amine condensation presents significant challenges in terms of scope, efficiency, and substrate compatibility. In this regard, amine oxidation represents a highly attractive conceptual alternative to the condensation approach for iminium ion formation.[1] When coupled with subsequent nucleophilic trapping, amine oxidation also offers a useful means to achieve amine α-functionalization. In this communication, we describe the use of tropylium ion as a powerful reagent for amine oxidation and α-cyanation.

The value of amine oxidation has long been recognized, and a variety of amine oxidation methods have been reported that make use of transition metals,[2] DDQ,[3] $PhI(OAc)_2$,[4] or singlet oxygen[5] as oxidants. On the other hand, the substrate scope reported with metal oxidants has been notably narrow, and is often focused on *N,N*-dialkylaniline or tetrahydroisoquinoline motifs. In addition, circumstances often exist in which the use of metal reagents is undesirable, either for reasons of cost or toxicity. While the use of DDQ or singlet oxygen for amine oxidation has been shown in more diverse contexts, these reagents are not highly amenable to broad structural modification. For these reasons, the development of mild and selective new approaches to amine oxidation stands as an important goal.[6]

As a highly intriguing conceptual alternative, the use of carbocations, such as trityl[7] and tropylium ions,[8] to oxidize amines via hydride abstraction has been demonstrated in a limited context, although the synthetic utility of such processes has not been broadly explored. Because of their wide steric and electronic tunability, we have become interested in the development of aromatic cations, such as tropylium ion, as versatile hydrocarbon-based oxidizing agents.

Tropylium ion,[9] (Figure 1) the 6π-electron one-carbon homologue of benzene, was first prepared by Doering and Knox in 1954[10] and is now commercially available as one of several stable and easily handled salts. Our interest in this reagent was piqued by a report that tropylium ion could effect the conversion of amines to the corresponding α-tropylated iminium ions.[11] Although of rather limited synthetic utility, this finding led us to consider whether the hydride abstracting ability of tropylium ion could be employed in synthetically useful ways.

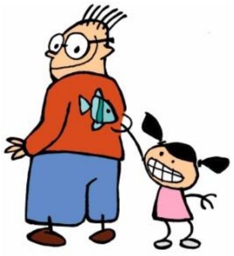
- 6π-electron aromatic system
- first prepared by Doering and Knox in 1954
- aromatic carbocation

Figure 1. Tropylium ion.

With this aim, we first examined the action of tropylium ion on an amine substrate that would not be prone to enamine formation/α-alkylation, namely, triisobutylamine (eq 1). After stirring *i*-Bu_3N (**1**) and tropylium tetrafluoroborate for 30 min in acetonitrile, we observed quantitative formation of iminium ion **2**, along with cycloheptatriene. Notably, when potassium cyanide was added to the reaction mixture *prior to oxidation*, we observed the α-cyanated product **3** in 81% yield (eq 2). The compatibility of tropylium and cyanide ions was surprising, since Doering had reported the preparation of cycloheptatrienylnitrile by this very combination.[12] Nevertheless, we recognized that the fact that tropylium did not undergo quenching by cyanide under these conditions offered a practical new means to achieve the mild and convenient α-cyanation of amines. Indeed, it is worth noting that the only byproducts of this transformation were cycloheptatriene, a volatile hydrocarbon (bp 116 °C), and the water-soluble salt potassium tetrafluoroborate.

Our rationale for the success of the reaction shown in eq 2 is centered on the fact that KCN is essentially insoluble in acetonitrile, which therefore prevents the formation of cycloheptatrienylnitrile (9) and allows tropylium ion to oxidize the amine substrate (Figure 2, cf. 4 → 5). Indeed, the addition of

Received: October 26, 2010
Published: January 4, 2011



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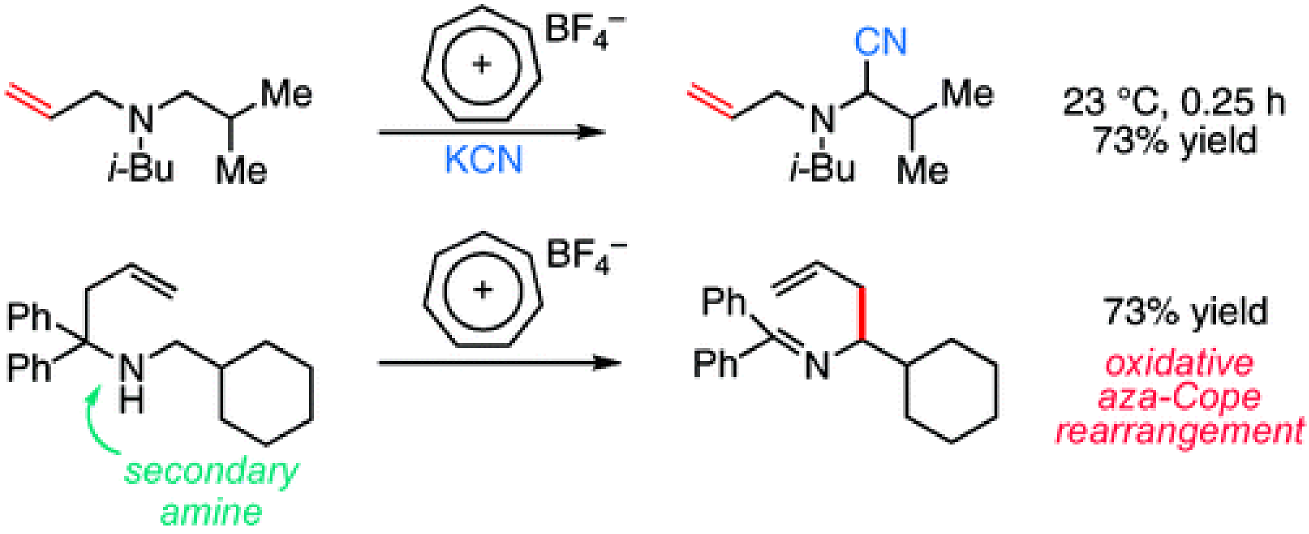

Julia M. Allen and Tristan H. Lambert *J. Am. Chem. Soc.* **2011**, *133*, 1260-1262.

Lambert Group

Tristan H. Lambert
Born 1976

Research interests

- Aromatic Ions
- Multicatalysis
- Reaction Design

2006-present: Assistant Professor, *Columbia University*
2004-2006: Postdoc, S. Danishefsky
Memorial Sloan-Kettering Cancer Center
2004: Ph.D. Chemistry, *Caltech*, D. C. MacMillan
2000: M.S. Chemistry, *UC Berkeley*, D. C. MacMillan
1998: B.S. Chemeistry, *Univ. of Wisconsin*, D. Klaassen

Last 5 papers

16. **Aromatic Ions.** Kelly, B. D. *Org. Lett,***2011**, *13*, *740-743.*
15. **Aromatic Ions.** Allen, J. M. *J. Am. Chem. Soc.,* **2011**, *133,* 1260-1262.
14. **Aromatic Ions.** Vanos, C. M. *Chemical Science,* **2010**, *1*, 705-708.
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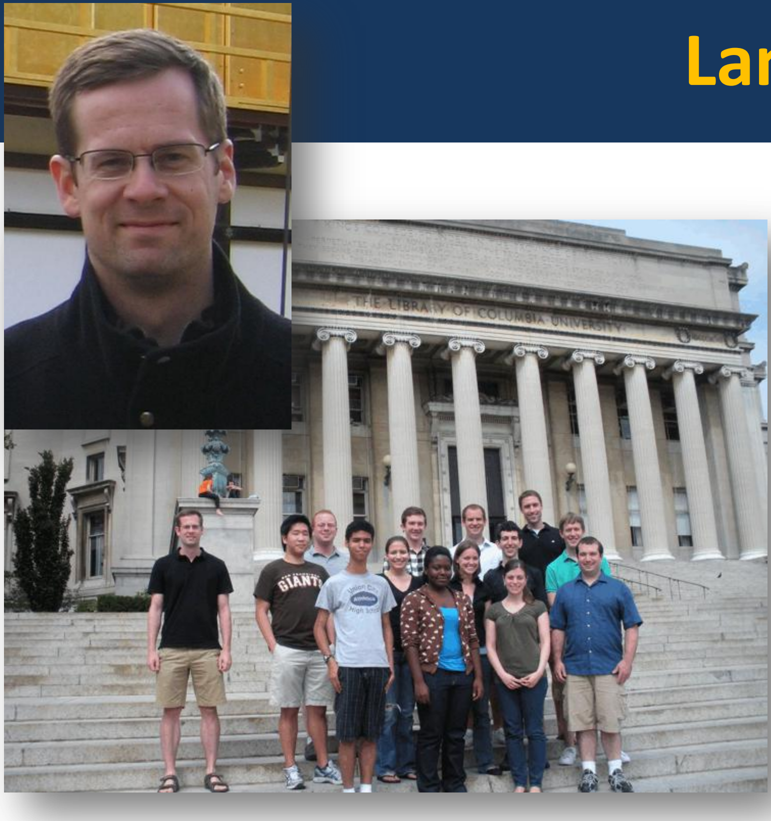

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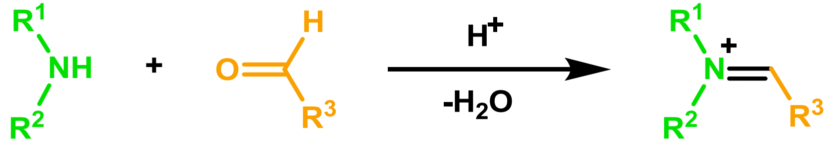
Previous Amine Oxidations Reports

- Iminiums traditionnal approach: **carbonyl-amine condensation**



«challenges in terms of scope, efficiency and substrate compatibility.»

➮ Alternative: **amine oxidation.**

- Main promoters are TM, DDQ, PhI(OAc)$_2$ and singlet oxygen.

- This work: **tropylium ion.**

tropylium ion

- 6π-electron aromatic system
- first prepared by Doering and Knox in 1954
- aromatic carbocation

TpBF$_4$: 60€/5g

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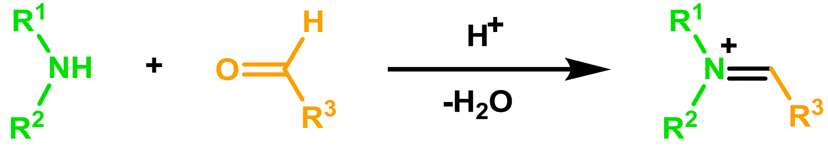

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A Johnson Matthey Company

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For a review on amine oxidation see
C.-J. Li *Acc. Chem. Res.* **2009**, *42*, 335.

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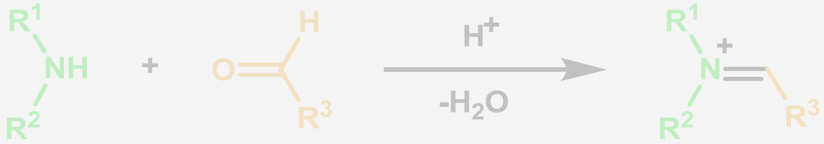

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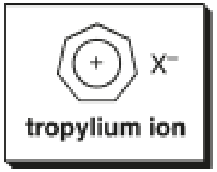

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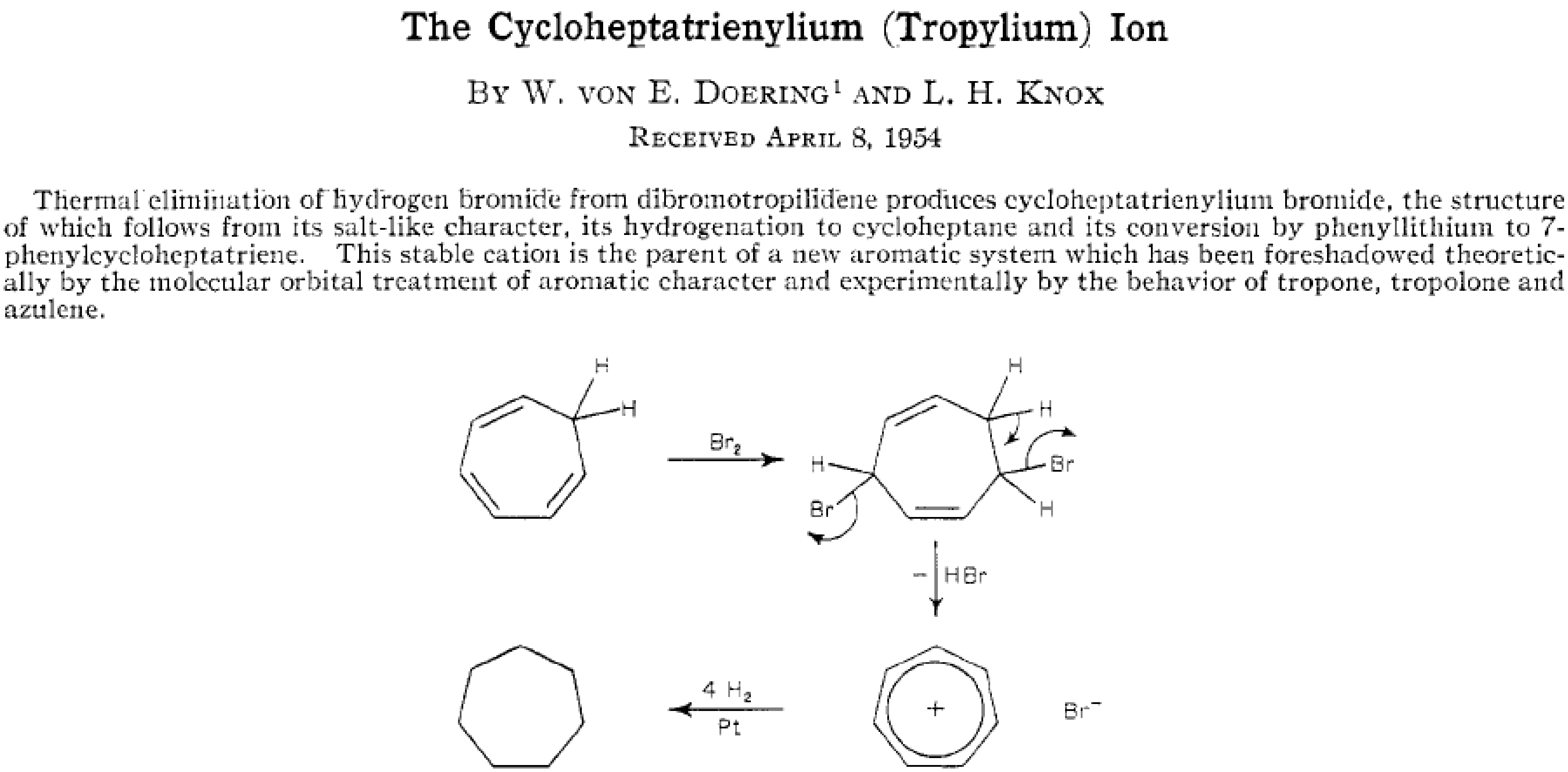
For a review on tropylium ion see
F . Pietra *Chem. Rev.* **1973**, *73*, 293.

Historical Tropylium Reports



The Cycloheptatrienylium (Tropylium) Ion

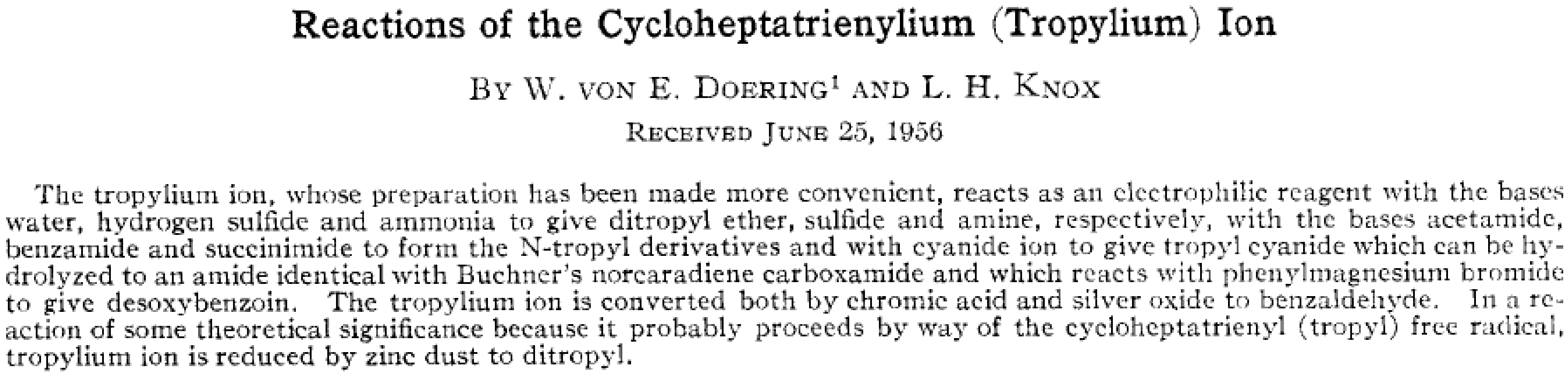
By W. von E. Doering[1] and L. H. Knox

Received April 8, 1954

Thermal elimination of hydrogen bromide from dibromotropilidene produces cycloheptatrienylium bromide, the structure of which follows from its salt-like character, its hydrogenation to cycloheptane and its conversion by phenyllithium to 7-phenylcycloheptatriene. This stable cation is the parent of a new aromatic system which has been foreshadowed theoretically by the molecular orbital treatment of aromatic character and experimentally by the behavior of tropone, tropolone and azulene.

W. v. E. Doering, L. H. Knox *J. Am. Chem. Soc.* **1954**, *76*, 3203.

Historical Tropylium Reports

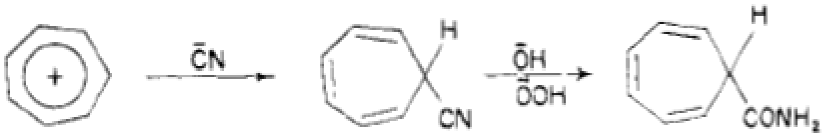


Reactions of the Cycloheptatrienylium (Tropylium) Ion

By W. von E. Doering[1] and L. H. Knox

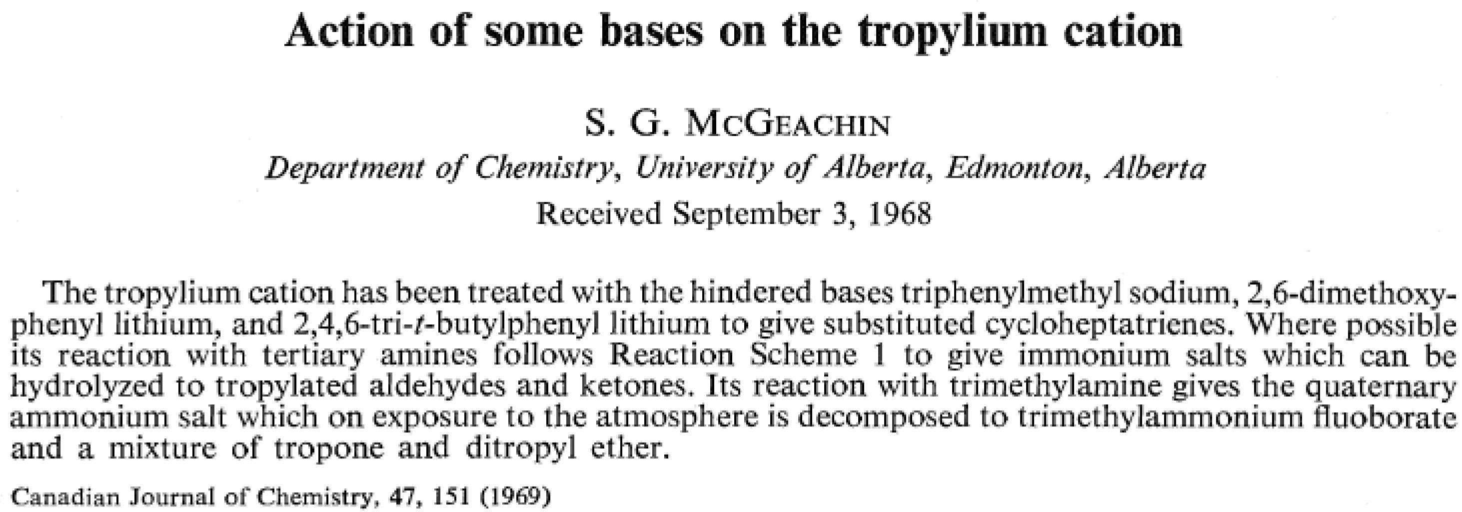
Received June 25, 1956

The tropylium ion, whose preparation has been made more convenient, reacts as an electrophilic reagent with the bases water, hydrogen sulfide and ammonia to give ditropyl ether, sulfide and amine, respectively, with the bases acetamide, benzamide and succinimide to form the N-tropyl derivatives and with cyanide ion to give tropyl cyanide which can be hydrolyzed to an amide identical with Buchner's norcaradiene carboxamide and which reacts with phenylmagnesium bromide to give desoxybenzoin. The tropylium ion is converted both by chromic acid and silver oxide to benzaldehyde. In a reaction of some theoretical significance because it probably proceeds by way of the cycloheptatrienyl (tropyl) free radical, tropylium ion is reduced by zinc dust to ditropyl.



W. v. E. Doering, L. H. Knox *J. Am. Chem. Soc.* **1957**, *79*, 352.

Historical Tropylium Reports



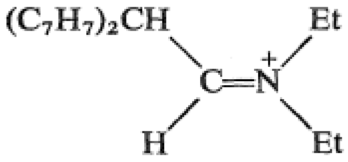
Action of some bases on the tropylium cation

S. G. McGeachin
Department of Chemistry, University of Alberta, Edmonton, Alberta

Received September 3, 1968

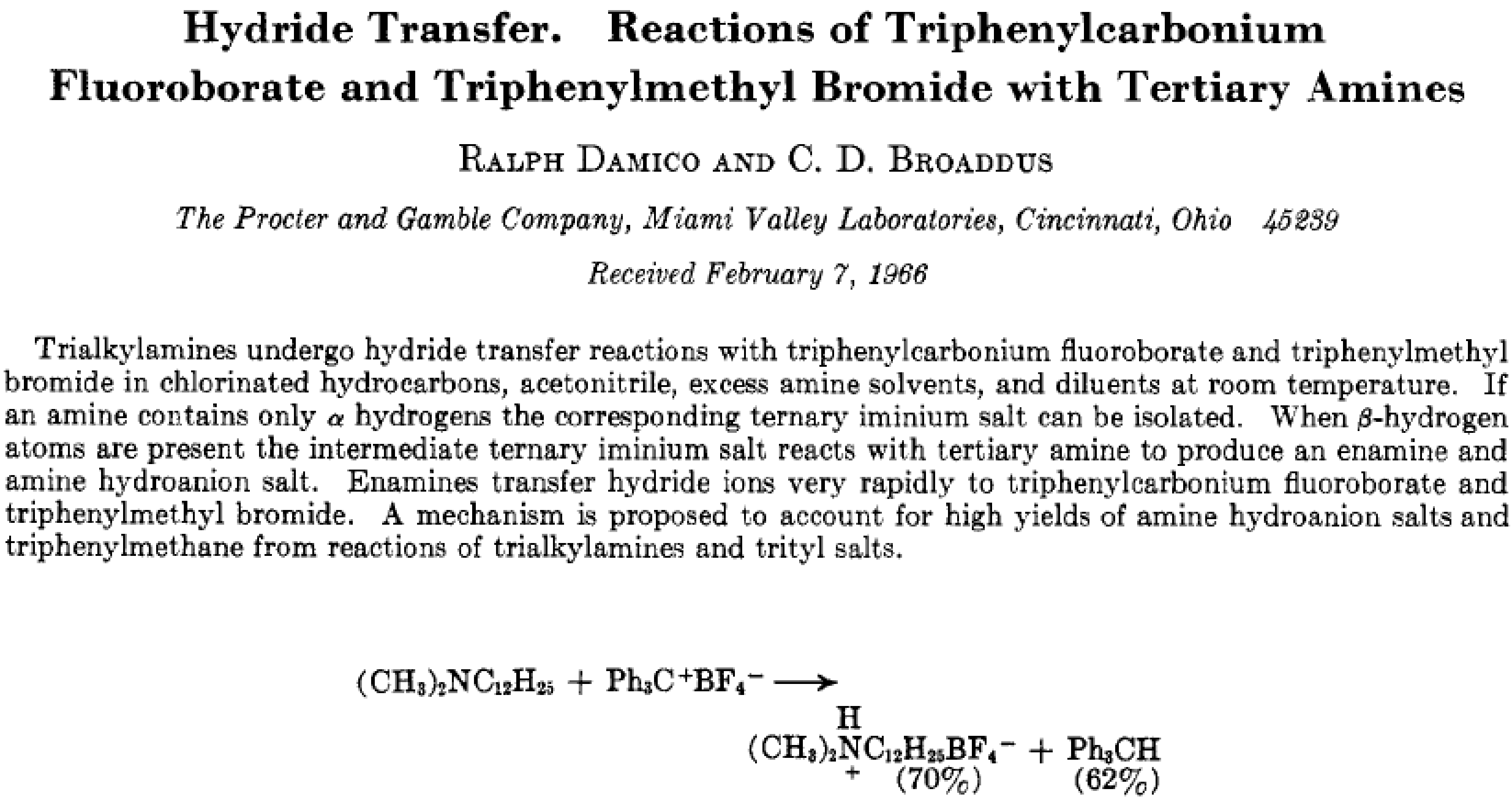
The tropylium cation has been treated with the hindered bases triphenylmethyl sodium, 2,6-dimethoxyphenyl lithium, and 2,4,6-tri-*t*-butylphenyl lithium to give substituted cycloheptatrienes. Where possible its reaction with tertiary amines follows Reaction Scheme 1 to give immonium salts which can be hydrolyzed to tropylated aldehydes and ketones. Its reaction with trimethylamine gives the quaternary ammonium salt which on exposure to the atmosphere is decomposed to trimethylammonium fluoborate and a mixture of tropone and ditropyl ether.

Canadian Journal of Chemistry, 47, 151 (1969)



S. G. McGeachin *Can. J. Chem.* **1969**, 47, 151.

Historical Tropylium Reports



Hydride Transfer. Reactions of Triphenylcarbonium Fluoroborate and Triphenylmethyl Bromide with Tertiary Amines

Ralph Damico and C. D. Broaddus

The Procter and Gamble Company, Miami Valley Laboratories, Cincinnati, Ohio 45239

Received February 7, 1966

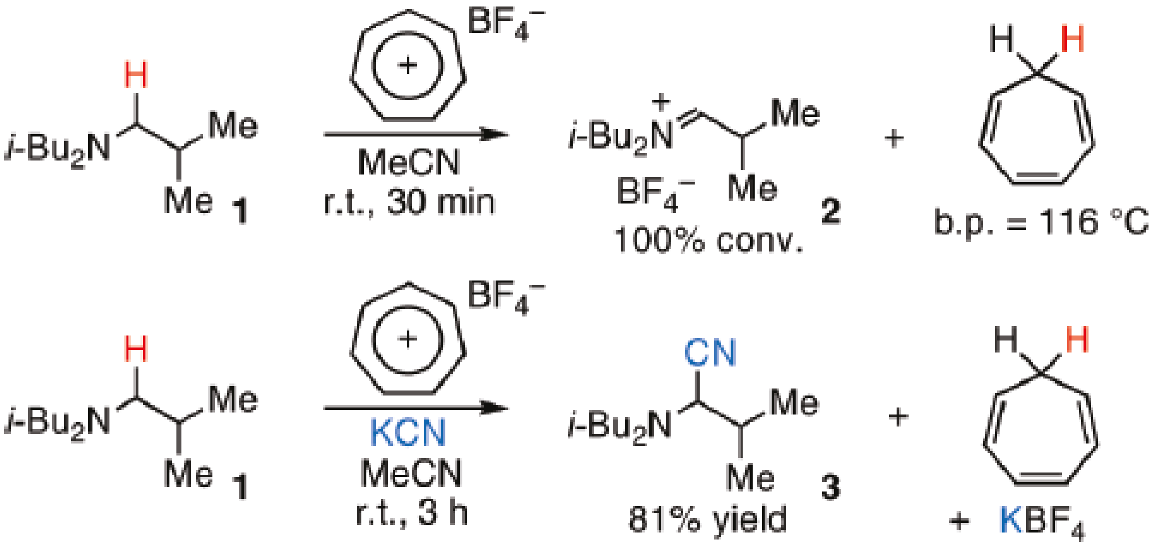
Trialkylamines undergo hydride transfer reactions with triphenylcarbonium fluoroborate and triphenylmethyl bromide in chlorinated hydrocarbons, acetonitrile, excess amine solvents, and diluents at room temperature. If an amine contains only α hydrogens the corresponding ternary iminium salt can be isolated. When β-hydrogen atoms are present the intermediate ternary iminium salt reacts with tertiary amine to produce an enamine and amine hydroanion salt. Enamines transfer hydride ions very rapidly to triphenylcarbonium fluoroborate and triphenylmethyl bromide. A mechanism is proposed to account for high yields of amine hydroanion salts and triphenylmethane from reactions of trialkylamines and trityl salts.

$$(CH_3)_2NC_{12}H_{25} + Ph_3C^+BF_4^- \longrightarrow$$

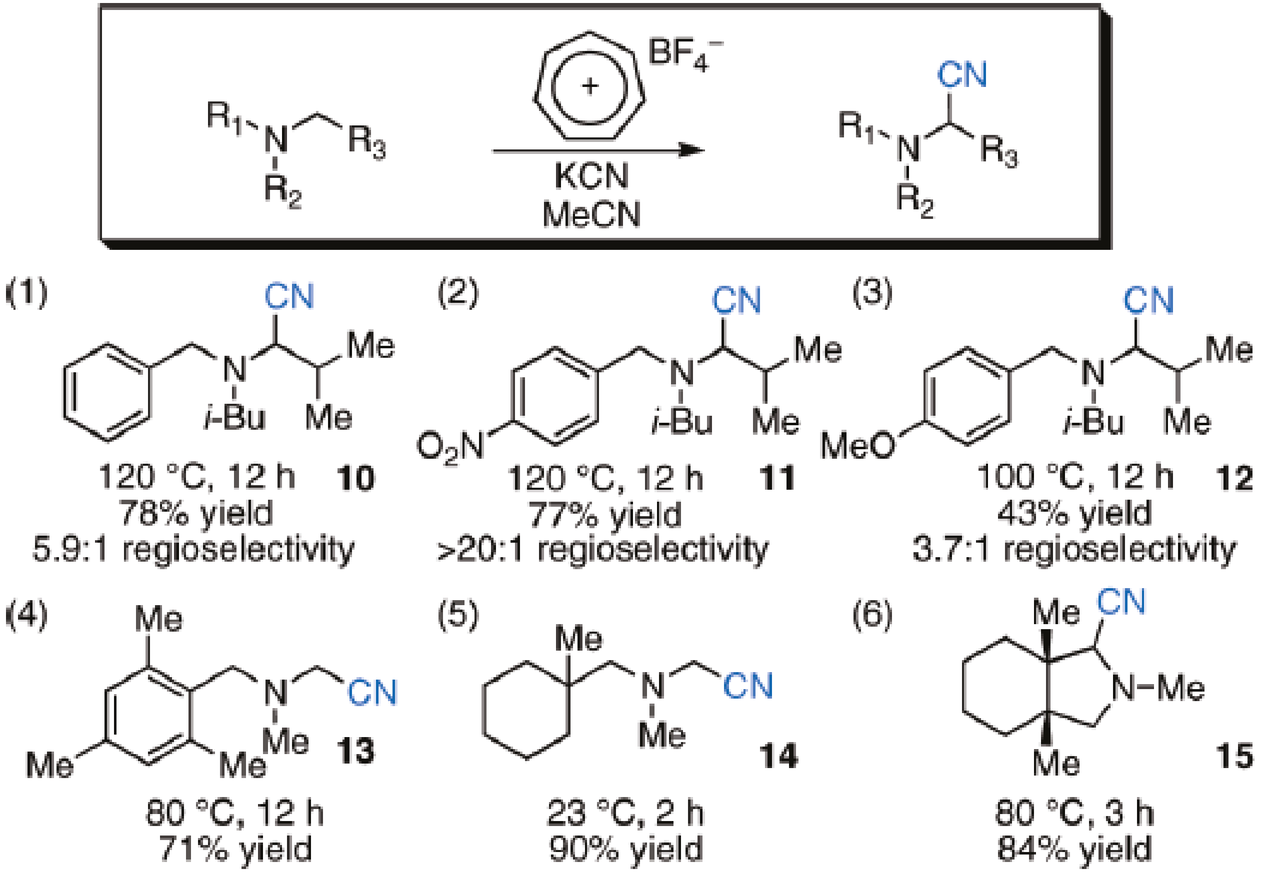
$$\underset{(70\%)}{(CH_3)_2\overset{H}{\underset{+}{N}}C_{12}H_{25}BF_4^-} + \underset{(62\%)}{Ph_3CH}$$

R. Damico, C. D. Broaddus *J. Org. Chem.* **1966**, 31, 1607.

This Work


H
i-Bu2N
Me
Me
1
BF4−
+
MeCN
r.t., 30 min
i-Bu2N+
Me
BF4−
Me
2
100% conv.
+
H
H
b.p. = 116 °C
H
i-Bu2N
Me
Me
1
BF4−
+
KCN
MeCN
r.t., 3 h
CN
i-Bu2N
Me
Me
3
81% yield
+
H
H
+ KBF4

Subtrate Scope Studies



(1) 120 °C, 12 h **10**
78% yield
5.9:1 regioselectivity

(2) 120 °C, 12 h **11**
77% yield
>20:1 regioselectivity

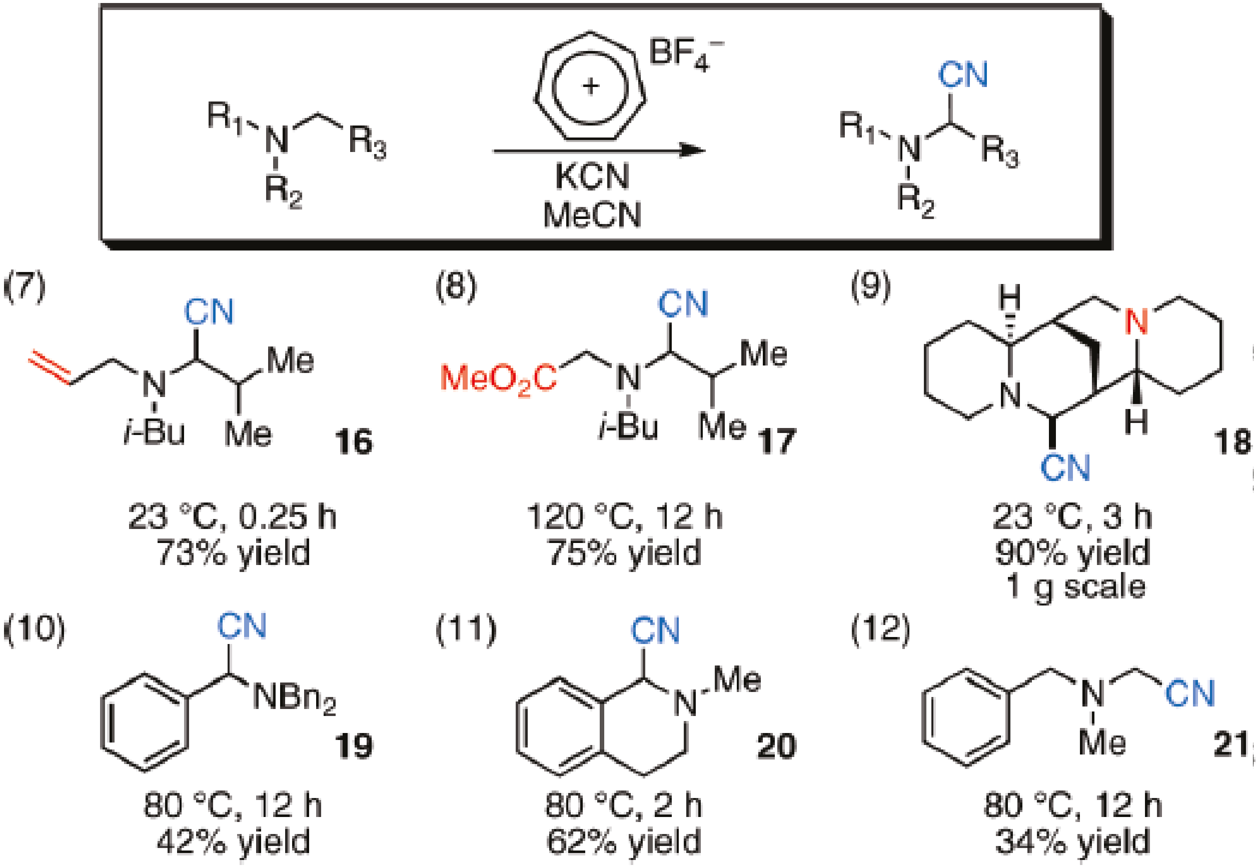
(3) 100 °C, 12 h **12**
43% yield
3.7:1 regioselectivity

(4) **13**
80 °C, 12 h
71% yield

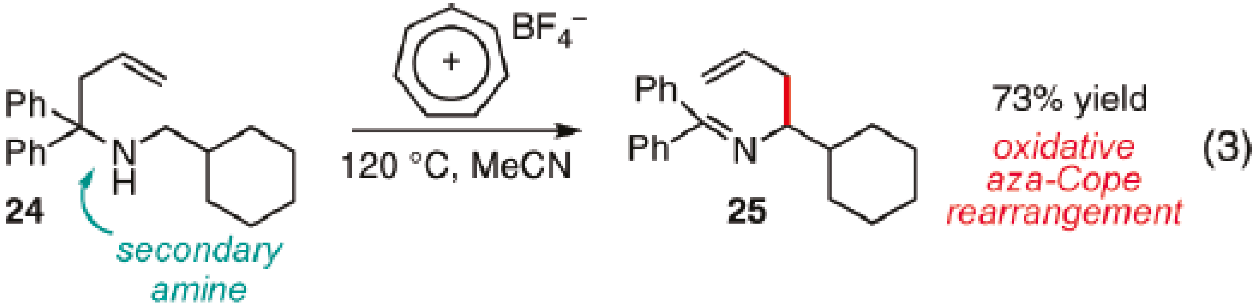
(5) **14**
23 °C, 2 h
90% yield

(6) **15**
80 °C, 3 h
84% yield

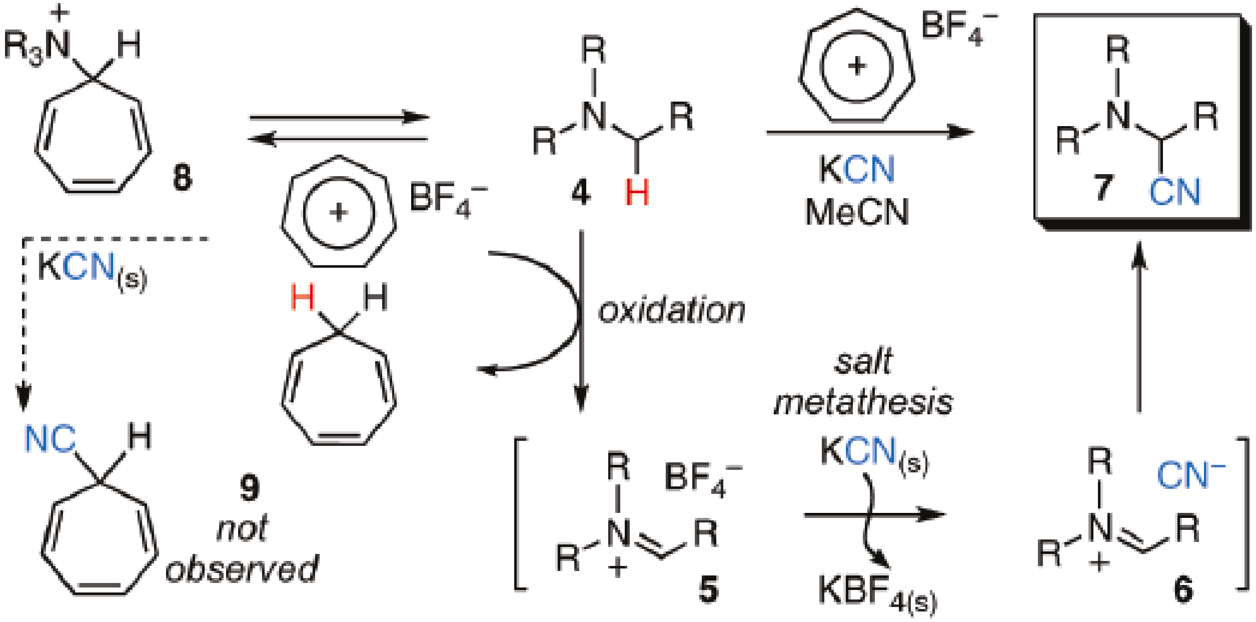
Subtrate Scope Studies



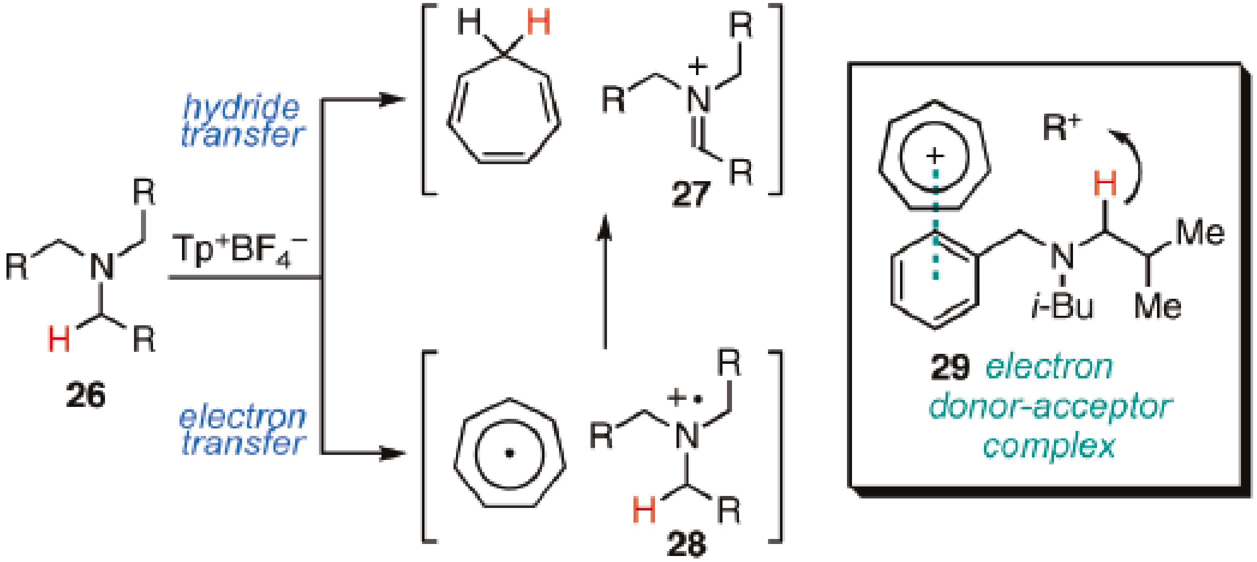
Oxydative Aza-Cope Rearrangement



Mechanistic Analysis

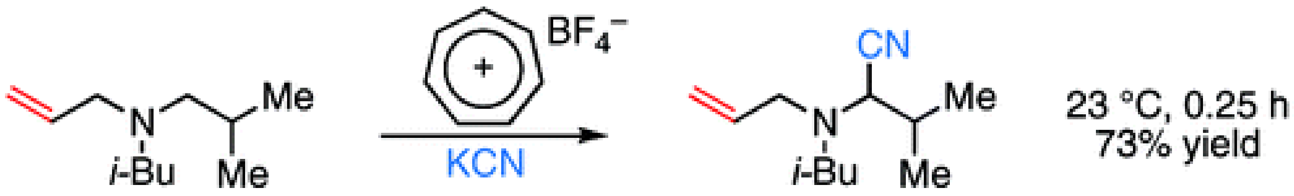


Mechanistic Alternatives



Outlook

- **Tropylium ion mediated α-cyanation of amines.**



❶ Broad scope of **amine** oxidation *(13 total substrates).*

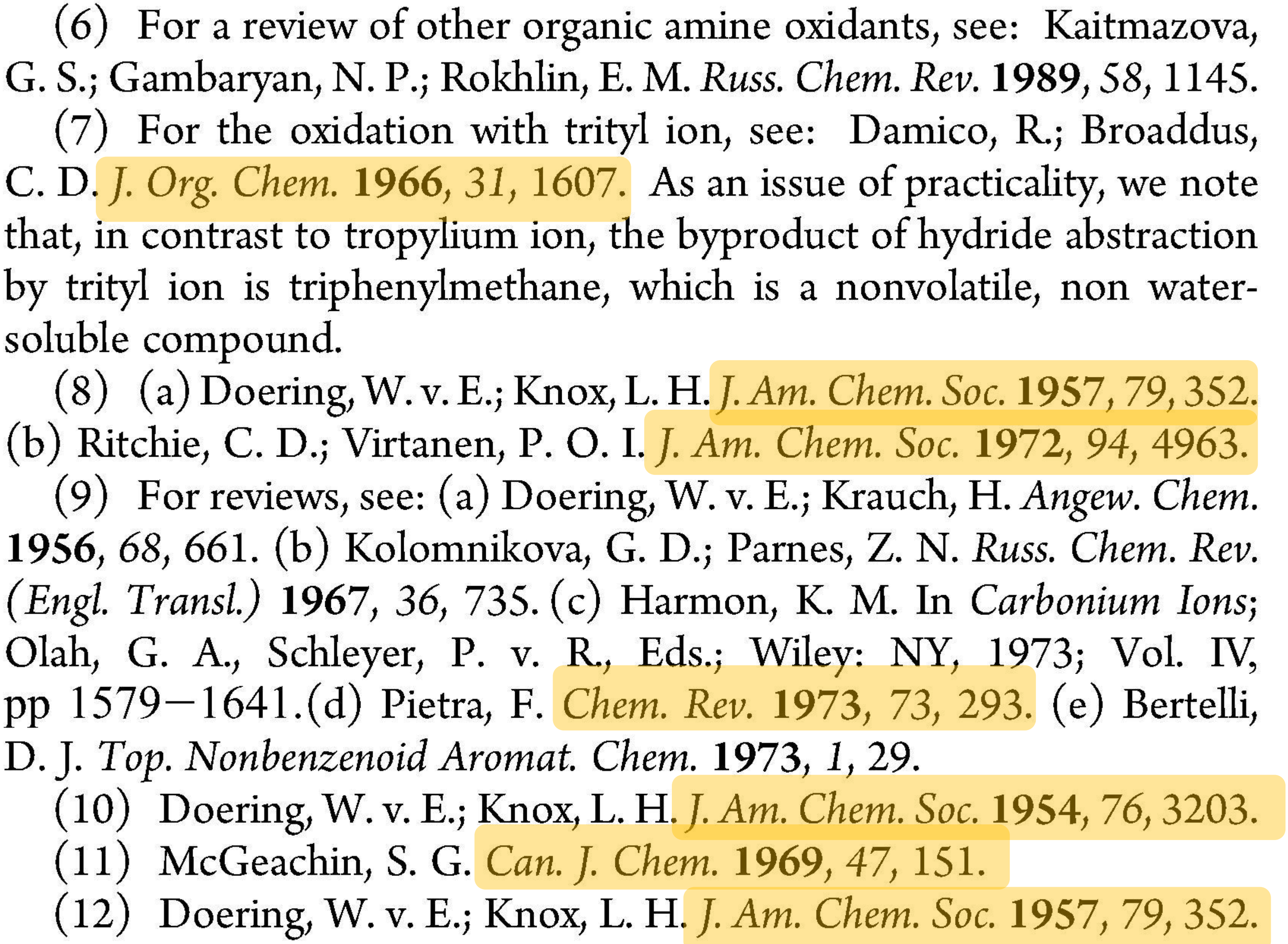
❷ Resulting **iminiums** undergo salt metathesis with cyanide (*+ 1 aza-Cope rear. example*).

❸ It produces **aminonitriles**.

- Byproducts are simply:
  - **cycloheptatriene** *(volatile hydrocarbon)*
  - **potassium tetrafluoroborate** *(water-soluble).*

☺ Thank you STeRéo! ☺

References



(6) For a review of other organic amine oxidants, see: Kaitmazova, G. S.; Gambaryan, N. P.; Rokhlin, E. M. *Russ. Chem. Rev.* **1989**, *58*, 1145.

(7) For the oxidation with trityl ion, see: Damico, R.; Broaddus, C. D. *J. Org. Chem.* **1966**, *31*, 1607. As an issue of practicality, we note that, in contrast to tropylium ion, the byproduct of hydride abstraction by trityl ion is triphenylmethane, which is a nonvolatile, non water-soluble compound.

(8) (a) Doering, W. v. E.; Knox, L. H. *J. Am. Chem. Soc.* **1957**, *79*, 352. (b) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1972**, *94*, 4963.

(9) For reviews, see: (a) Doering, W. v. E.; Krauch, H. *Angew. Chem.* **1956**, *68*, 661. (b) Kolomnikova, G. D.; Parnes, Z. N. *Russ. Chem. Rev. (Engl. Transl.)* **1967**, *36*, 735. (c) Harmon, K. M. In *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: NY, 1973; Vol. IV, pp 1579−1641.(d) Pietra, F. *Chem. Rev.* **1973**, *73*, 293. (e) Bertelli, D. J. *Top. Nonbenzenoid Aromat. Chem.* **1973**, *1*, 29.

(10) Doering, W. v. E.; Knox, L. H. *J. Am. Chem. Soc.* **1954**, *76*, 3203.

(11) McGeachin, S. G. *Can. J. Chem.* **1969**, *47*, 151.

(12) Doering, W. v. E.; Knox, L. H. *J. Am. Chem. Soc.* **1957**, *79*, 352.