Nathan Kornblum Joseph F. Bunnett Roberto A. Rossi

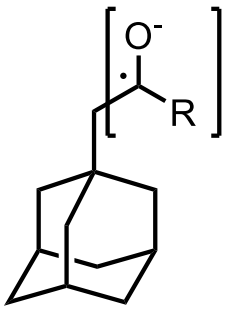
Electron Transfer-Mediated Substitution: $S_{RN}1$ Reaction Discovery, Elucidation, and Legacy

N. Ian Rinehart

Denmark Group Meeting

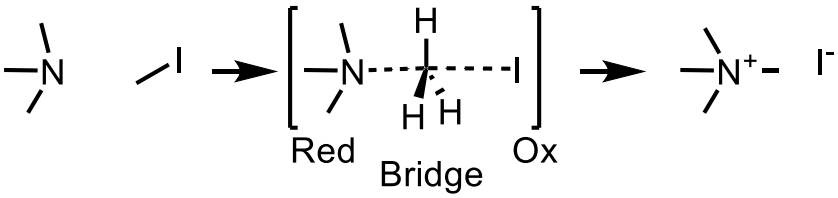
Scope of Meeting

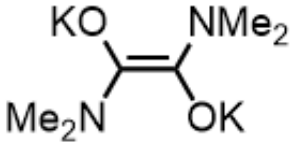
1. Description and elucidation of $S_{RN}1$ mechanism
    1. Early observations of electron transfer (ET) mediated substitution
    2. Christening of the $S_{RN}1$ mechanism
    3. Key studies elucidating mechanism and limitations of $S_{RN}1$ chemistry
2. The legacy of $S_{RN}1$ chemistry
    1. Conceptual discourse inspired by ET mediated substitution reactions
    2. Polar reactions that may actually be ET mediated
3. Intermission
4. Modern resurgence
    1. $S_{RN}1$'s cousin, Homolytic Aromatic Substitution (HAS)
    2. Modern ET mediated substitution research



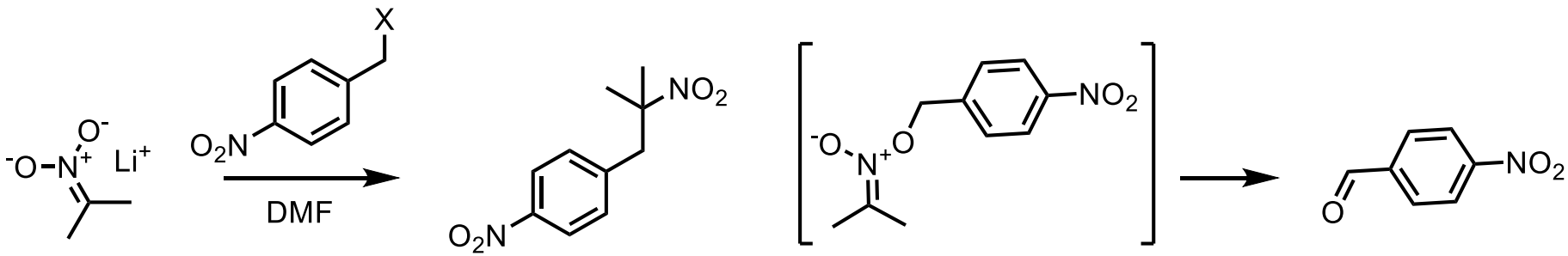
R = Me *less stable*
R = Ph *more stable*

Using ISET terminology:





Kornblum's Observations for Nitro-Substituted Benzylation of Nitronate



At -16 °C in DMF:

X = NMe_3^+
X = $O_2CC_6Cl_5$
X = Cl
} Exclusive *C*-alkylation

X = OTs — 4:3 *C*- vs *O*-alkylation

X = Br
X = I
} Dominant *O*-alkylation

X = Cl
X = Br
X = I

Rate studies:

O-alkylation increases 900x
C-alkylation increases 6x

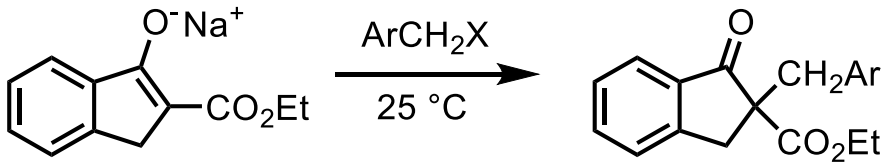
EPR signals were resolvable for lithium nitronate + nitrobenzene and the electrophile

C-alkylation is proposed to occur through a mode of action independent of the nucleofuge

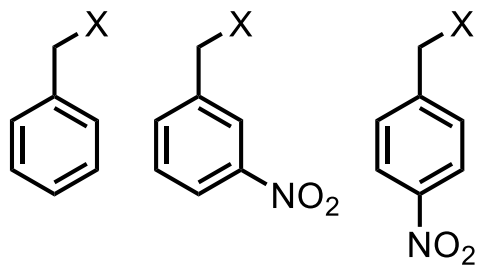
O-alkylation is proposed to occur through an S_N2 displacement

Kornblum and coworkers *J. Am. Chem. Soc.,* **1961**, 83, 2779
Kornblum, and coworkers *J. Am. Chem. Soc.,* **1964**, 86, 3904

Kornblum's Observations for Nitro-Substituted Benzylation of Enolate



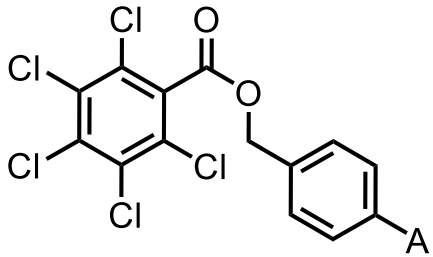
1 **2** **3**



X = I Rate doubles from 1 to 3

X = Br Rate quadruples from 1 to 3

X = Cl 3 is 375x faster than 1, 2 is 158x faster than 1



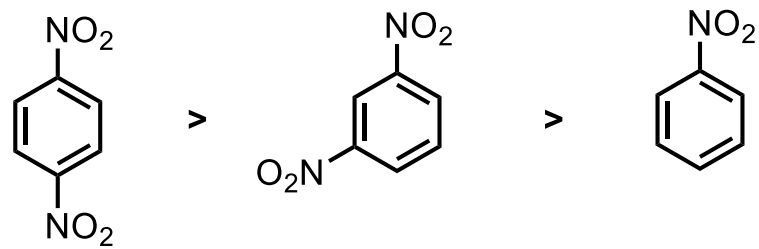
A = NO_2 72% 112 h

A = H 100% rsm 960 h

Evidence for radical mechanism:

- Electron acceptors inhibited reaction and turned on *O*-alkylation
- Substitution was turned on/off by electronics of ring, *not* nature of the leaving group
- *p*-NO_2ArCH_2-Cl or -$O_2CC_6Cl_5$ gave exclusive *C*-alkylation

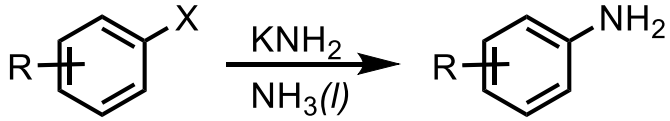
Rate of inhibition ~ ease of reduction by single electron:



1:1 *O* vs *C* 1:2 *O* vs *C* 1:2 *O* vs *C*

Kornblum, Kerber, and Urry *J. Am. Chem. Soc.,* **1965**, 87, 4520
Kornblum and coworkers, *J. Am. Chem. Soc.,* **1966**, 83, 5660

Bunnett Christens "$S_{RN}1$" Mechanism



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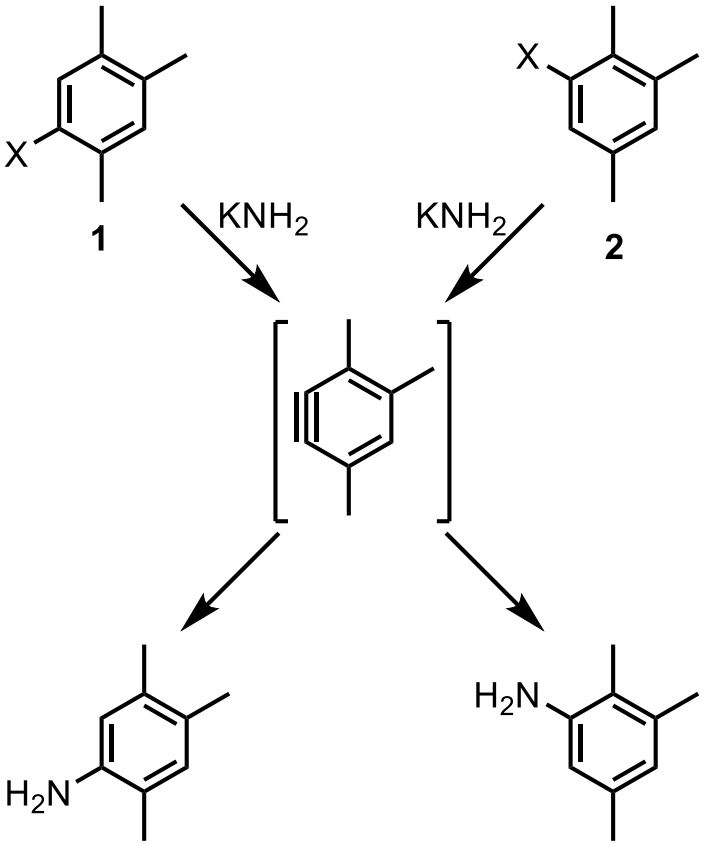
Benzyne mechanism predicts a mixture of retentive and cine substitution:



Slightly disfavored **1'**

Slightly favored **2'**

Non-rearranged product *not* via S_NAr:

Aryne formation reactivity: Br ~ I > Cl

S_NAr reactivity: Cl > Br > I

Cl shows ~ 3:5 prouct ratio consistent with aryne mechanism from both isomers, ruling out S_NAr

X = Cl, Br

1 or 2 formed 1':2' 1:1.5, within experimental error

X = I

1 formed 1':2' 1.6:1

2 formed 1':2' 1:5.86

with Et_2O or NOtBu:

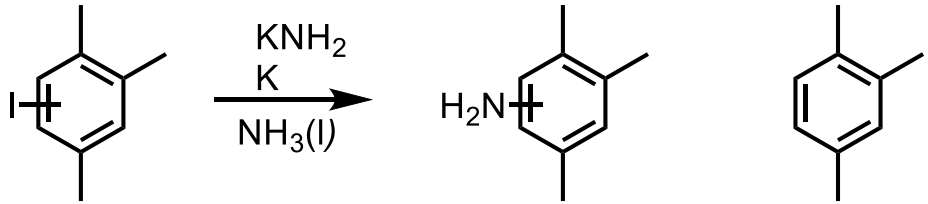
1:1.5

1:2.5

Bunnett and coworkers, *J. Am. Chem. Soc.*, **1970**, 92, 7463

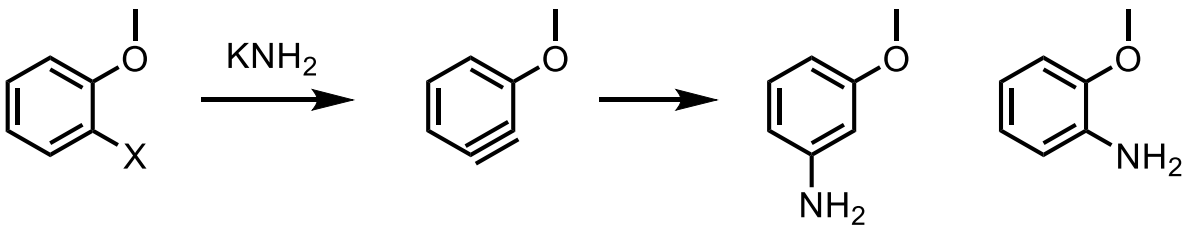
Bunnett, J. F. *J. Chem. Ed.*, **1974**, 51, 312

Single Electron Reductants Suppress Cine Substitution

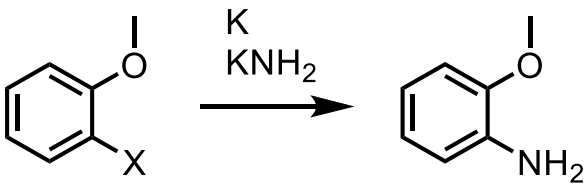


65-70% yield (*reduction*)

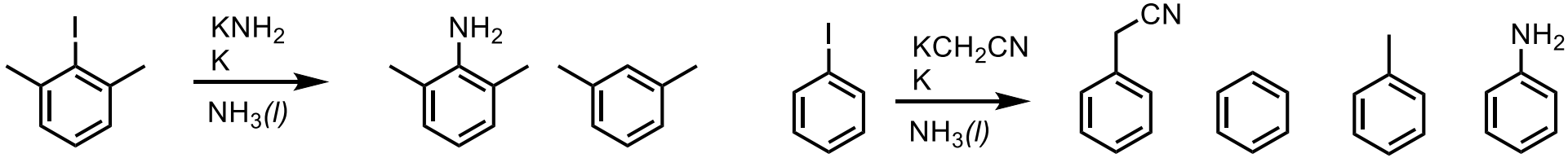
Ipso substitution with I



Known example of *cine* substitution



175-340% yields vs sub-stoichiometric K imply chain mechanism
Excess K shuts down *m*-anisidine formation for X = I and Br

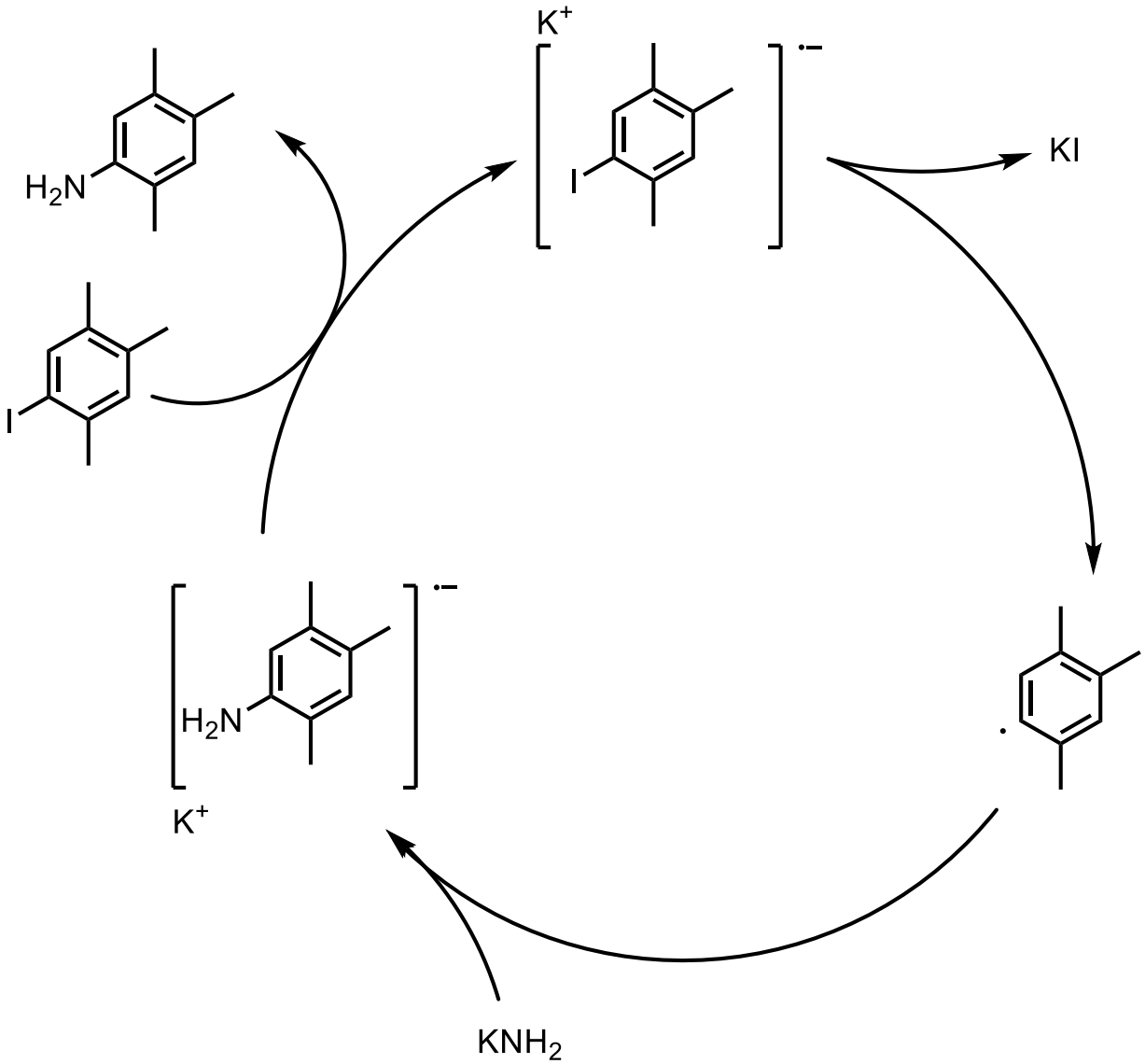


65% 25%

36% 26% 18% 3%

Bunnett and coworkers, *J. Am. Chem. Soc.*, **1970**, 92, 7464

Bunnett Christens "$S_{RN}1$" Mechanism



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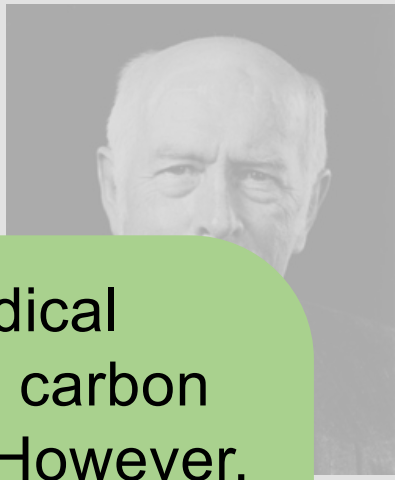
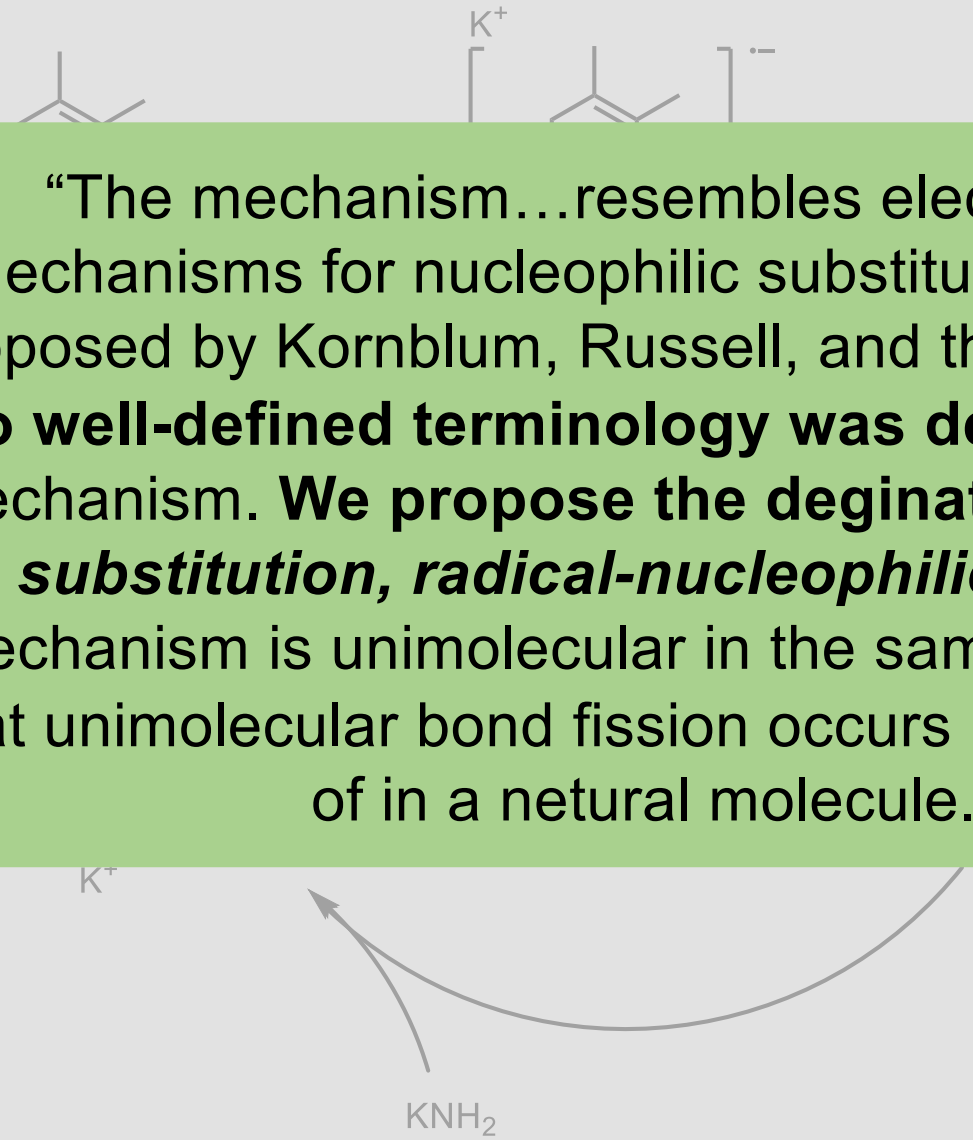
Bunnett and coworkers, *J. Am. Chem. Soc.*, **1970**, 92, 7463
Bunnett, J. F. *J. Chem. Ed.*, **1974**, 51, 312

Bunnett Christens "$S_{RN}1$" Mechanism

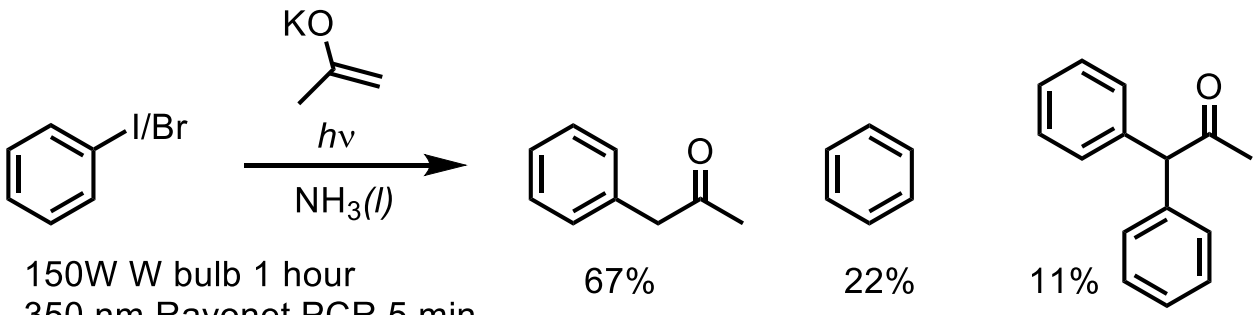




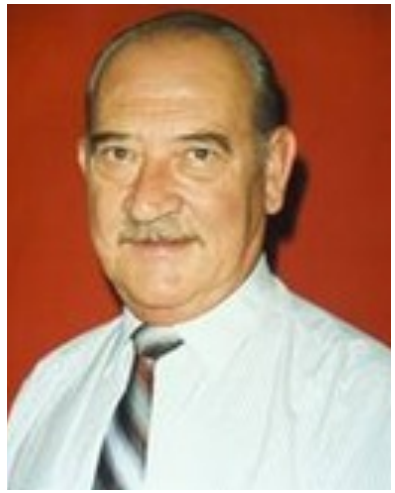
"The mechanism…resembles electron-transfer radical mechanisms for nucleophilic substitution at saturated carbon proposed by Kornblum, Russell, and their associates. However, **no well-defined terminology was developed** for this type of mechanism. **We propose the degination 'SRN1,'** standing for ***substitution, radical-nucleophilic, unimolecular***. The mechanism is unimolecular in the same sense as SN1, except that unimolecular bond fission occurs in a radical anion instead of in a netural molecule." (Bunnett)

Bunnett and coworkers, *J. Am. Chem. Soc.*, **1970**, 92, 7463
Bunnett, J. F. *J. Chem. Ed.*, **1974**, 51, 312

$S_{RN}1$ Utility Expanded by Photochemical Initiation



150W W bulb 1 hour
350 nm Rayonet PCR 5 min
95% rsm in dark
K and *t*-BuOH used to prepare enolate



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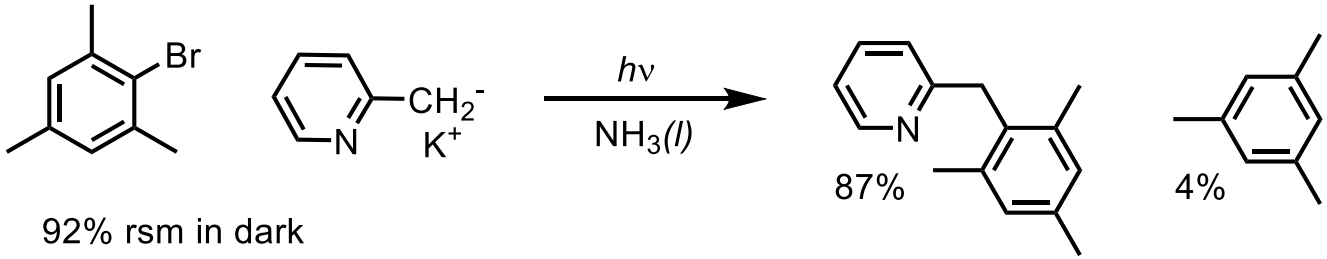
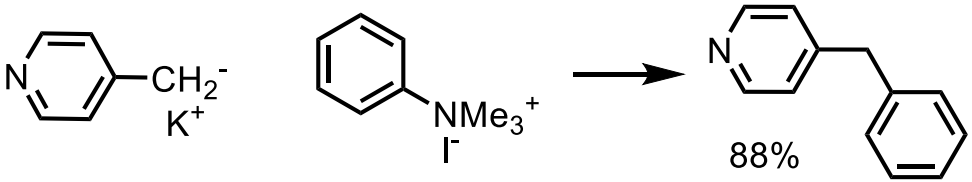


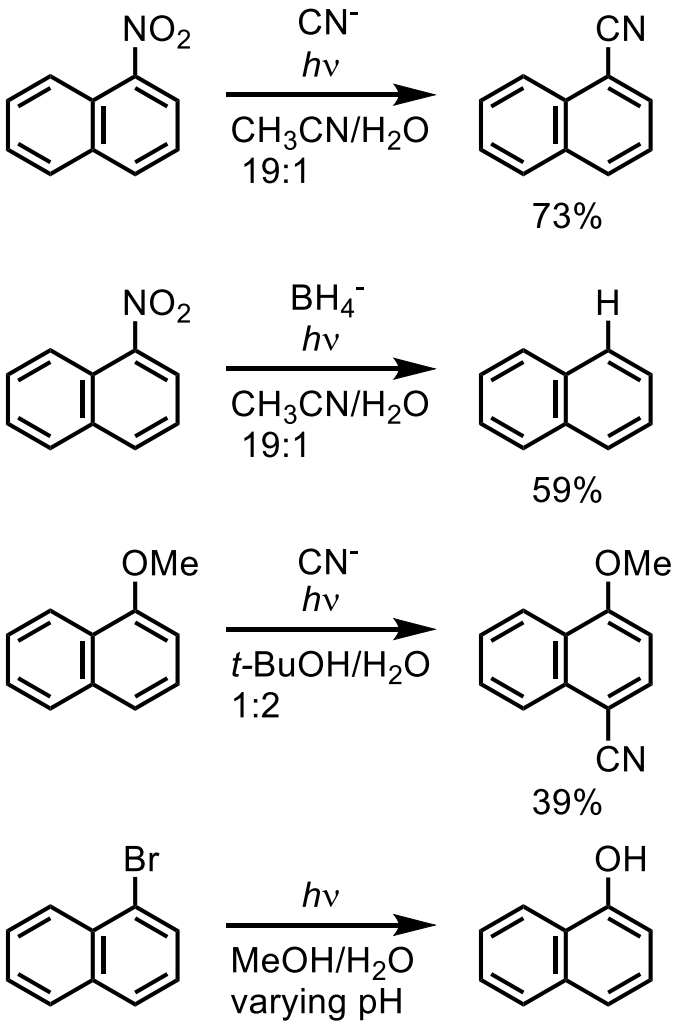
92% rsm in dark



Joseph F. Bunnett

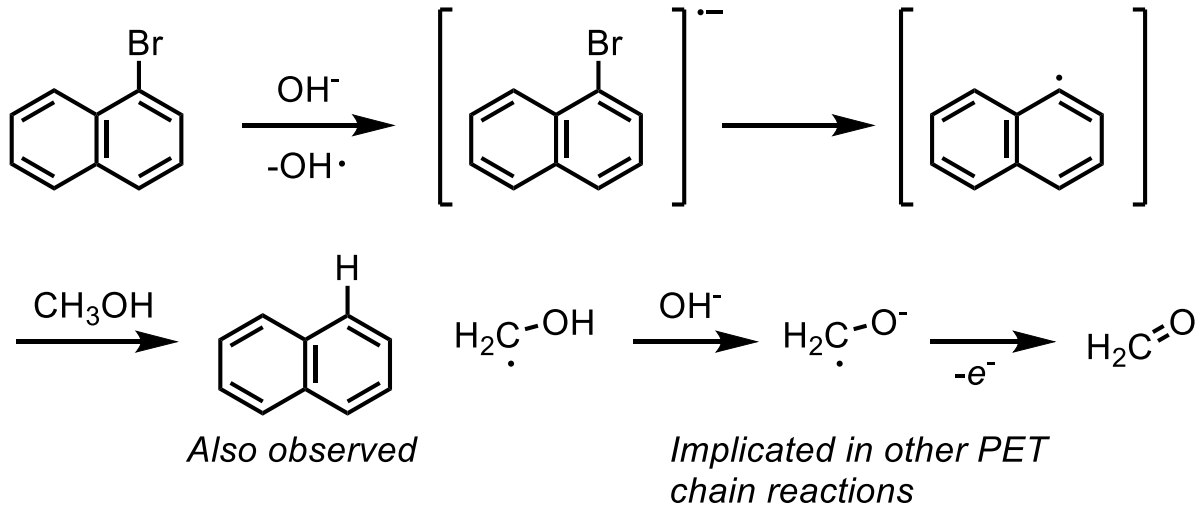
Bunnett and Rossi, *J. Org. Chem.,* **1973**, 38, 1407
Bunnett and coworkers, ibid, **1973**, 39, 382

$S_{RN}1$ vs "Classical" Aromatic Photosubstitution

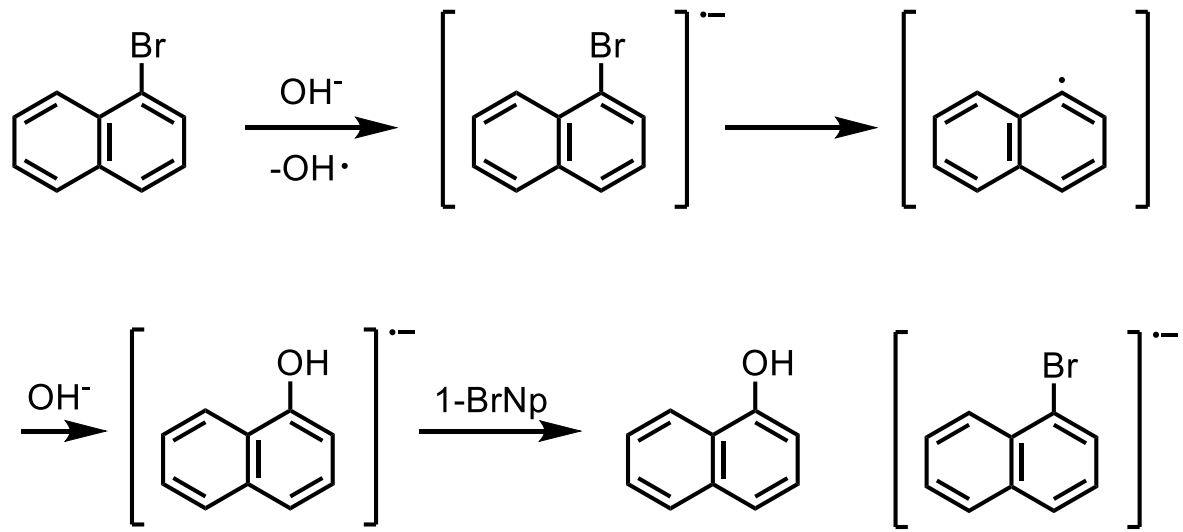


pH <8: Φ independent of pH
pH >8: Φ dependent of pH

Proposed Explanation for pH dependence:



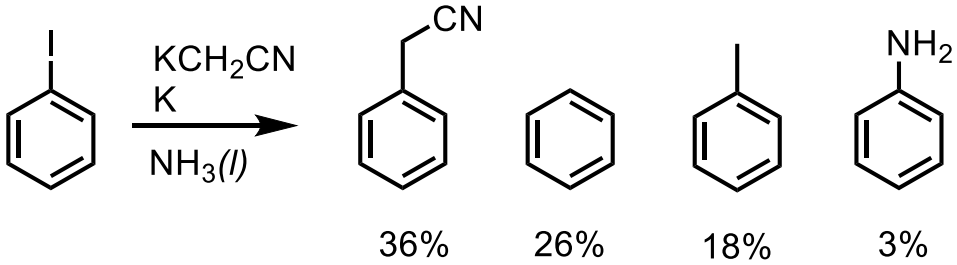
Possible $S_{RN}1$ Mechanism:

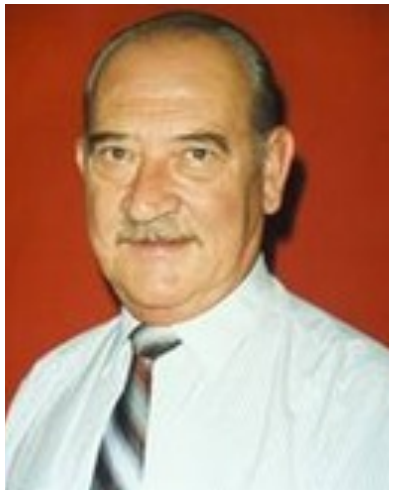


Havinga and Cornelisse, *Chem. Rev.*, **1975**, 75, 353.

$S_{RN}1$ Fragmentation in C-C Bond Formation

Recall:





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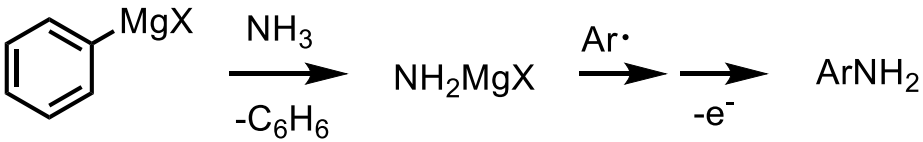
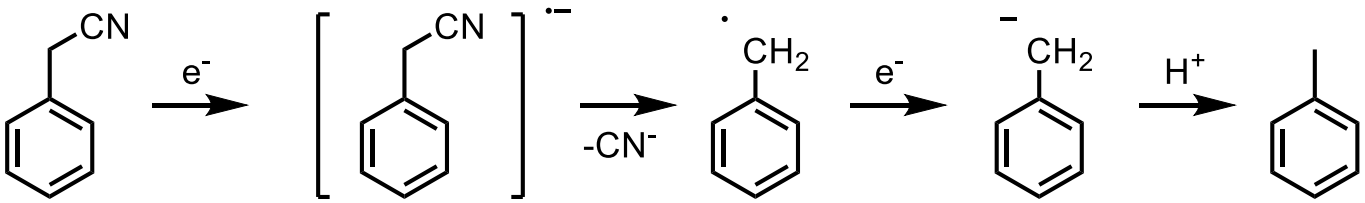
NB:
Radical abstraction of H from ethereal or hydrocarbon solvents limits their use in $S_{RN}1$ chemistry
Most C fragments are Z-substituted, enabling deprotonation in $NH_3(l)$ or DMSO



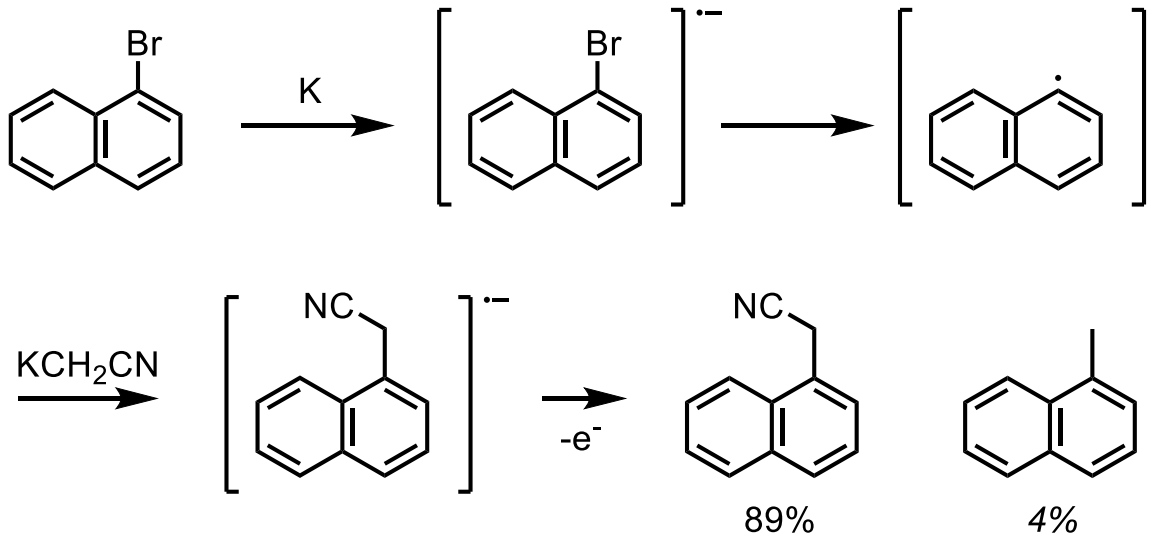
A common problem with C-C bond formation:

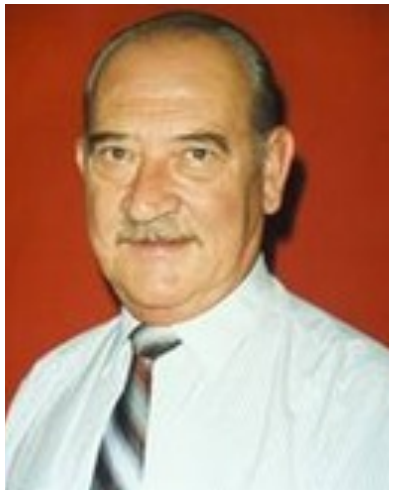


Rossi and coworkers *J. Org. Chem.,* **1976,** 41, 3367

$S_{RN}1$ Fragmentation in C-C Bond Formation

Problem solved using Molecular Orbital Analysis:





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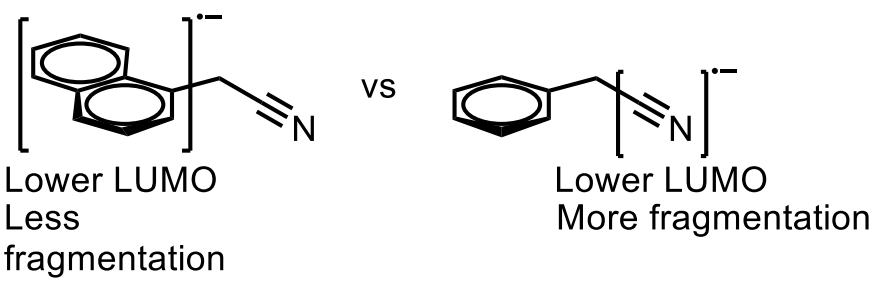
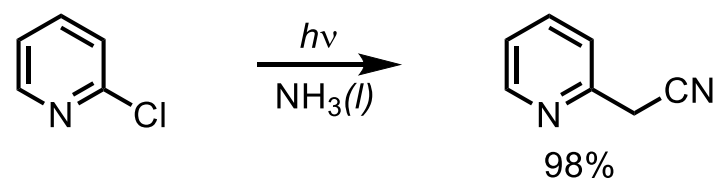
Rationale:



Extended to heteroaromatics (now Cl works)

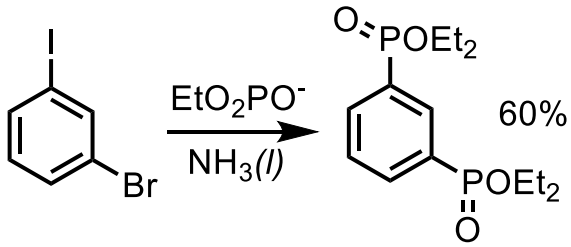


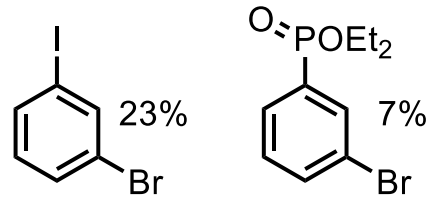
These systems work because propagation (OSET) outcompetes fragmentation

Rossi and coworkers *J. Org. Chem.,* **1976,** 41, 3367
Ibid., 3373

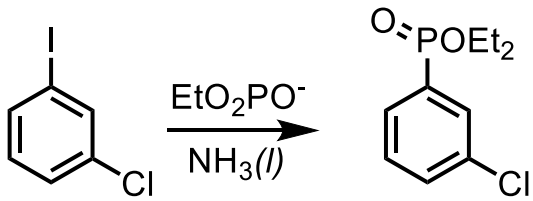
$S_{RN}1$ Substitution in Dihalides

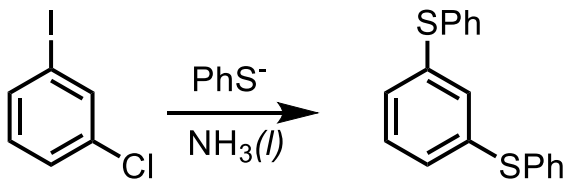
Curious case of dihalobenzenes:

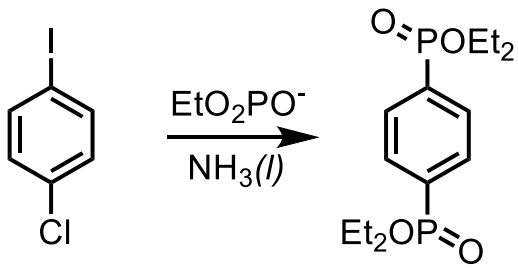




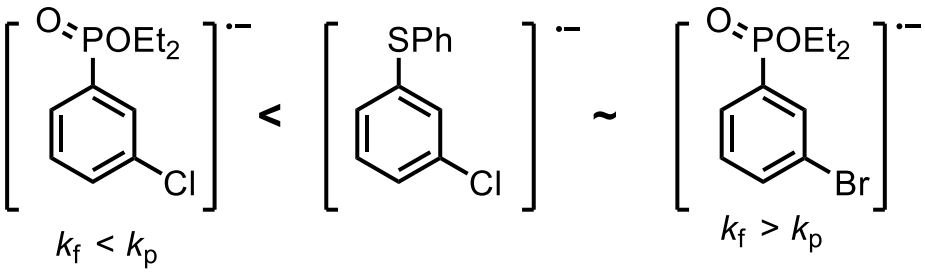
Re-subjected to conditions:
Slower *than the dihalobenzene!*







Rate of fragmentation dictates mono- or disubstitution:



in DMSO determined to be ~50 and rate $\alpha\ \phi^{0.84}$

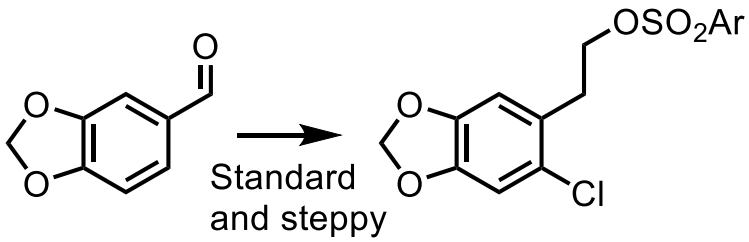
ϕ light flux (measured by actinometry)

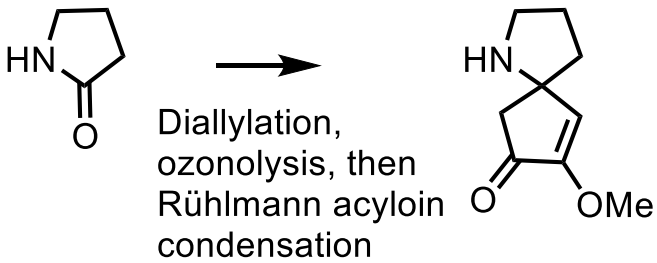
quantum yield

This is all compelling evidence for the chain character of the $S_{RN}1$ mechanism in these reactions

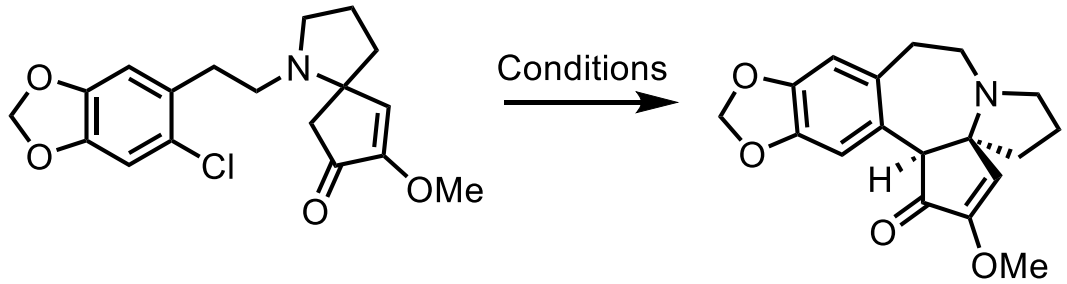
Rossi and coworkers *Acc. Chem. Res.,* **1982, 15**, 164
Bunnett, *Acc. Chem. Res.,* **1978**, 11, 413

Ring Closure: Application in Total Synthesis of a Cephalotaxus Alkaloid





Key step in a total synthesis by Semmelhack:



cephalotaxine

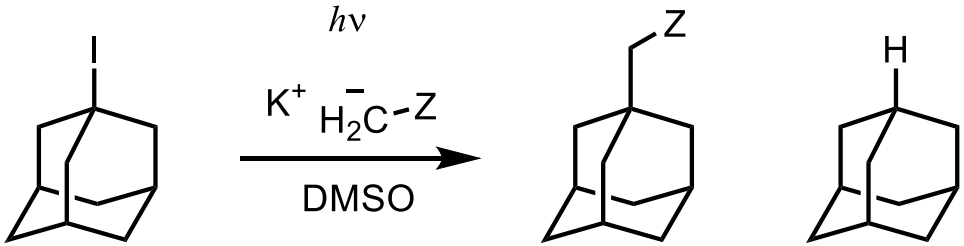
Conditions:	**Result:**
4 eq Ph_3CK, DME, X = Cl, 3 h 30 °C	12-15%, complex mixture
KNH_2/NH_3*(l)*	Aniline formed
$NiCOD_2$/THF 30 °C	30%, rest reduced THF-d_8 gave *D*-sub
Cu(I)PBu_3/THF :HMPA 25 °C	Complex mixtures
Na-K/NH_3*(l)* -33 °C	45% yield
7 eq KO*t*-Bu, $h\nu$/NH_3*(l)* -33 °C	94% *only product detected*

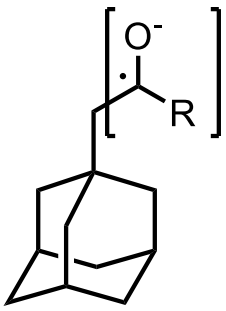
$S_{RN}1$ conditions

Semmelhack and coworkers, *J. Am. Chem. Soc.,* **1975,** 97, 2507.

Photostimulated Substitution of 1-Iodoadamantane

Sacrificial initiator rescues failed reactions





R = Me *less stable*
R = Ph *more stable*

Z = NO_2	N/R	N/R
with excess *t*-BuOK	27%	trace
with $PhC(O)CH_2^-$ + 18-C-6	58%	nd
with $MeC(O)CH_2^-$	87%	2%
Z = C(O)Ph	48%	5%
with 18-C-6	65%	9%
Z = $C(O)CH_3$	20%	17%

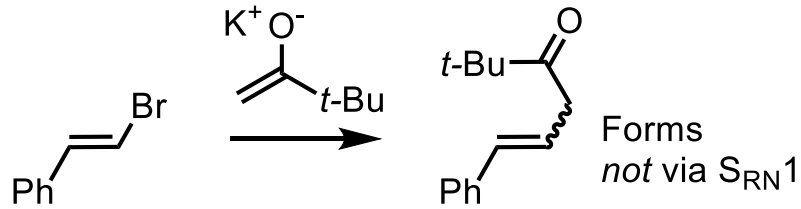
These competition experiments demonstrate that:

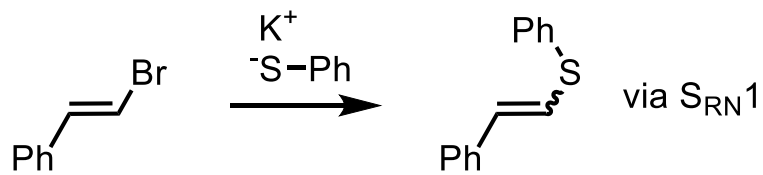
- Initiation α pK_a of nucleophile
- Propagation α stability of radical anion

In later work: $Fe(II)SO_4$ and SmI_2 thermally initiate reaction

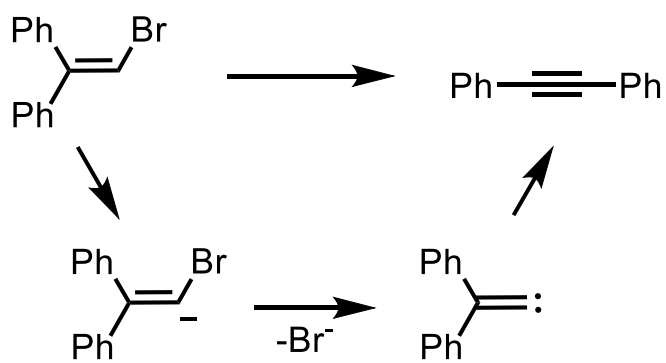
Rossi and coworkers, *J. Org. Chem.*, **1990**, 55, 3705
Ibid, **1996**, 61, 1645.

Limited Scope for Vinyl $S_{RN}1$

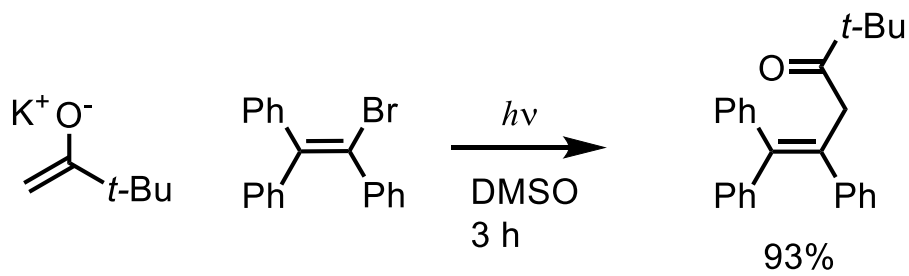




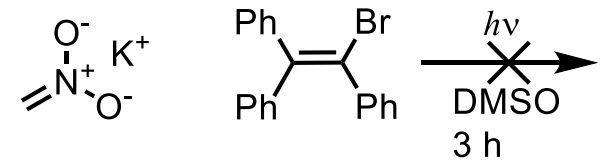
Basicity of Nu tends to dominate:

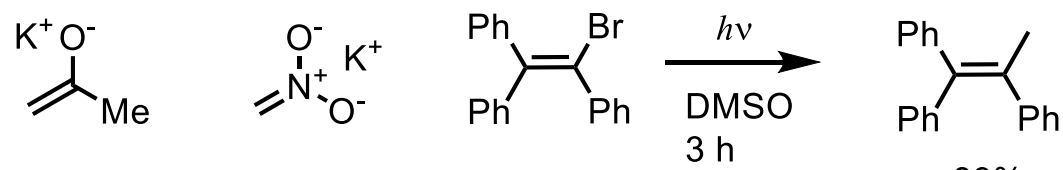


Fritsch-Buttenberg-Wiechell rearrangement



93%





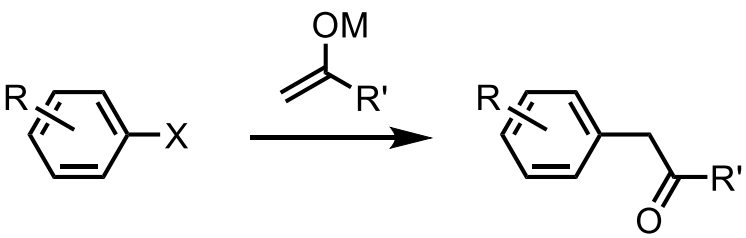
89%

Again, sacrificial reductant turns on reactivity

Galli and coworkers, *Acc. Chem. Res.,* **2003**, 36, 580
Rossi and coworkers, *J. Org. Chem.*, **1990**, 55, 3705

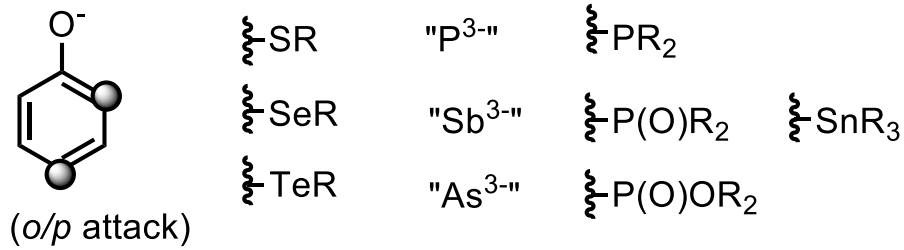
The Outlook for $S_{RN}1$ Research: 1990's

Transition metal catalyzed cross coupling outpaced $S_{RN}1$ methodology in most C-C bond forming reactions

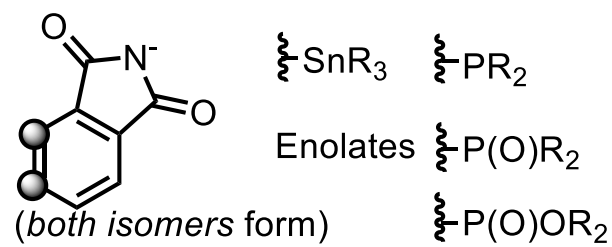


$S_{RN}1$ chemistry focused more esoteric substitutions or challenging substitutions at bridgehead atoms

Nucleophiles that can be coupled to aryl halides:



Nucleophiles that can be coupled to bridgehead sp^3 halides:



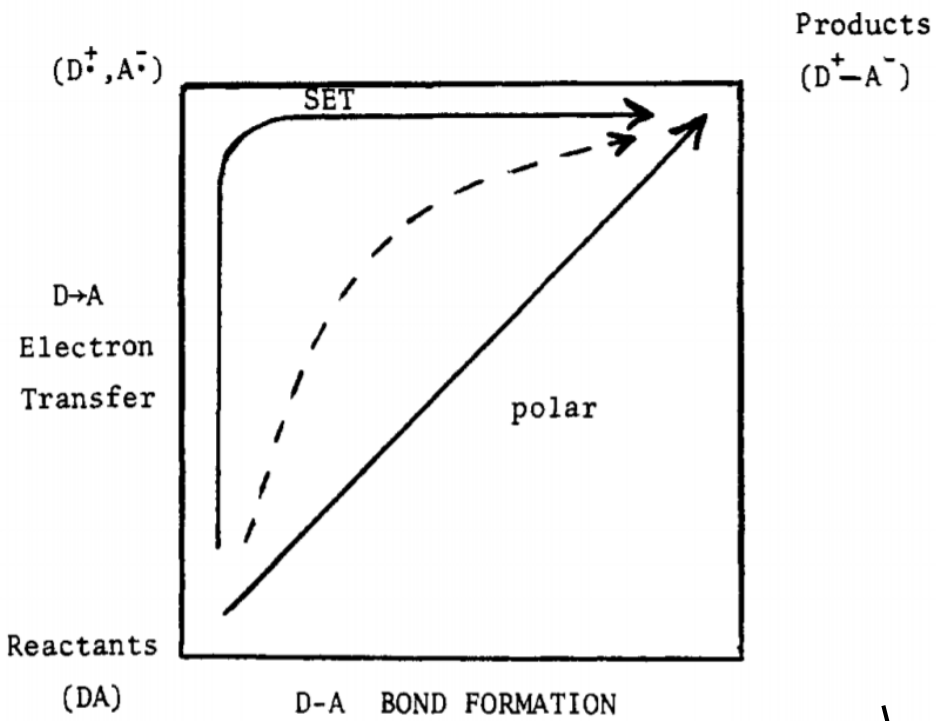
Two excellent and extensive reviews:

Rossi, *Organic Reactions,* **1999**, 54 (up to 1996)
Rossi, *Chem. Rev.*, **2003**, 103, 71

Legacy of $S_{RN}1$ Research: Discourse on the Role of SET in Substitution

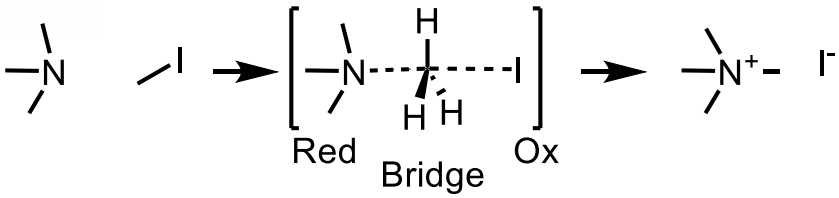
The Single Electron Shift as a Fundamental Process in Organic Chemistry: The Relationship between Polar and Electron-Transfer Pathways

ADDY PROSS



"This paper has attempted to demonstrate the **central role of electron transfer in organic chemistry**. Interestingly, within inorganic chemistry…[s]ingle electron transfer is universally recognized as a fundamental process governing inorganic reactivity…**an S_N2 reaction may be considered analogous to an inner-sphere electron transfer**!"

Using ISET terminology:

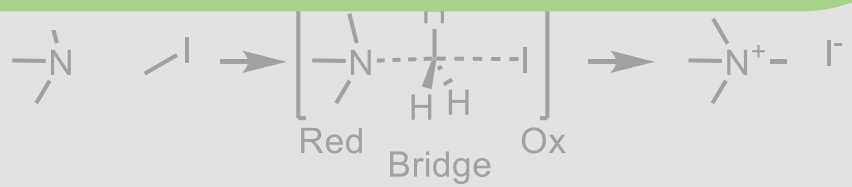


Addy Pross, *Acc. Chem. Res.*, **1985**, 18, 212

Legacy of $S_{RN}1$ Research: Discourse on the Role of SET in Substitution

The Single Electron Shift as a Fundamental Process in Organic Chemistry: The Relationship between Polar and Electron-Transfer Pathways

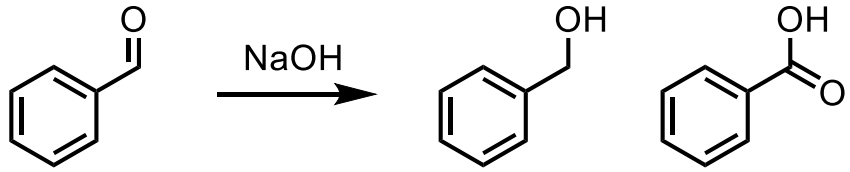
"The notion of the curly arrow…is of undoubted utility… However, **the physical significance of such curly arrows should not be exaggerated**. The curly arrow is a most useful mnemonic for describing organic mechanisms but should not be interpreted as a physical description of what actually occurs…[Pross] opened this paper with the statement that chemical reactions take place as a result of the rearrangement of valence electrons. **What could be intellectually more satisfying than the profound realization that the simplest possible electronic reorganization…is the fundamental act that governs so much of chemical reactivity**." (Pross)



Addy Pross, *Acc. Chem. Res.*, **1985**, 18, 212

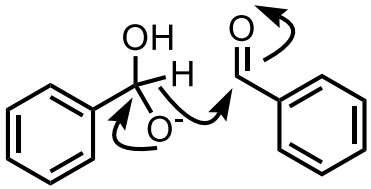
Ashby: is SET a Major Pathway in Organic Chemistry?

Cannizzaro reaction:

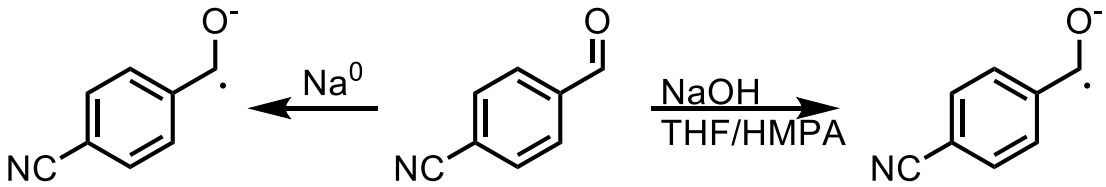


Base-mediated electronic disproportionation of aldehydes (1:1 ratio)

Disproportionation proposed via H^- transfer:

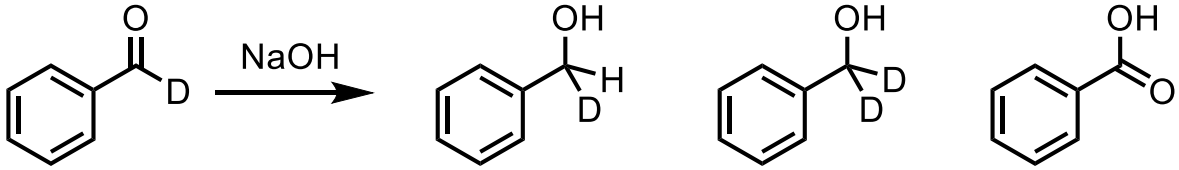


Ketyl radical intermediate forms under Cannizzaro conditions:



Known *Same EPR*

D-Labelling experiment taken as evidence for radical intermediates



Consistent with radical pathway

Consistent with polar pathway

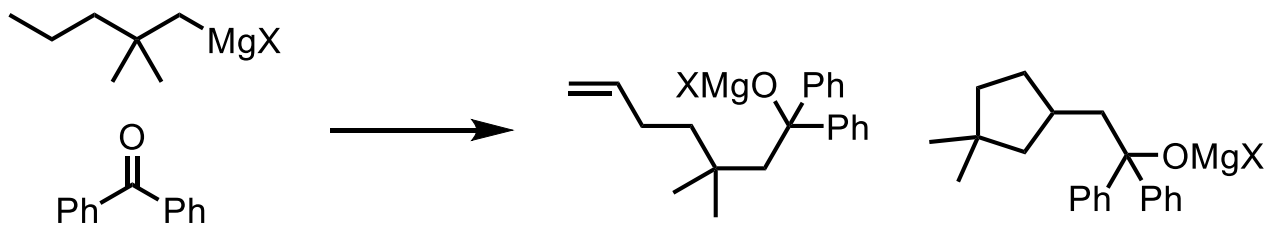
Inconclusive evidence has been presented for the Cannizzaro reaction undergoing an electron transfer *then* an H atom abstraction instead of a H^- transfer

A radical intermediate whose EPR matches the ketyl radical of the sm and whose disappearance tracks with product formation was identified

Chung and coworkers, *J. Chem. Soc. Chem. Commun.,* **1982** 480.
Ashby and coworkers, *J. Org. Chem.* **1987**, 52, 4079

Ashby: Excellent Acceptor Carbonyls May Engage SET Pathways

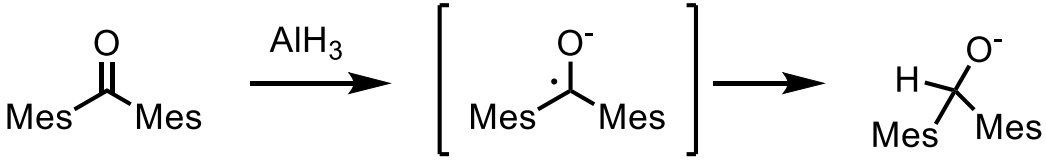
Grignard:



88% 12%

A catalog of reactions have been investigated for radical intermediates

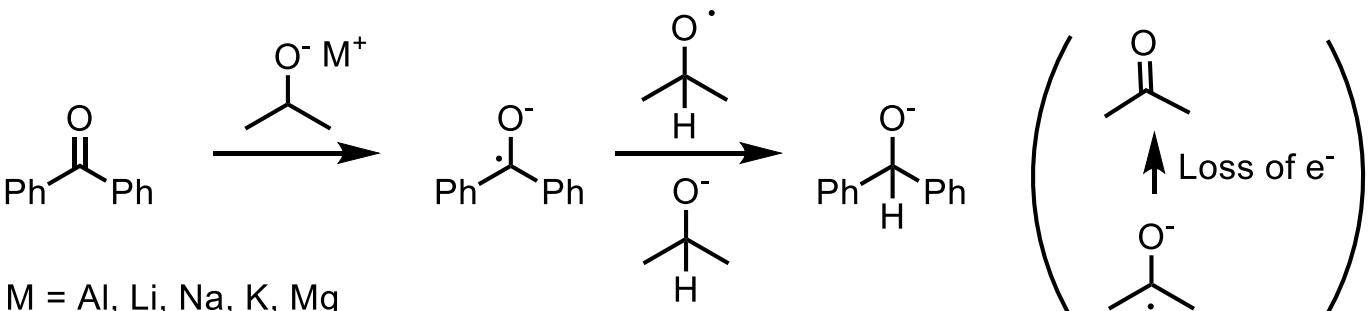
Alane:



Observed by EPR
Rate of disappearance matched rate of pdt formation

Diaryl ketones *can* accept an electron under some "normal" reaction conditions

MPV reduction:



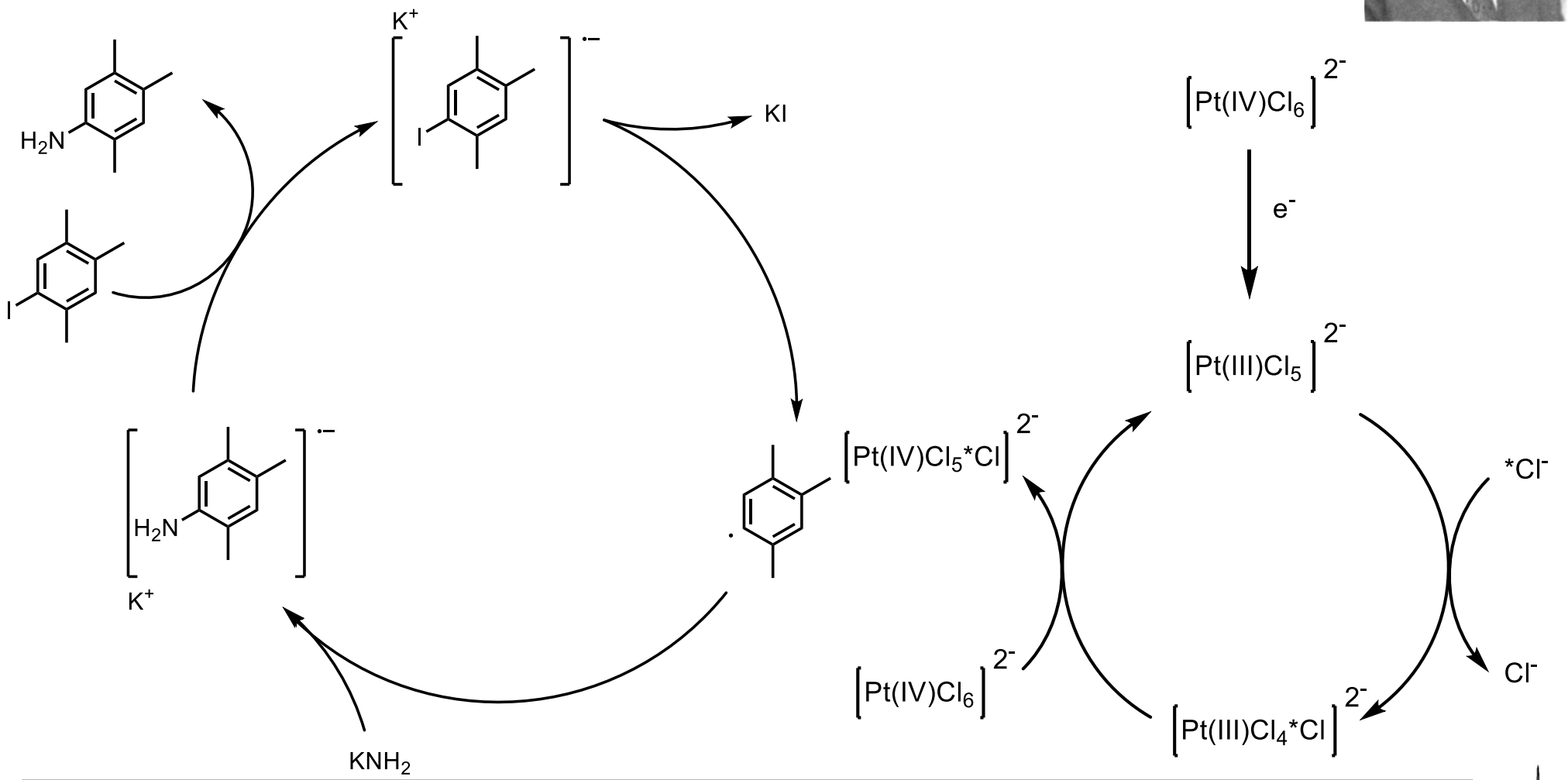
M = Al, Li, Na, K, Mg

H atom abstraction from either radical or alkoxide

Chanon Questions the Nature of Chain vs Catalysis

If a chain mechanism regenerates a common intermediate, is that just a catalytic species in that reaction?

If ET mediates substitutions in both areas, it must be a general phenomenon



Michel Chanon, *Acc. Chem. Res.,* **1987**, 20, 214
Chanon and coworkers, *Chem. Rev.,* **1983**, 83, 425

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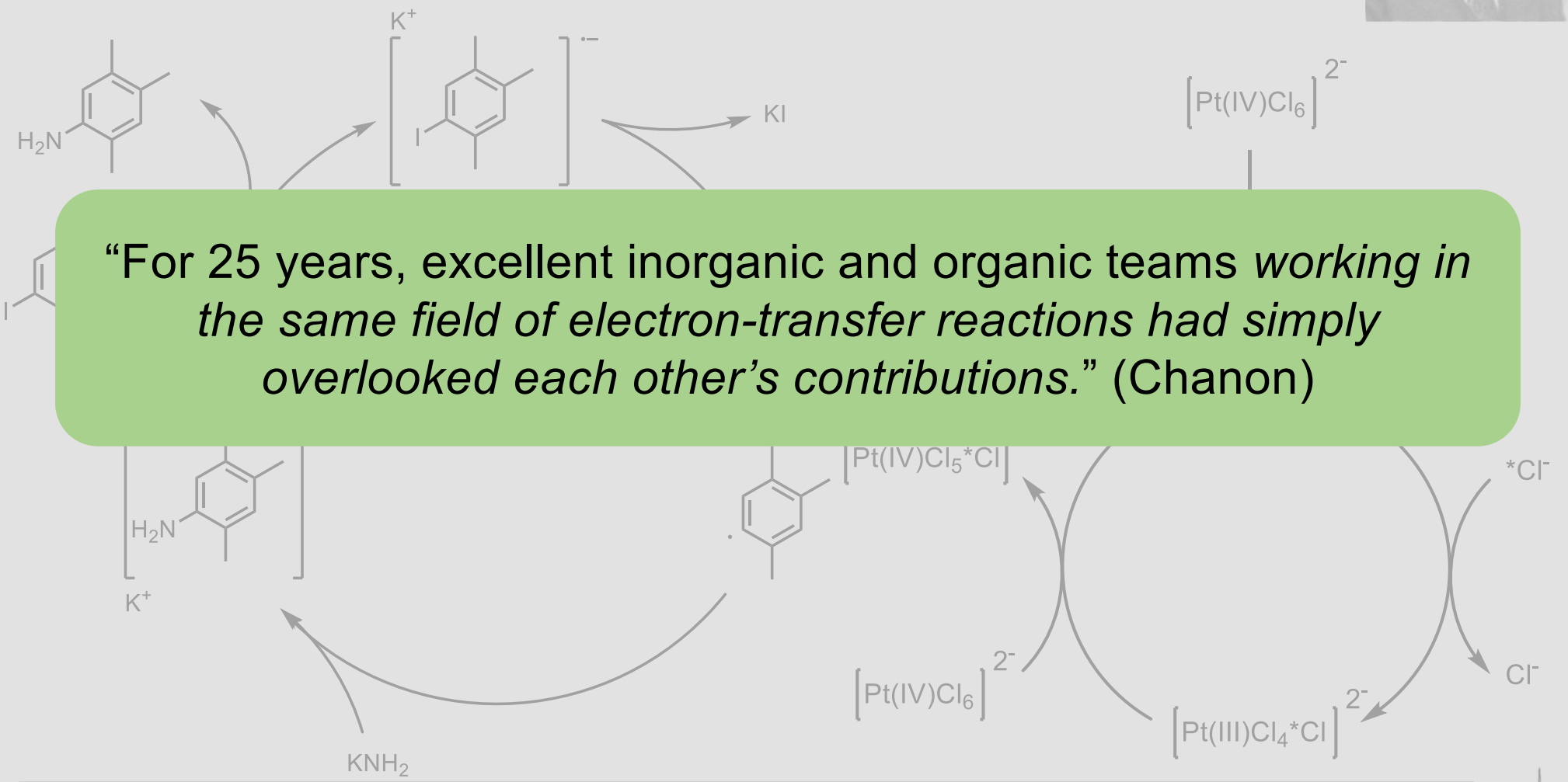


"For 25 years, excellent inorganic and organic teams *working in the same field of electron-transfer reactions had simply overlooked each other's contributions.*" (Chanon)

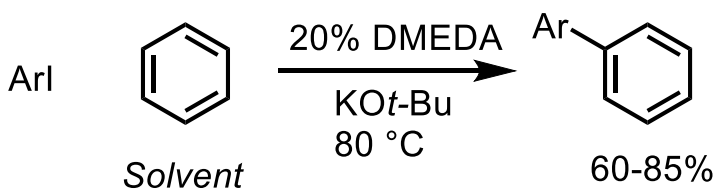
Michel Chanon, *Acc. Chem. Res.*, **1987**, 20, 214
Chanon and coworkers, *Chem. Rev.*, **1983**, 83, 425

Intermission

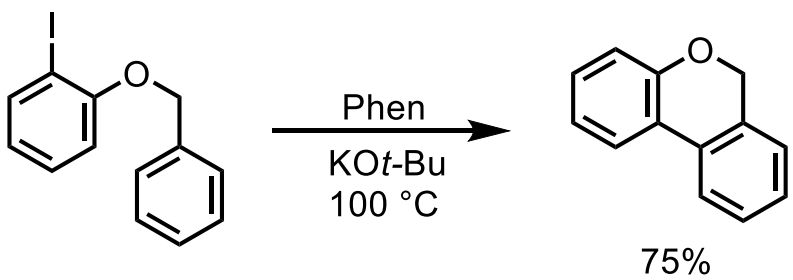
Consequence of Transition Metal Catalysis Outpacing ET Mediated Substitution

Described as "Metal Free C-H Activation":

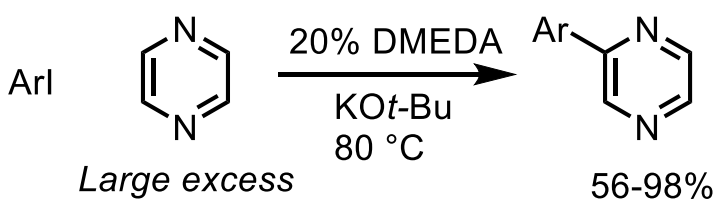
Kwong, Lei and coworkers 2010



Shi and coworkers 2010



Itami and coworkers 2010



- Eventually, avoiding the use of transition metals became desirable
- C-H activation “sells”
- A “new conceptual breakthrough” was presented between 2008 and 2010 by four laboratories

Is this even C-H activation?

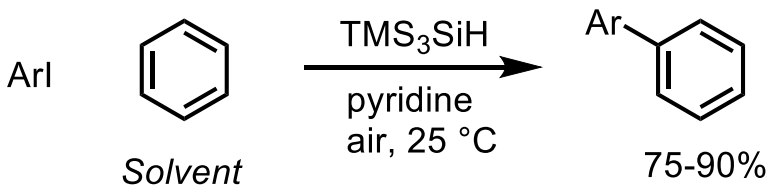
Armido Studer says no more than a Friedel-Crafts alkylation

Studer and Curran, *Angew. Chem. Int. Ed.*, **2011**, 50, 5018

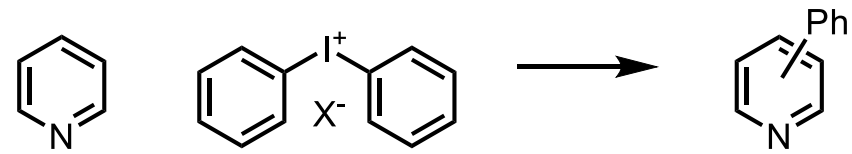
Old and New Examples of Related Chemistry

Literature from the same era:

Curran 2006

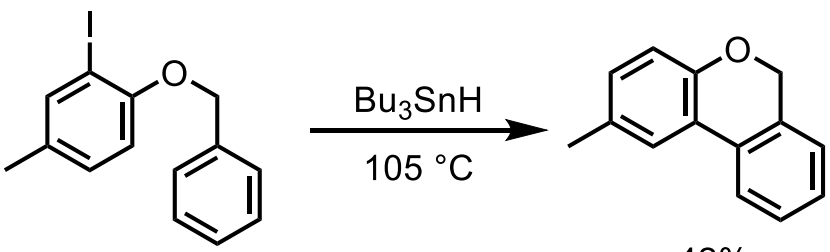


*Brown and Sandin **1947***



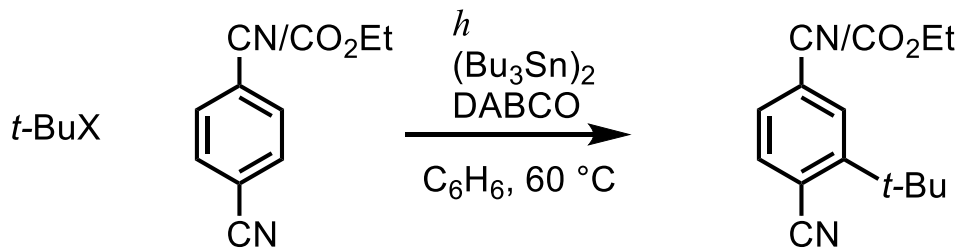
ca 50% yield

Bowman and coworkers 2000



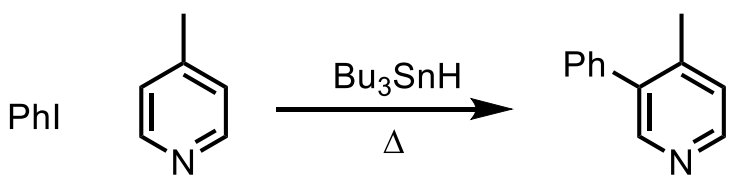
42%

Trahanovsky 1998



70%

Aldabbagh 2004



Large excess

56%, both isomers

A thorough volume by G. H. Williams titled "Homolytic Aromatic Substitution"

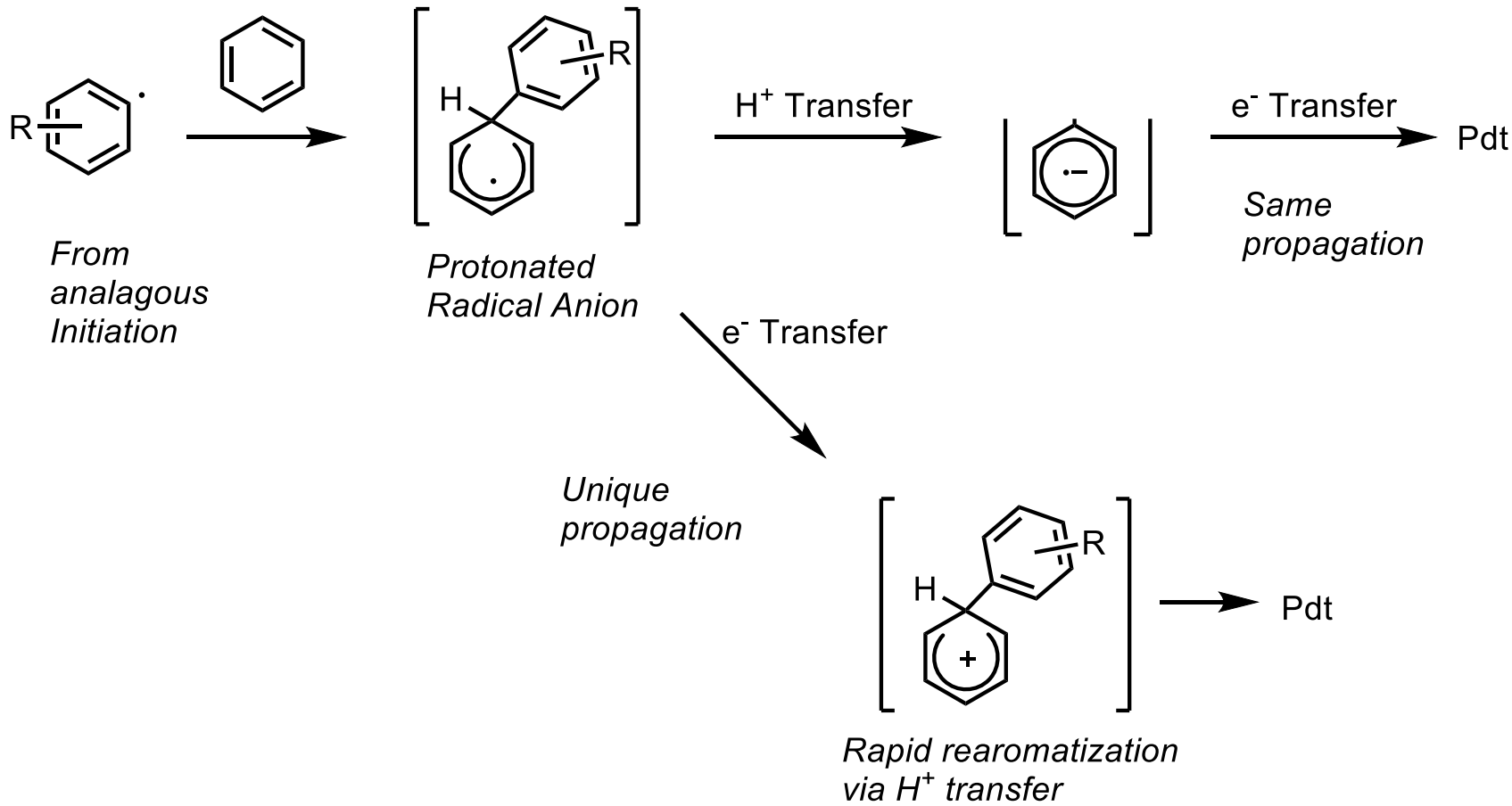
This passes the Denmark test!

Curran and coworkers, *J. Am. Chem. Soc.,* **2006**, 128, 13706
Bowman and coworkers, *J. Chem. Soc. Perkin Trans. I,* **2000**, 2991-2999
Aldabbagh and coworkers, *Tetrahedron*, **2004**, 60, 8065
Brown R. K. and coworkers, *J. Am. Chem. Soc.,* **1947**, 69, 2253
Trahanovsky and coworkers, *J. Org. Chem.,* **1998**, 63, 9956

The Embarassing Conceptual Breakthrough: Reading the Literature is Important

These "new conceptual breakthroughs" are actually Base-promoted Homolytic Aromatic Substitution (BHAS), a well-understood reaction type conceptually related to $S_{RN}1$

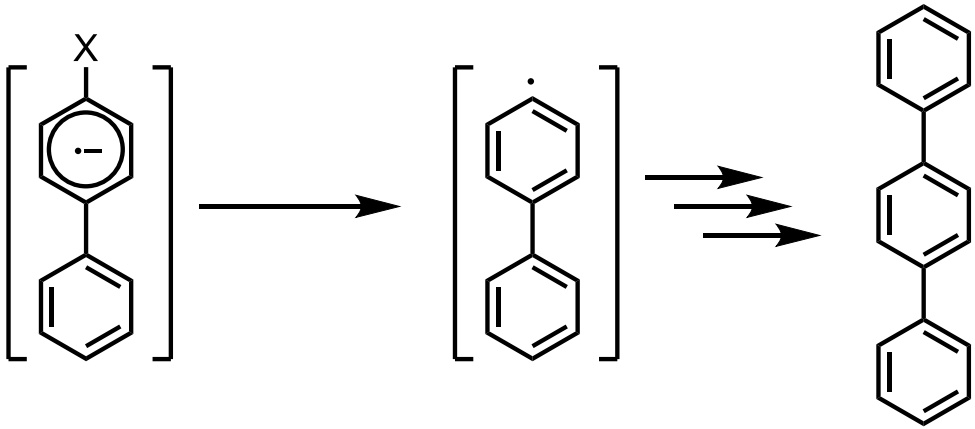
Divergence from the $S_{RN}1$ mechan



The Embarassing Conceptual Breakthrough: Reading the Literature is Important

Bunnett RA probe gave a positive result:

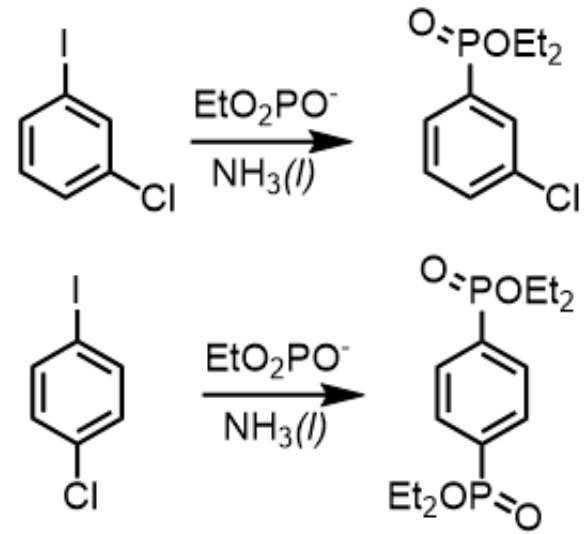
If R = X, we saw earlier that RA can fragment, causing disubstitution:



Base promotes initial H^+ transfer to form radical anion

Observed by Kwong, Lei and coworkers

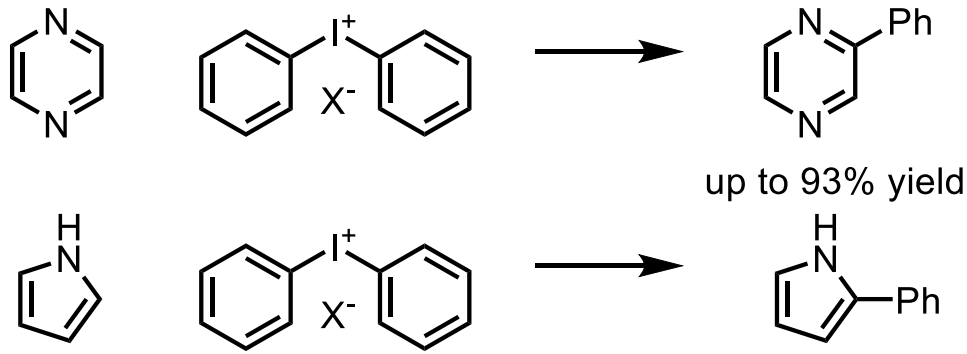
This experiment mirrors the di- vs monosubstitution phenomenon we discussed for *m*-dihalobenzenes earlier:



This "new" chemistry is actually a re-imagination of old chemistry using KO*t*-Bu/Ligand complexes as a purported electron donor/initiator

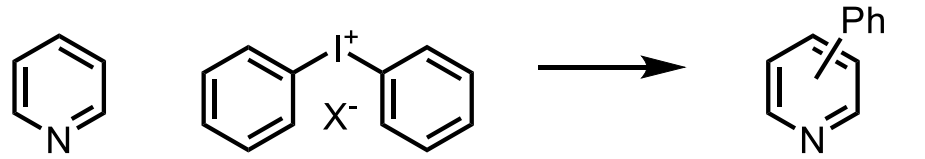
Repetition in the Literature

Xiao-Qi Yu, Li Zhang Chen **2011**



up to 93% yield

*Brown and Sandin **1947***



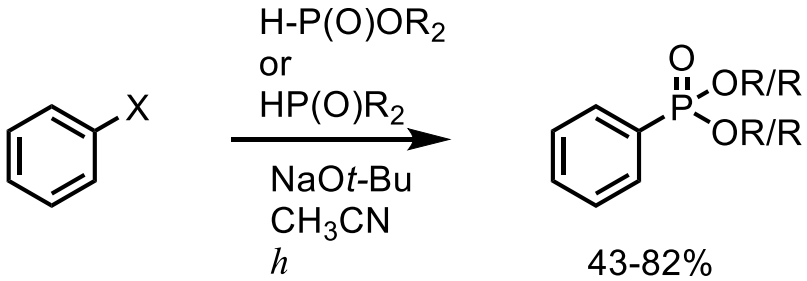
ca 50% yield

"In conclusion, we report here a novel and simple cross-coupling between an inert aromatic C-H and diaryliodonium salts in the absence of any transition metal catalyst…Mechanistic studies suggest that this reaction is possibly a phenyl radical pathway by decomposition of the diaryliodonium salts"

Brown R. K. and coworkers, *J. Am. Chem. Soc.,* **1947**, 69, 2253
Xiao-Qi Yu and coworkers, *J. Org. Chem.,* **2012**, 77, 766

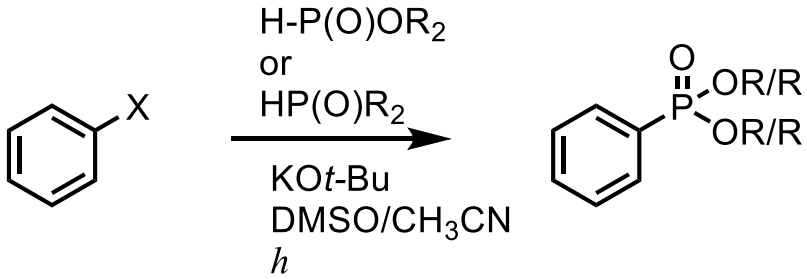
…And the Problem Hasn't Ended

"Photoinduced Transition-Metal-Free Cross-Coupling of Aryl Halides with H-Phosphonates" **2019**

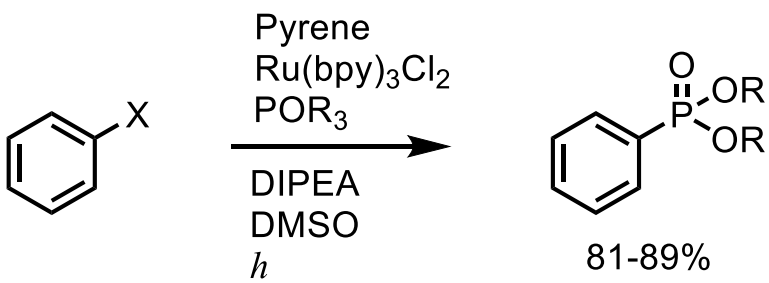


vs

Entire section of the $S_{RN}1$ O.R. chapter dedicated to this:

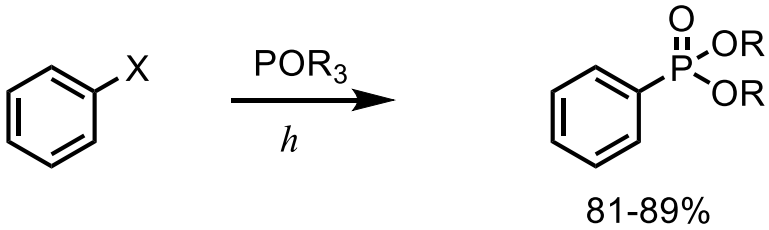


Photosensitized Photo-Arbuzov **2017**



vs

Bentrude and coworkers, *J. Am. Chem. Soc.*, **1972** 94, 7717



$POEt_3$ reacts 34x faster than $MP(O)OEt_2$ and 100x faster than 1,4-cyclohexadiene with Ph radical

Huiying Zeng, Qian Dou, and Chao-Jun Li *Org. Lett.* **2019**, 21, 1301
Konig and coworkers, *Angew. Chem. Int. Ed.,* **2017**, 56, 8544

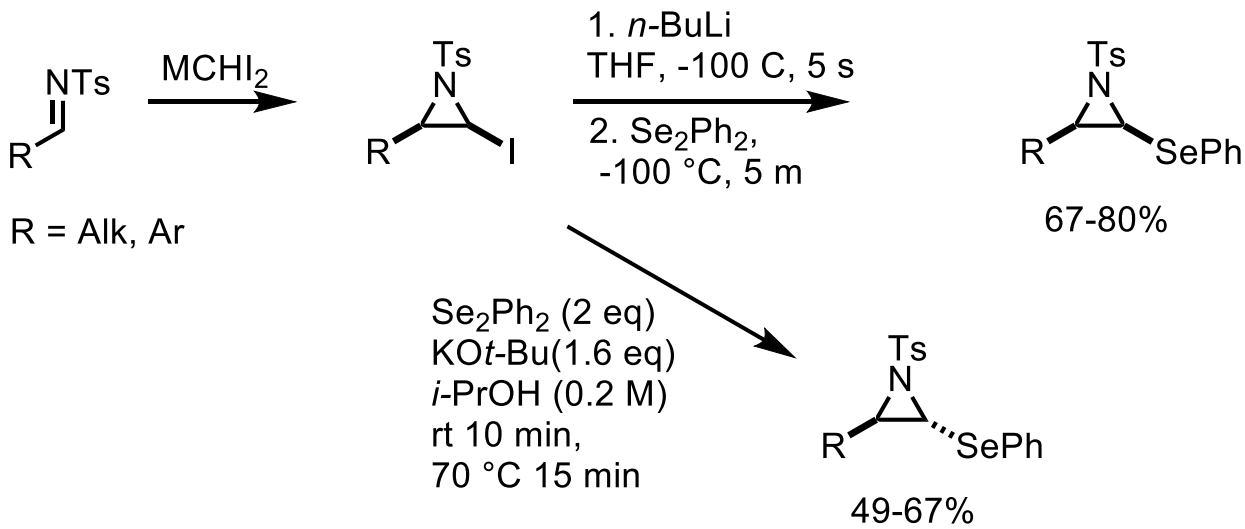
Comment on Modern Resurgence of ET Mediated Substitutions

The value of further method development in ET mediated substitutions is unmistakable

Despite some repetitions in the literature, advances are being made

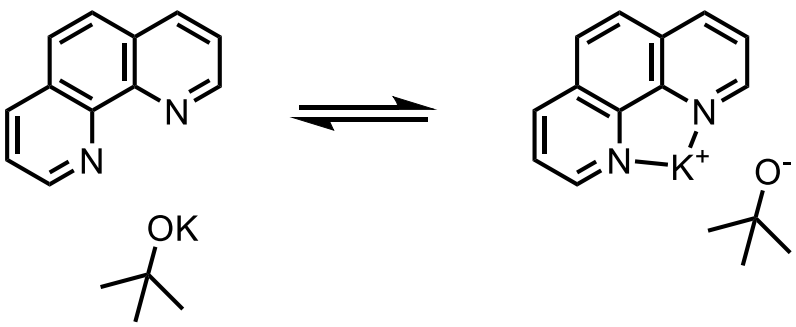
Now, more than ever, we have a plethora of ways known to generate aryl radicals efficiently.

KO*t*-Bu in organic solvents is the initiator of choice. However, its mode of action has been elucidated by a recent JACS publication

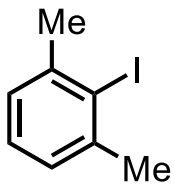


KOt-Bu as a SET Initiator

From 2008-2016 phen was used as an organic additive to promote reductions by KOt-Bu

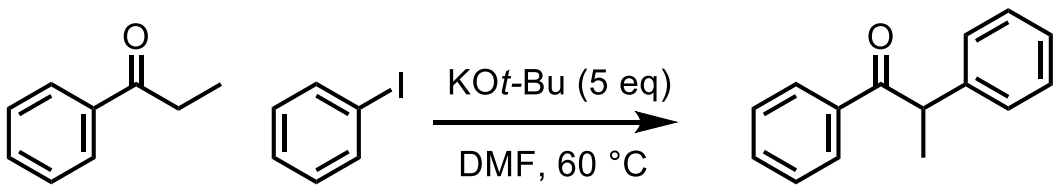


Reduction potential of KO*t*-Bu in DMF is -0.3V

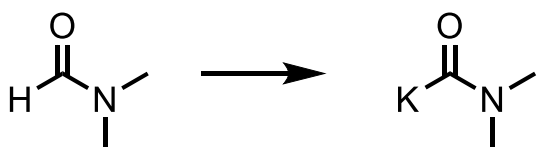


Reduction potential in DMF is -2.0V

2015 report by Taillefer:



99%



Reductant?

SET ruled out by mismatched reduction potentials

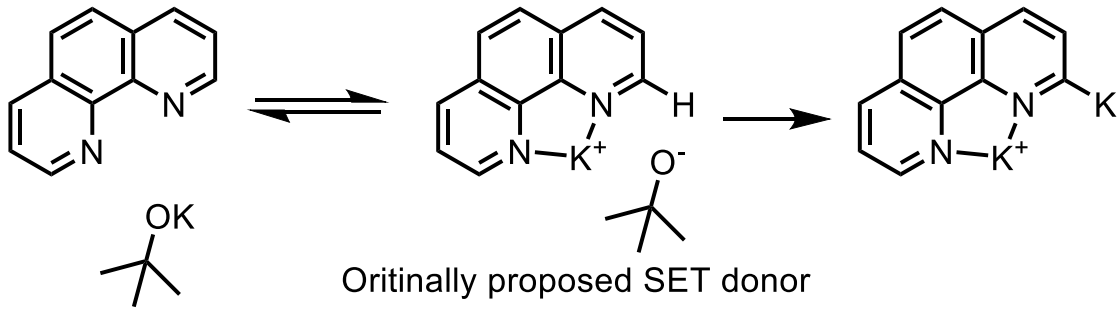
Proposed DMF carbamoyl anion as reductant

No phen was necessary, and DMF was crucial

Taillefer and coworkers, *Angew. Chem. Int. Ed.,* **2015**, 54, 10587

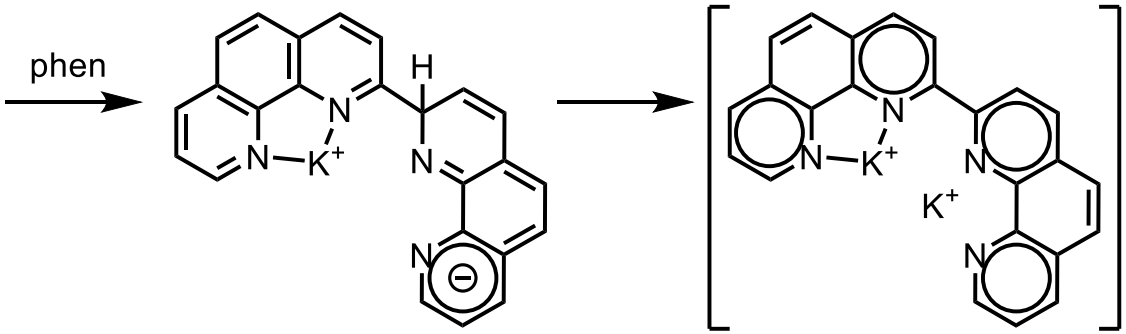
KOt-Bu as a SET Initiator

In a control experiment in 2008, Kwong and coworkers left out Co and still saw coupling with phen/KO*t*-Bu



Oritinally proposed SET donor

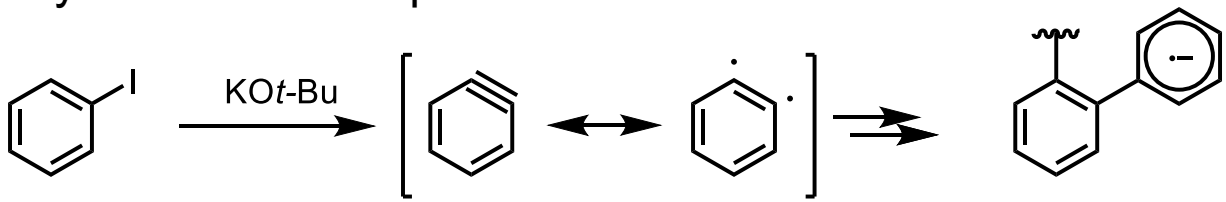
Role of 1,10-phenanthroline explained:



CV shows reversible reduction potential at -2.19 V for dianion

(Dianion, electronic structure ambiguous)

When benzyne formation is possible:



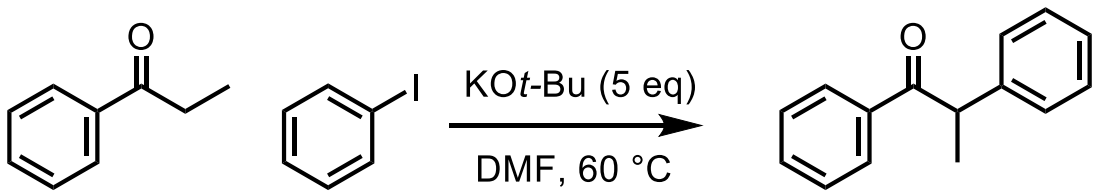
Competent chain propagator for HAS

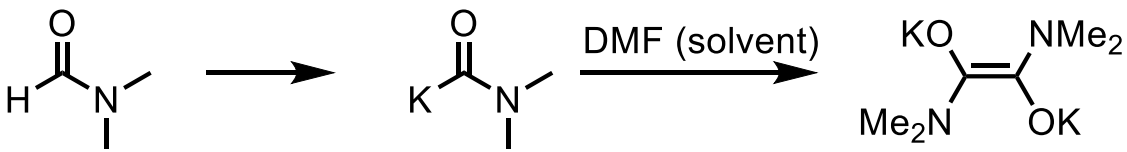
HAS propagation
Deprotonation

Tuttle and coworkers, *J. Am. Chem. Soc.*, **2016**, 138, 7402

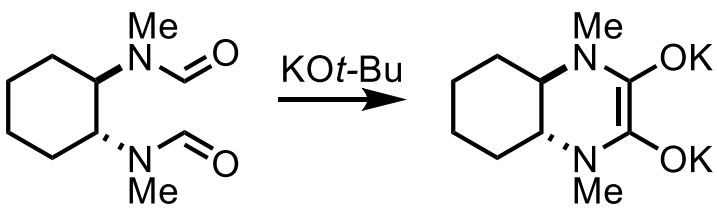
KOt-Bu as a SET Initiator

Explanation for role of DMF:





Dianion is competent electron donor
DMF needs to be solvent for efficient dimerization



Intramolecular reaction initiation efficient at 0.5% loading

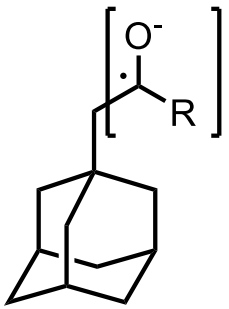
Takeaways:

- Electrochemistry doesn't lie; KO*t*Bu isn't reducing enough to initiate by reducing ArI directly
- Base-mediated reactions of organic additives (or solvent) *can* create strongly reducing organic species

Tuttle and coworkers, *J. Am. Chem. Soc.*, **2016**, 138, 7402

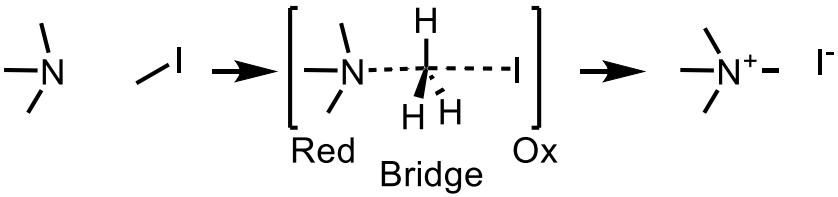
Summary

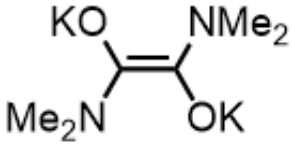
1. Description and elucidation of $S_{RN}1$ mechanism
   1. Early observations of electron transfer (ET) mediated substitution
   2. Christening of the $S_{RN}1$ mechanism
   3. Key studies elucidating mechanism and limitations of $S_{RN}1$ chemistry
2. The legacy of $S_{RN}1$ chemistry
   1. Conceptual discourse inspired by ET mediated substitution reactions
   2. Polar reactions that may actually be ET mediated
3. Modern resurgence
   1. $S_{RN}1$'s cousin, Homolytic Aromatic Substitution (HAS)
   2. Modern ET mediated substitution research



R = Me *less stable*
R = Ph *more stable*

Using ISET terminology:





Ruminations and Future Directions

Our understanding of SET in organic mechanisms develops nuance when chemists accept that radical chemistry is capable of selective, synthetically-useful transformations

Photoredox catalysis, ET mediated couplings, preparative electrochemistry, Baran/Shenvi/Knowles-esque methods are contributing to the modern renaissance in radical synthesis methodology.

Some of the most abundantly used chemistry in industry involve chain mechanisms (ATRP, CP, AP). When they work, it can provide an exceptionally economical method with only a sub-stoichiometric amount of initiator.

Questions?