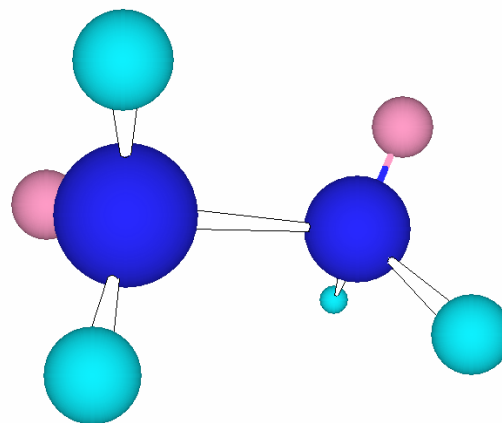# The Late Show with Rob! Tonight's Special Guest: Hydrazine

Robert Matunas
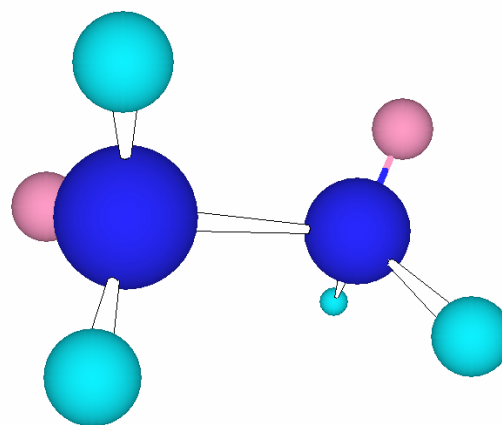
December 8th, 2004

Last One of the Year!!

Schmidt, E. W., *Hydrazine and Its Derivatives*, Wiley-Interscience, New York, 2nd edn., 2001

Ragnarsson, U. Synthetic methodology for alkyl substituted hydrazines, *Chem. Soc. Rev.,* **2001**, *30*, 205-213

The Late Show with Rob! Tonight's Special Guest: Hydrazine

Robert Matunas

January 5th, 2005

Happy New Year!!!

Schmidt, E. W., *Hydrazine and Its Derivatives*, Wiley-Interscience, New York, 2nd edn., 2001
Ragnarsson, U. Synthetic methodology for alkyl substituted hydrazines, *Chem. Soc. Rev.,* **2001**, *30*, 205-213

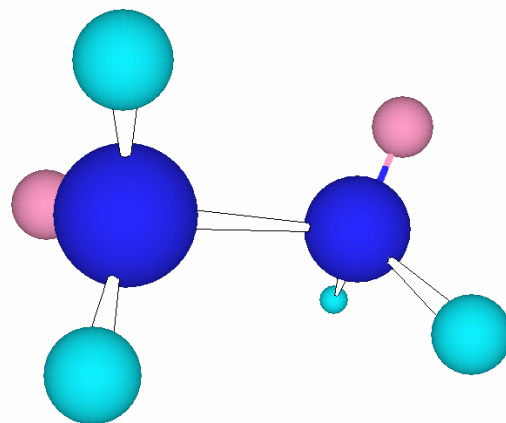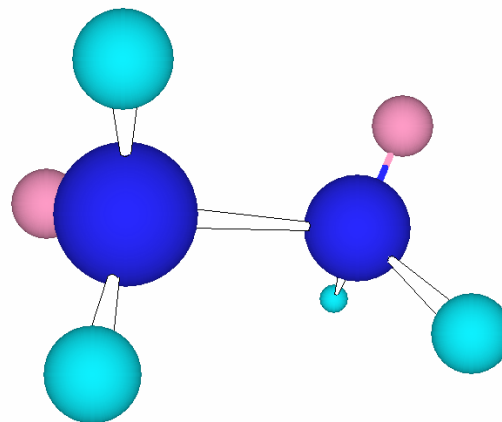# The Late Show with Rob! Tonight's Special Guest: Hydrazine

Robert Matunas

January 12th, 2005

(Third Time's the Charm!)

Schmidt, E. W., *Hydrazine and Its Derivatives*, Wiley-Interscience, New York, 2nd edn., 2001

Ragnarsson, U. Synthetic methodology for alkyl substituted hydrazines, *Chem. Soc. Rev.,* **2001**, *30*, 205-213

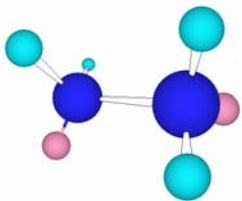# The Late Show with Rob! Tonight's Special Guest: Hydrazine
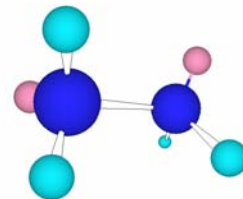

Robert Matunas

January 19th, 2005

(I've Forgotten Everything)

Schmidt, E. W., *Hydrazine and Its Derivatives*, Wiley-Interscience, New York, 2nd edn., 2001
Ragnarsson, U. Synthetic methodology for alkyl substituted hydrazines, *Chem. Soc. Rev.,* **2001**, *30*, 205-213
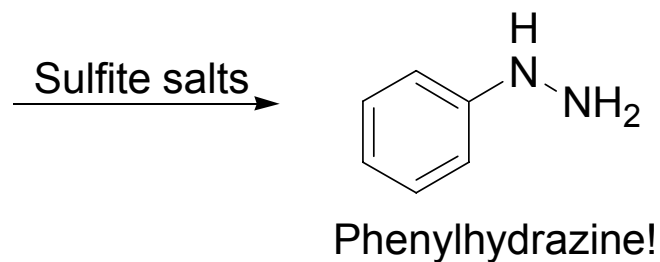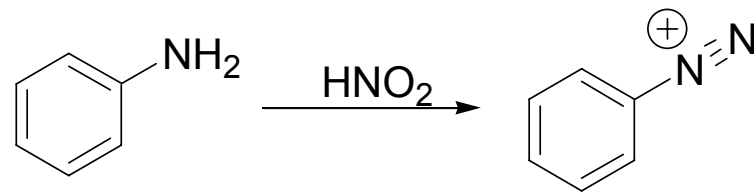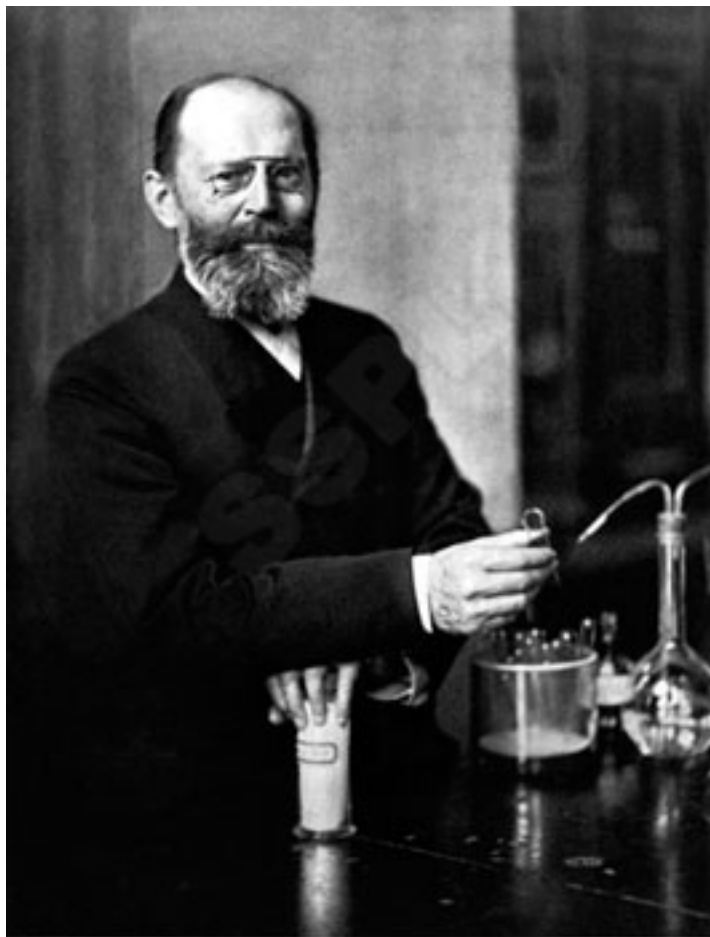
Overview

- Historical development of hydrazine (and friends)

- Industrial outlook on hydrazine compounds

- Selected synthetic methods for preparing simple alkyl hydrazines

- Some Myers Hydrazine Chemistry
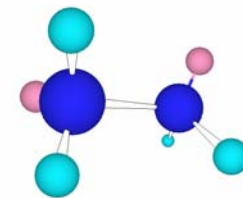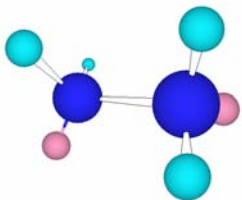
It All Started with H. Emil Fischer (1852-1919)…
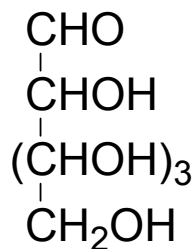

Phenylhydrazine!

Phenylhydrazine was the first hydrazine compound discovered; Fischer synthesized it serendipitously in 1875 by reduction of the corresponding diazonium salt.
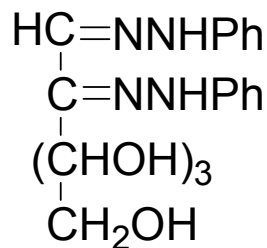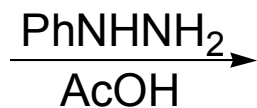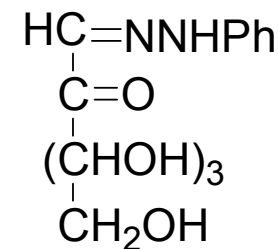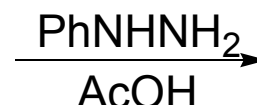
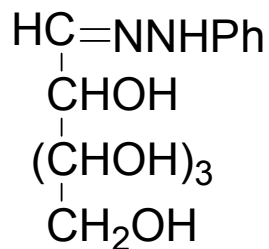Fischer, E. *Ber. Dtsch. Chem. Ges.,* **1875**, *8*, 589.

Some "Sweet" Synthesis

Fischer had been working on sugar syntheses, but lacked methods for obtaining the pure compounds. Imagine making a sugar from scratch and then failing to isolate it!
Phenylhydrazine to the rescue!

$$
\begin{array}{c}
\text{CHO} \\
\text{CHOH} \\
(\text{CHOH})_3 \\
\text{CH}_2\text{OH}
\end{array}
\xrightarrow[\text{AcOH}]{\text{PhNHNH}_2}
\begin{array}{c}
\text{HC}{=}\text{NNHPh} \\
\text{CHOH} \\
(\text{CHOH})_3 \\
\text{CH}_2\text{OH}
\end{array}
\xrightarrow[\text{AcOH}]{\text{PhNHNH}_2}
\begin{array}{c}
\text{HC}{=}\text{NNHPh} \\
\text{C}{=}\text{O} \\
(\text{CHOH})_3 \\
\text{CH}_2\text{OH}
\end{array}
$$

Sugar

$$
\xrightarrow[\text{AcOH}]{\text{PhNHNH}_2}
\begin{array}{c}
\text{HC}{=}\text{NNHPh} \\
\text{C}{=}\text{NNHPh} \\
(\text{CHOH})_3 \\
\text{CH}_2\text{OH}
\end{array}
$$

Osazone

Fischer, E. *J. Am. Chem. Soc.,* **1890**, *12*, 340-8.
Fischer, E. *Ber. Dtsch. Chem. Ges.,* **1884**, *17*, 579.

The osazones, which are almost insoluble in water, have proved to be still more valuable for the developement of work in the sugar group. They crystallize with comparative ease and precipitate even from most dilute solutions. In addition, they differ in solubility, melting point and in optical behavior, and they are now consequently used for recognizing natural sugars.

The derivatives of these latter, as well as the important marks of difference are put down in the following table :

Glucosazone, $C_{18}H_{22}N_4O_4$. Is formed from glucose, laevulose, mannose, glucosamine and isoglucosamine. Almost insoluble in water, difficultly soluble in hot alcohol. Melting point near 205° C. The solution in glacial acetic acid turns the plane of polarization to the left.

Galactosazone, $C_{18}H_{22}N_4O_4$. From galactose. Almost insoluble in water, a little more soluble in alcohol than the preceding. Melting point near 193° C. No noticeable action on polarized light when dissolved in glacial acetic acid.

Sorbinosazone, $C_{18}H_{22}N_4O_4$. From sorbinose. Almost insoluble in water, easily soluble in hot alcohol. Melting point 164° C.

Lactosazone, $C_{24}H_{32}N_4O_9$. From lactose. Soluble in 80 to 90 parts of hot water. Melting point near 200° C. Dilute sulphuric acid changes it into its anhydride $C_{24}H_{30}N_4O_8$, which is almost insoluble in water.

Maltosazone, $C_{24}H_{32}N_4O_9$. From maltose. Soluble in about 75 parts of hot water. Melting point near 206° C. Does not furnish an anhydride.

Arabinosazone, $C_{17}H_{20}N_4O_3$. From arabinose. Sparely soluble in hot water, easily soluble in hot alcohol. Melting points near 160° C. Its alcoholic solution shows no action upon the polarized light.

Xylosazone, $C_{17}H_{20}N_4O_3$. From xylose. Deceptively similar to arabinosazone, but, in alcoholic solution strongly turns polarized light to the left.

Rhamnosazone, $C_{18}H_{32}N_4O_3$. From rhamnose (isodulcite). Almost insoluble in water, easily soluble in hot alcohol. Melting point near 180° C.

# Some Other Early Fischer Syntheses…

Fischer used some of the following strategies to prepare ~20 different hydrazines, all before free hydrazine itself was known.
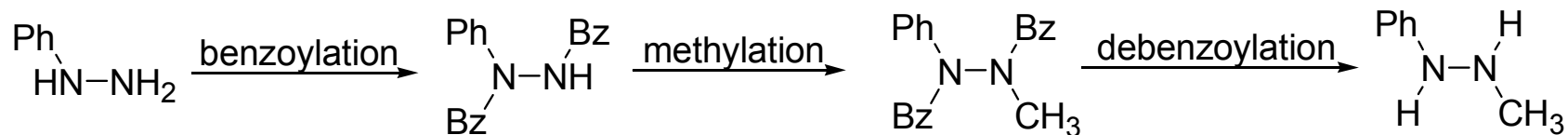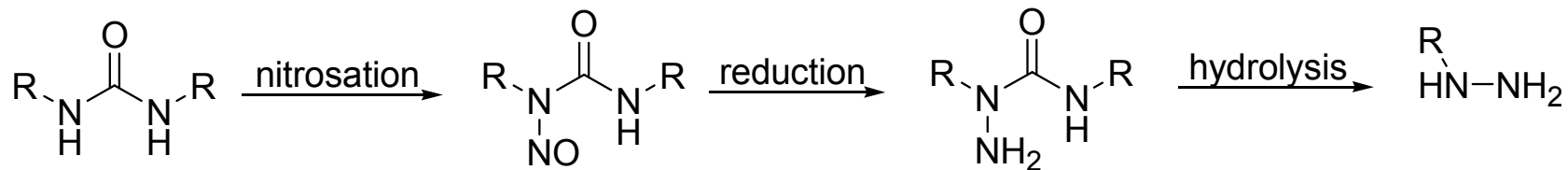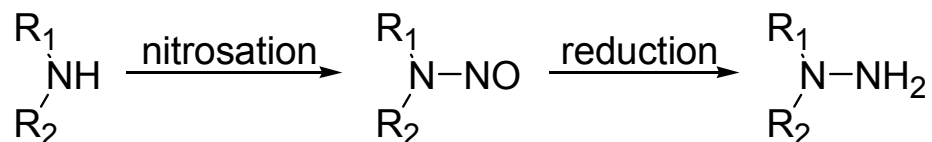
The last preparation of a 1,2-disubstituted hydrazine anticipates the modern dependence on protecting groups in synthesis.

Ragnarsson, U. *Chem. Soc. Rev.,* **2001**, *30*, 205-213.

…but Preparing Free Hydrazine Itself Took Time

Curtius eventually prepared free hydrazine (as the hydrate) via a circuitous route. The year was 1887, already 12 years after the discovery of phenylhydrazine. Since that time, about 20 other hydrazine derivatives were already known!

Curtius, *J. Prakt. Chem.* **1889**, *39*, 107-39.
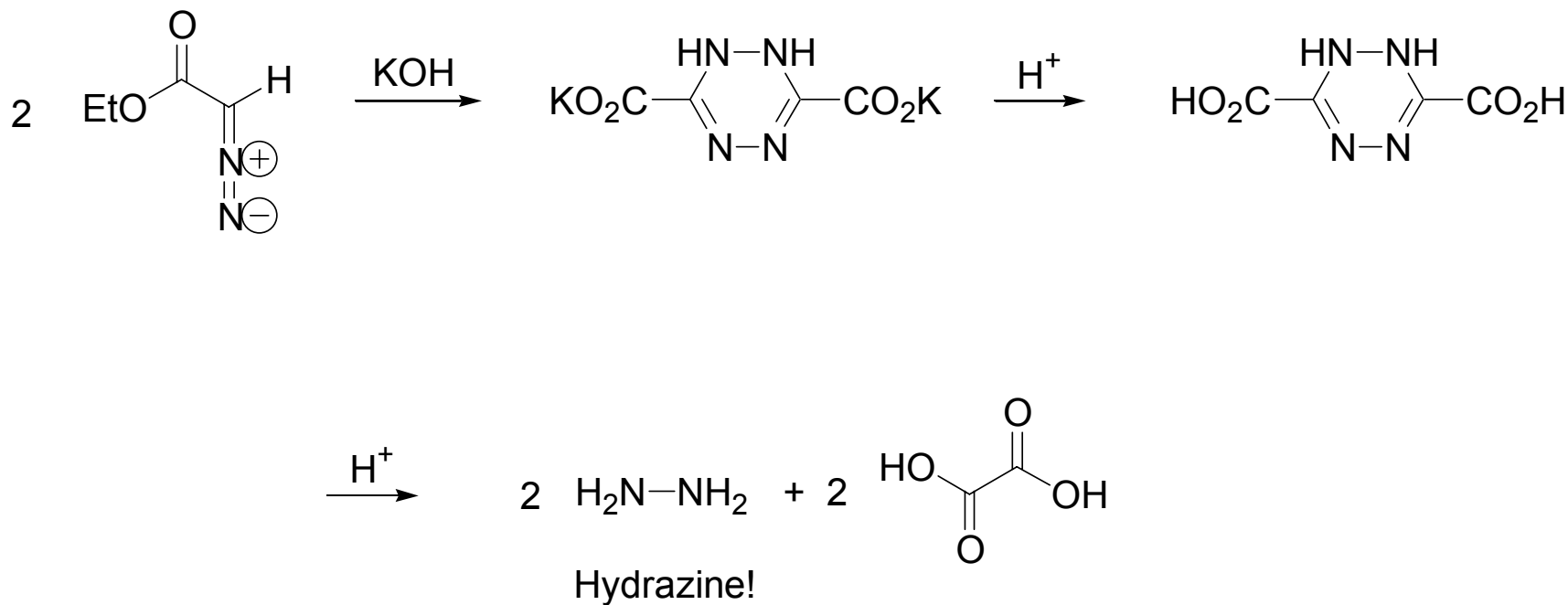
Molecular Properties of Hydrazine

Of the possible conformations for hydrazine, the gauche form is favored.
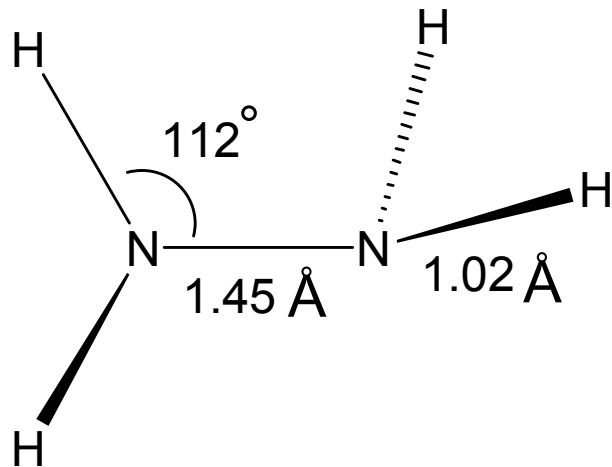
Bond Strengths:
N-N: ~ 50-60 kcal/mol
N-H: ~ 80-90 kcal/mol

Rotational Barrier:
6-10 kcal/mol
(vs. ~ 3 kcal/mol for ethane)

Hydrazine Production Today

Of the many methods available, the Raschig process is still in use (discovered 1907):

$$NH_3 + NaOCl \longrightarrow ClNH_2 + NaOH$$

$$ClNH_2 + NH_3 + NaOH \longrightarrow H_2NNH_2 + \boxed{NaCl + H_2O}$$
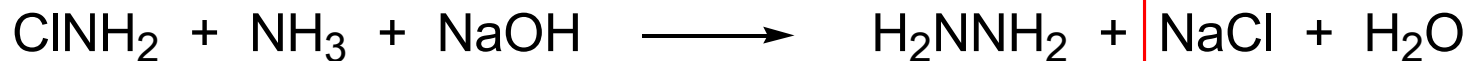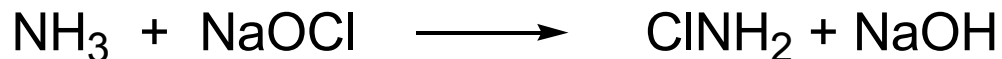
Optimal ratio of reactants is 33:1 NH_3:NaOCl!

The only waste produced is brine, but this is still a significant issue on plant scale.

$$H_2NNH_2 + ClNH_2 \longrightarrow 2\,NH_4Cl + N_2$$

The major side reaction is destruction of the product hydrazine by further reaction with chloramine.

An Improved Process for Hydrazine Production: The Atofina-PCUK "Cycle"

R_1, R_2 = Me or Et; R_3 = H

H_2NNH_2 !
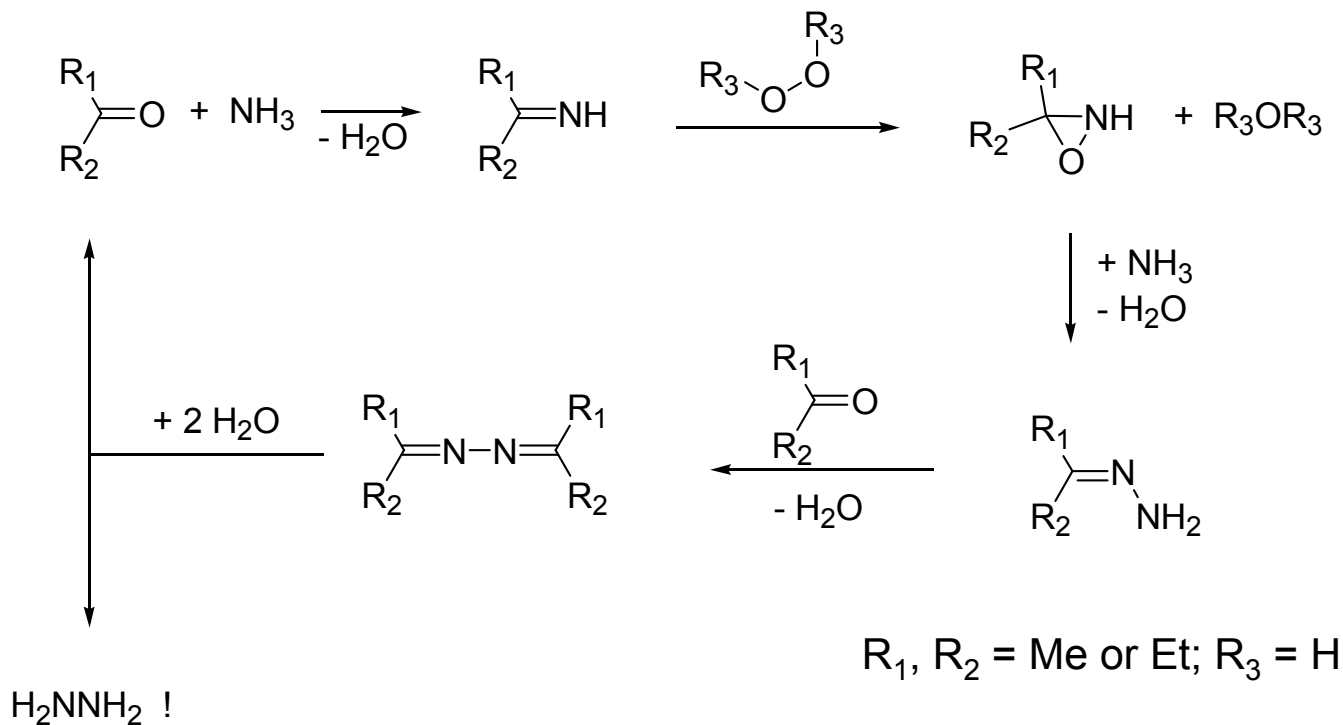
Raschig Process: 4 tons NaCl/ton of hydrazine; 60% yield (based on NH_3); 125 kWh/ton hydrazine required
Atofina-PCUK: No byproducts; >80% yield (based on NH_3); 16 kWh/ton hydrazine required

Hydrazine in the Wonderful World Around Us

- Free hydrazine on the Earth is not known (because of air oxidation), but was assumed to be present in the primordial environment.

- One major application of hydrazine today is as a rocket fuel (along with methylhydrazine as well). First developed by Germany for powering prototype jet engines in the Messerschmitt ME163 (WWII), simple hydrazines are still in use today by NASA for specific applications requiring certain types of thrust. For example, the International Space Station uses dimethylhydrazine for propulsion to maintain orbit and control attitude.

- Aside from pesticides and pharmaceuticals, the other major hydrazine application is in the deoxygenation of boiler feed water. This decomposition is catalyzed by metals such as copper and cobalt, and most likely also by metallic species leached gradually from pipe systems (especially nickel).

$$H_2NNH_2 + O_2 \longrightarrow N_2 + 2\,H_2O$$
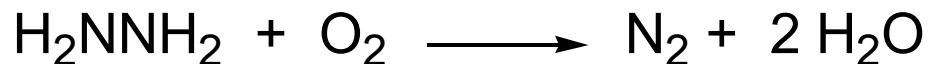
Naturally Occurring Hydrazines
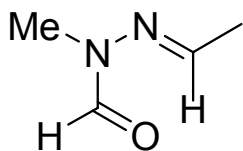
Gyromitrin, from the false morel mushroom, *Gyromitra esculenta*
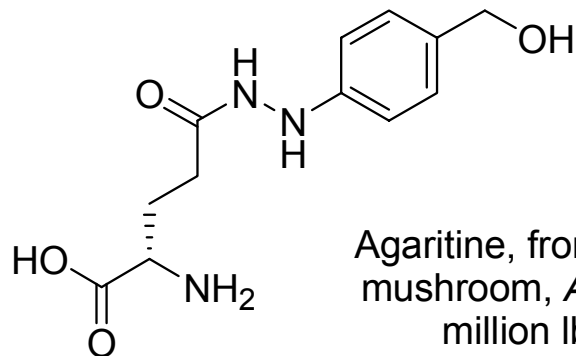
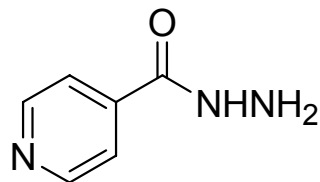Agaritine, from the N.A. commercial mushroom, *Agaricus bisporus,* 777 million lbs. grown in 1996
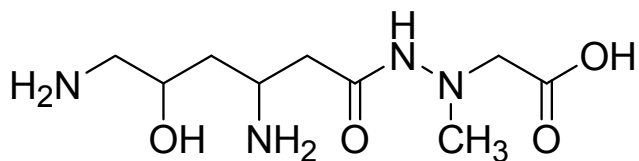
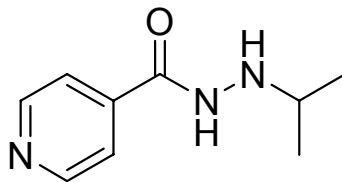Negamycin, antibiotic from *Streptomyces purpeofuscus*
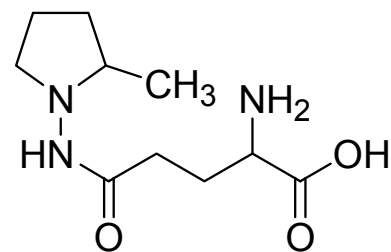
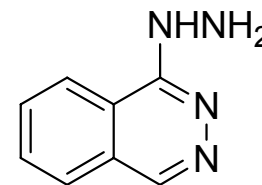Linatine, found in linsead meal and flax
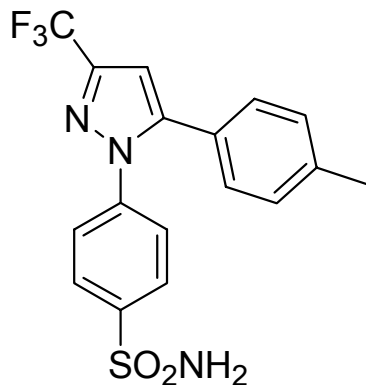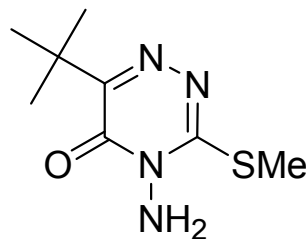
Some Synthetic Hydrazines with Useful Properties

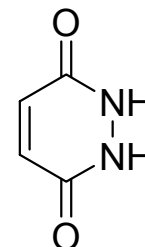Isoniazid (TB)

Iproniazid (early antidepressant, but toxic)

Hydralazine (antihypertensive)

Celebrex (NSAID)

Sencor (Herbicide)

Maleic hydrazide (plant growth retardant)

Maleic hydrazide is marketed under the amusing trade names Slo-Gro, Royal Slow-Gro, Slows-It, De-Sprout, De-Cut, Fair Plus, Sprout Stop, and Super Sucker-Stuff
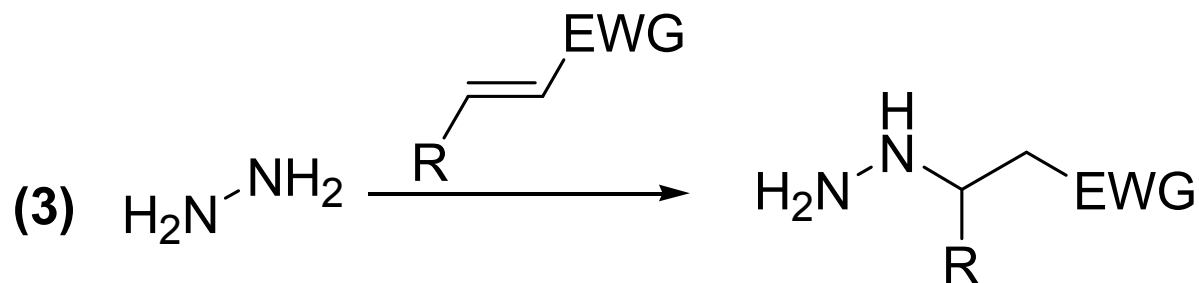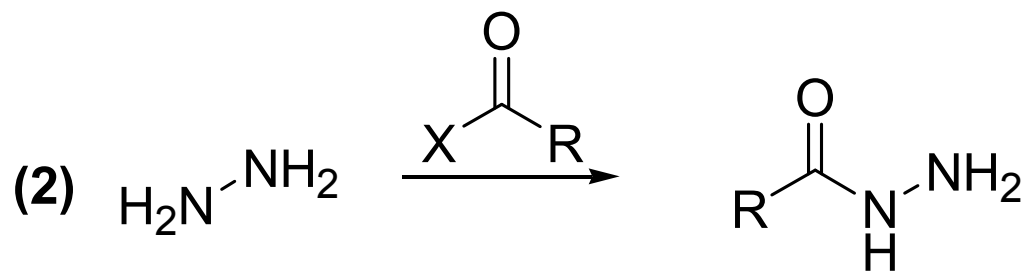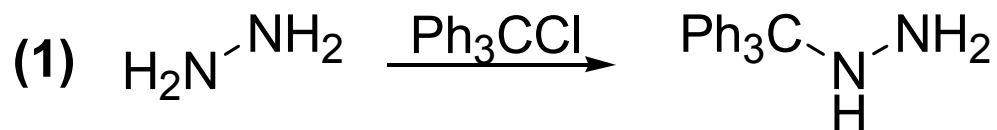
The Woes of Hydrazine Alkylation

Direct alkylation of hydrazine is problematic for the same reason that direct alkylation of primary amines is problematic: overalkylation is competitive with monoalkylation.

Anthoni, U.; Larsen, C.; Nielsen, P.H. *Acta Chem. Scand.*, **1968**, *22*, 1025-1035.
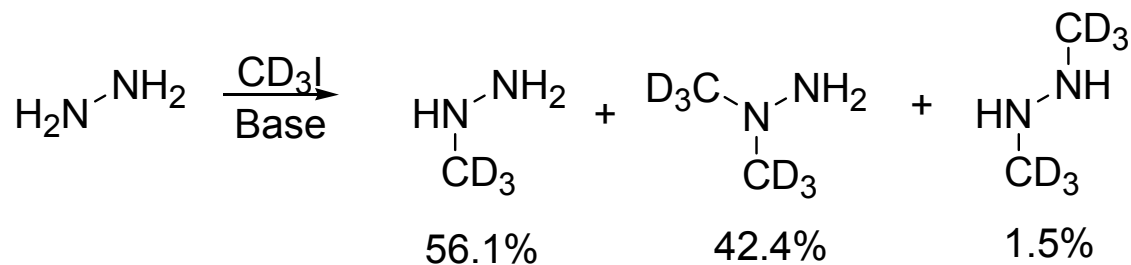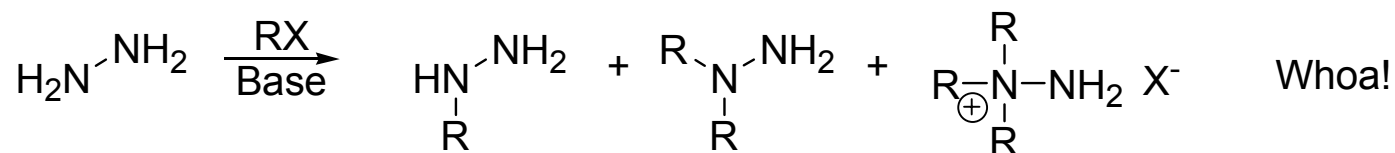
Direct Alkylation *Can* Sometimes Be Feasible…

Direct alkylation can occasionally be feasible if (1) the electrophile is very bulky; (2) the electrophile contains an EWG; or (3) an activated alkene is used.

(1) H_2N-NH_2 $\xrightarrow{Ph_3CCl}$ $Ph_3C-\underset{H}{N}-NH_2$

(2) H_2N-NH_2 $\xrightarrow{\begin{array}{c} O \\ \parallel \\ X-C-R \end{array}}$ $R-\underset{\underset{H}{N}}{\overset{O}{\parallel}}C-NH_2$

(3) H_2N-NH_2 $\xrightarrow{\begin{array}{c} EWG \\ R \end{array}}$ $H_2N-\underset{H}{N}-\underset{R}{CH}-CH_2-EWG$

Some Strategies for Monsubstituted Hydrazines

> These procedures are invariably reliant on protecting groups of one form or another. An important limitation is that only activated *primary* electrophiles are viable in these reactions.
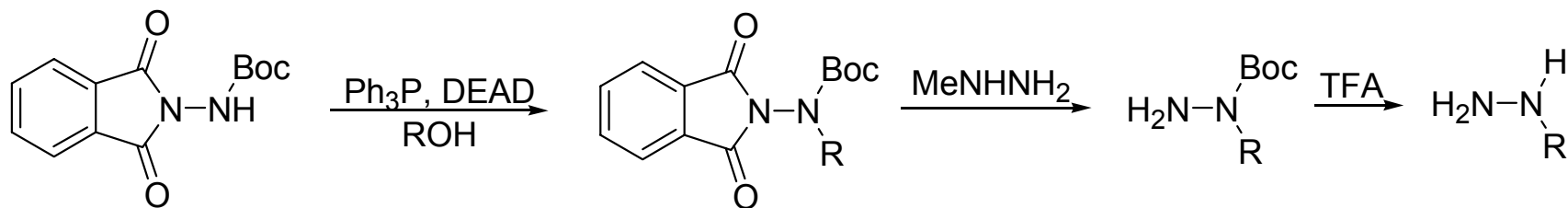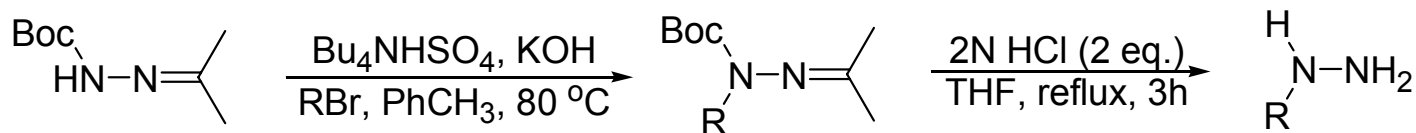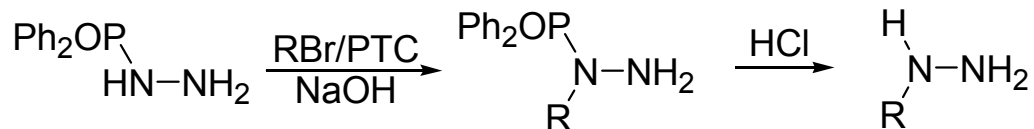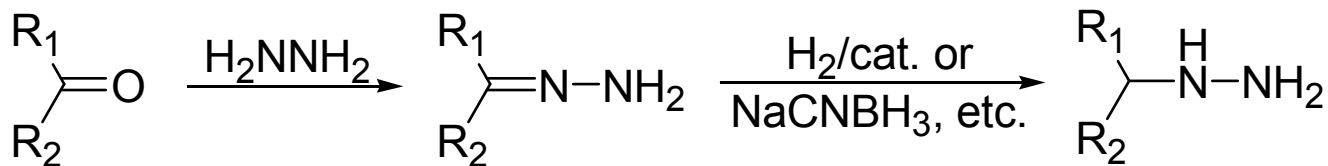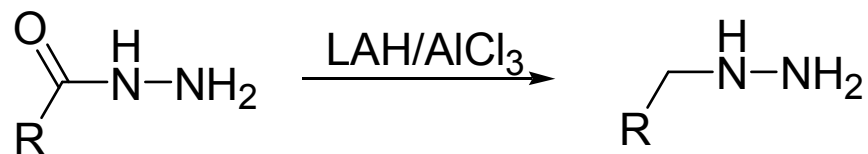
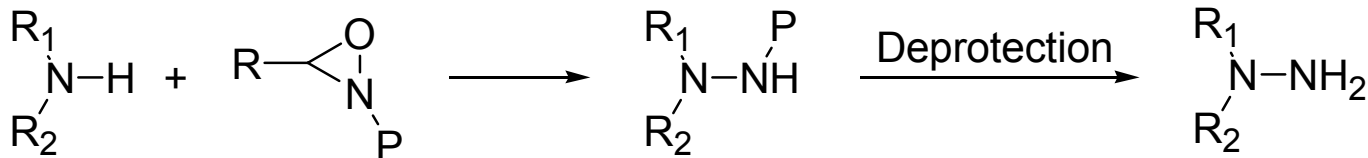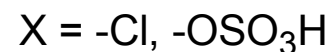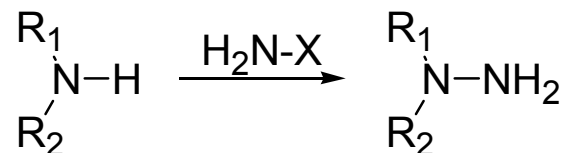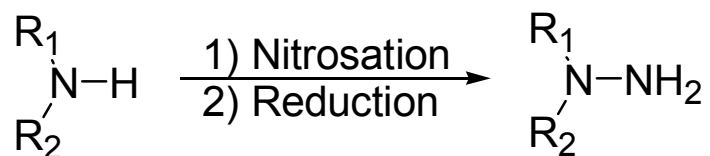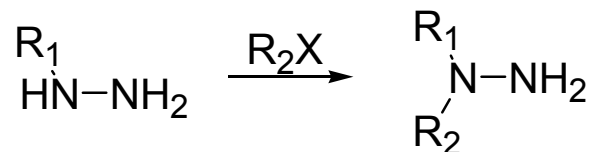Ragnarsson, U. *Chem. Soc. Rev.*, **2001**, *30*, 205-213.

Meyer, K. G. *Synlett*, **2004**, *13*, 2355-2356.

More on Monosubstitution

Reductions of hydrazones and hydrazides also leads to monosubstituted hydrazines, including ones with secondary alkyl groups.
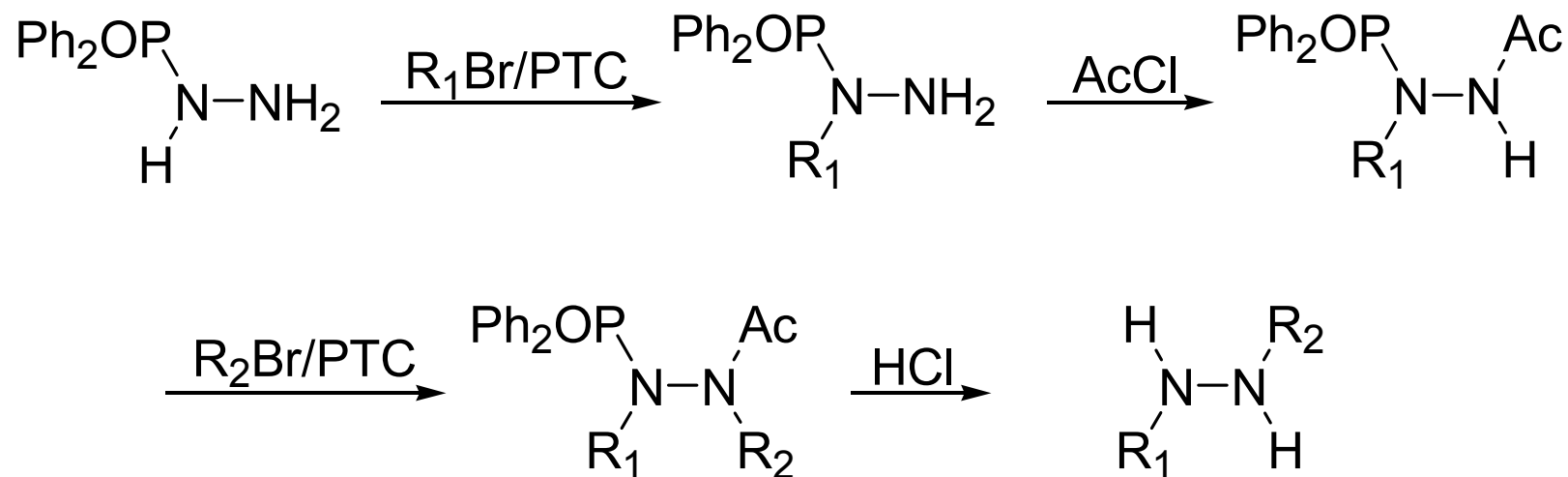
Ragnarsson, U. *Chem. Soc. Rev.,* **2001**, *30*, 205-213.

1,1-Disbustituted Hydrazines

Ragnarsson, U. *Chem. Soc. Rev.,* **2001**, *30*, 205-213.

1,2-Disubstituted Hydrazines

A bit more troublesome than the 1,1-disubstituted case:

Ragnarsson, U. *Chem. Soc. Rev.,* **2001**, *30*, 205-213.

"Higher" Hydrazines?

> No pain, no gain!
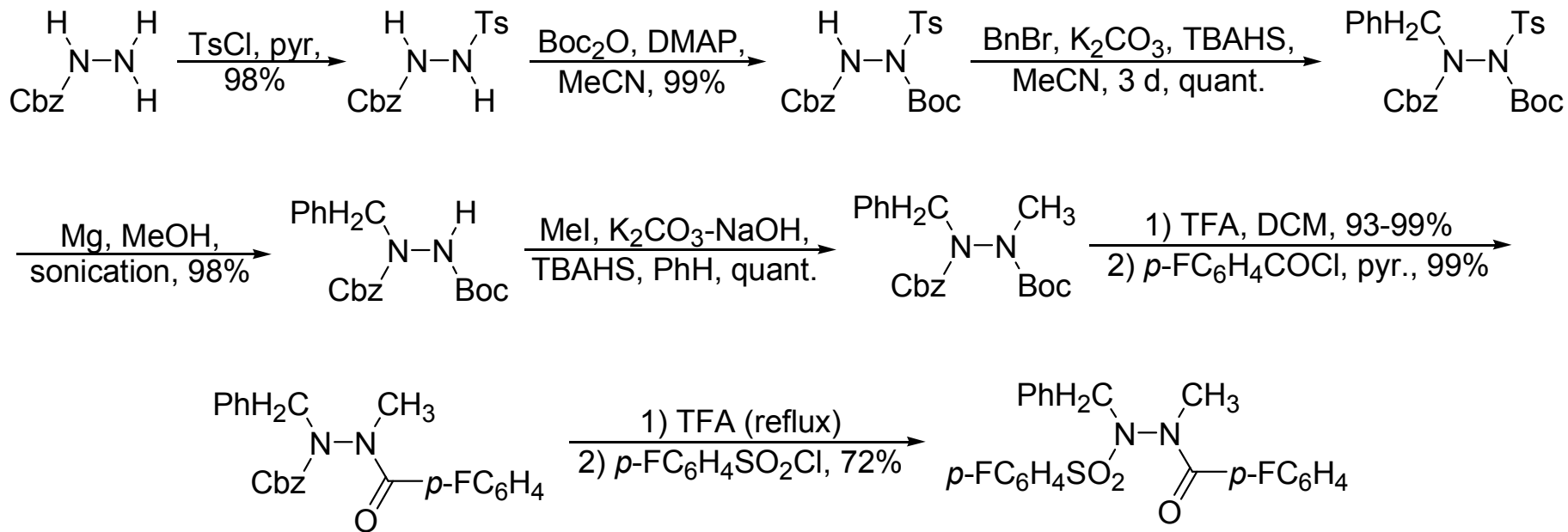
Grehn, L.; Lönn, H.; Ragnarsson, U. *Chem. Commun.*, **1997**, 1381-1382.
Greahn, L.; Nyasse, B.; Ragnarsson, U. *Synthesis*, **1997**, 1429-1432.

# Incorporation of Secondary Alkyl Groups

Using the same triprotected starting material, a single branched substituent can be introduced first by the usual condensation/reduction sequence. Surprisingly, the orthogonally *N,N*-diprotected motif was apparently unknown before this time.


Grehn, L.; Ragnrasson, U. *Tetrahedron*, **1999**, *55*, 4843-4852.
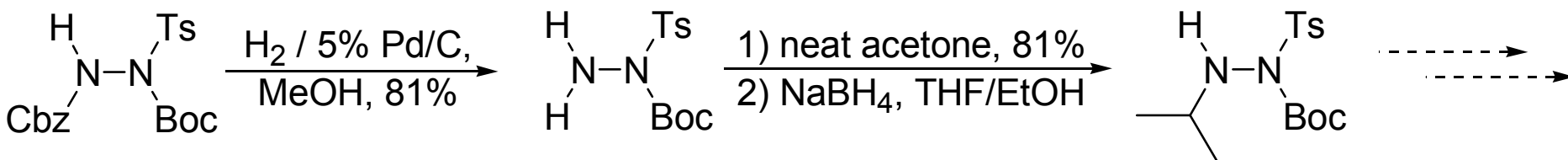
The Oxaziridine…

The oxaziridine reagent can be used to prepare Boc-protected peptidomimetics, but the reaction is hampered by a facile side reaction. This can be overcome by utilizing protected amino acids (but proline works OK by itself!).

Ragnarsson, U. *Chem. Soc. Rev.,* **2001**, *30*, 205-213.
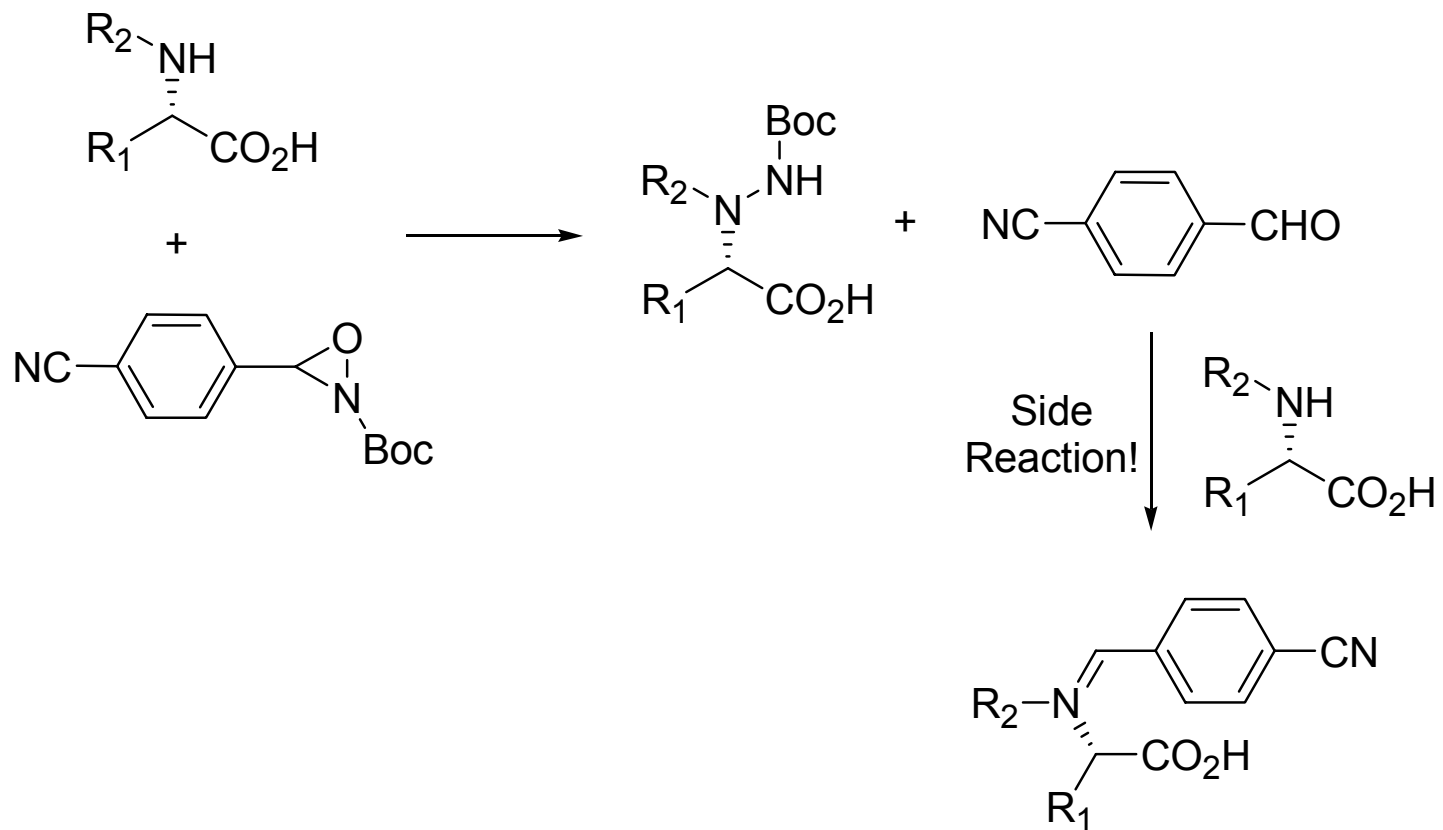
An Unusual Approach

Some trisubstituted hydrazines can be accessed by displacement of a benzotriazole moiety.

R_1 = H, Et, *n*-Pr, cyclohexyl
R_2 = Et, Ph, allyl
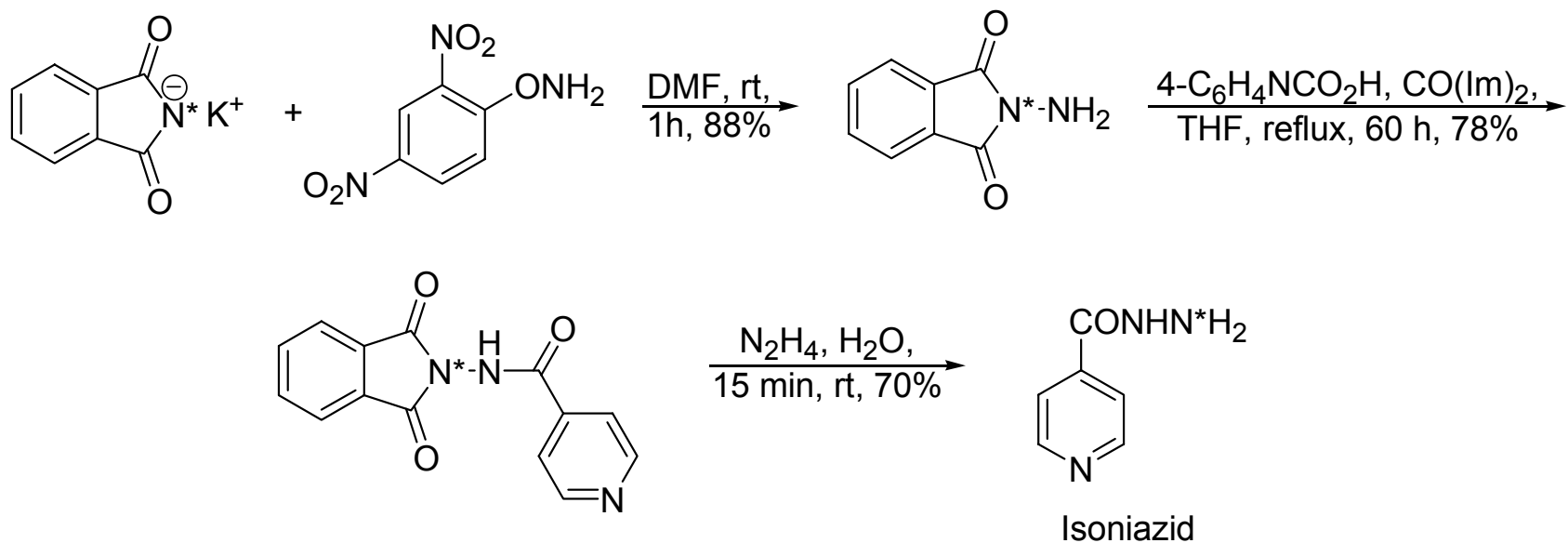
X = O, 62%
X = S, 53%

68-99%
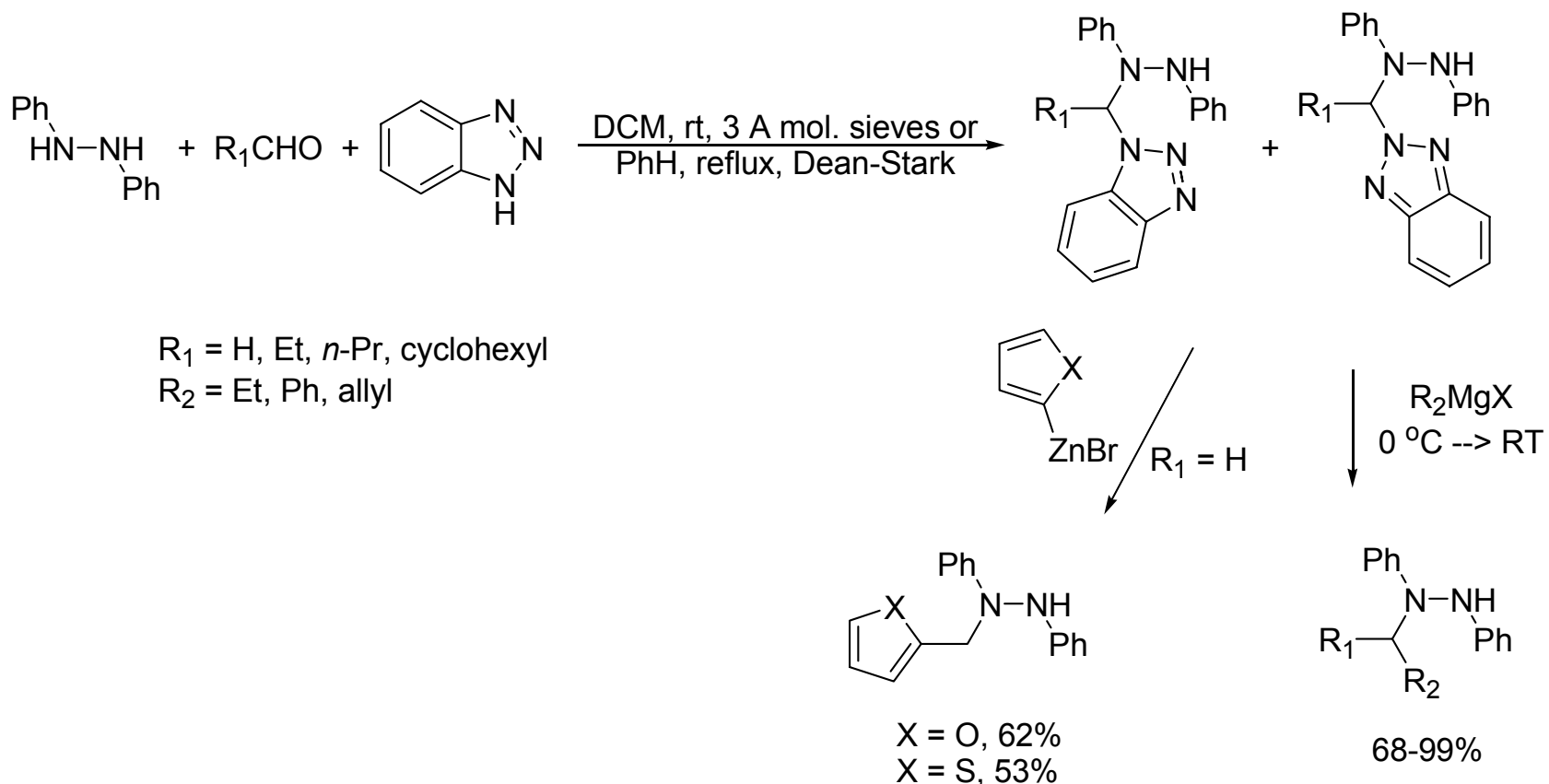
Ragnarsson, U. *Chem. Soc. Rev.* **2001**, *30*, 205-213.
Katritzky, A. R.; Qiu, G.; Yang, B. *J. Org. Chem.* **1997**, *62*, 8210-8214.

Isoniazid Studies: Hydrazines in Action

> To study the mechanism of action of Isoniazid, ^{15}N labeled analogs were required.
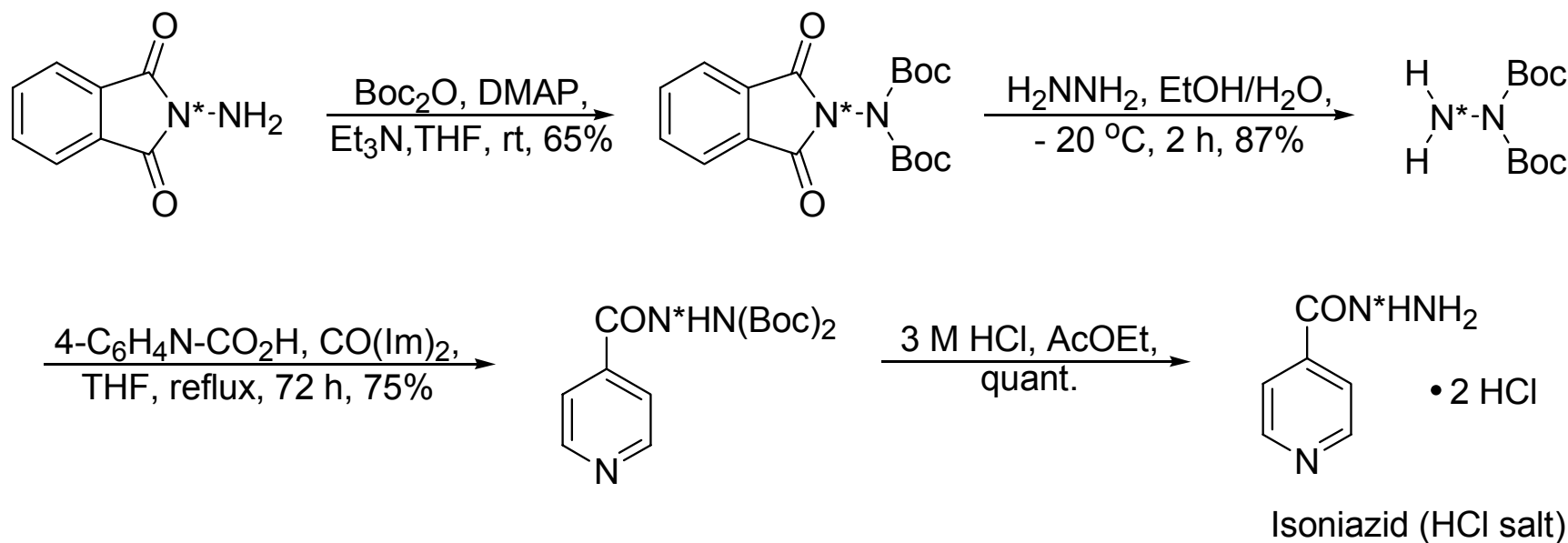> Here, the hydrazine was made by an electophilic amination protocol.

Isoniazid

Ragnarsson, U. *Chem. Soc. Rev.,* **2001**, *30*, 205-213.
Brosse, N.; Pinto, M. F.; Jamart-Gregoire, B. *J. Chem. Soc. Perkin Trans, 1*, **1998**, 3685-3688.
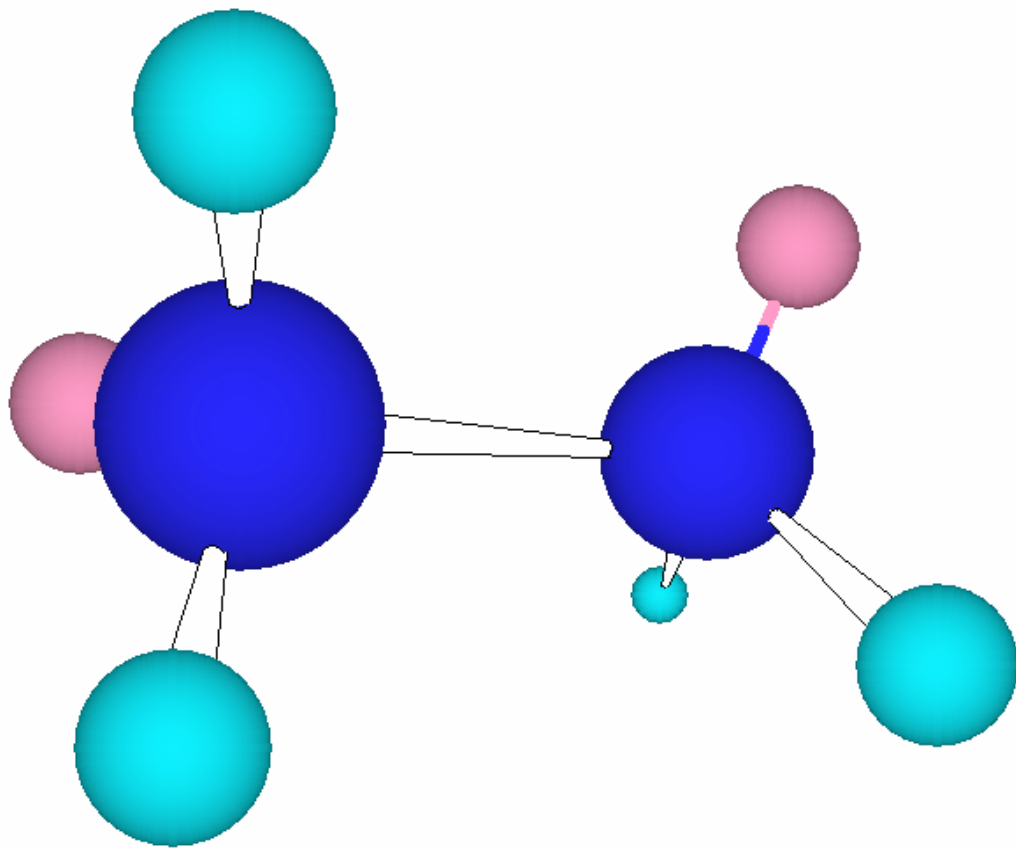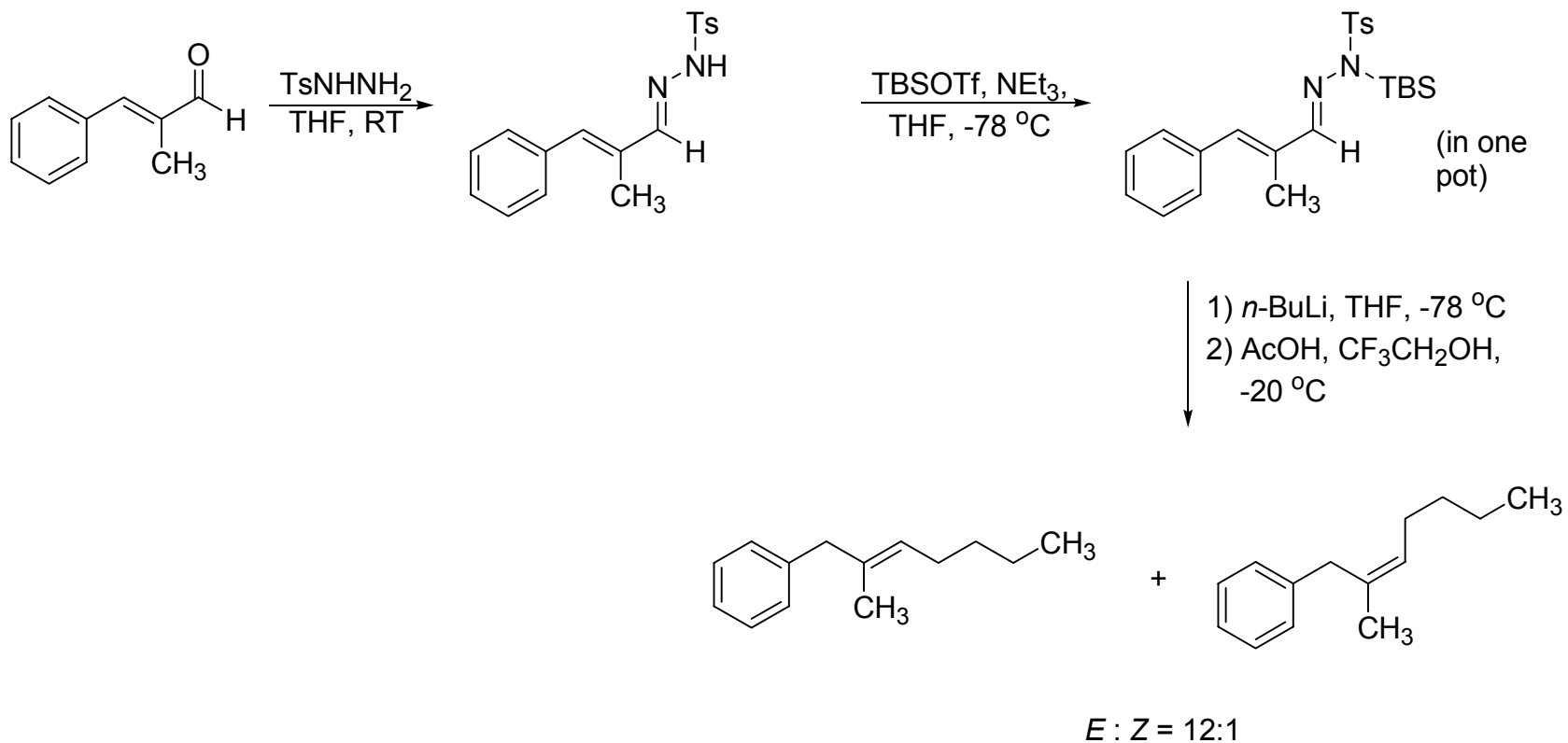
Isoniazid Continued…

Preparation of the other singly labeled Isoniazid…

Boc₂O, DMAP, Et₃N, THF, rt, 65%

H₂NNH₂, EtOH/H₂O, - 20 °C, 2 h, 87%

4-C₆H₄N-CO₂H, CO(Im)₂, THF, reflux, 72 h, 75%

3 M HCl, AcOEt, quant.

Isoniazid (HCl salt)

Ragnarsson, U. *Chem. Soc. Rev.,* **2001**, *30*, 205-213.

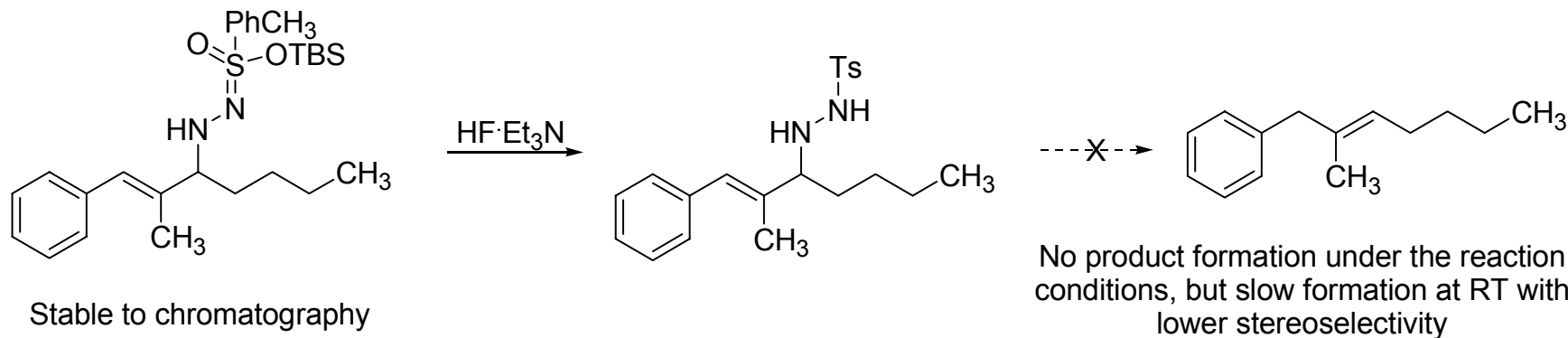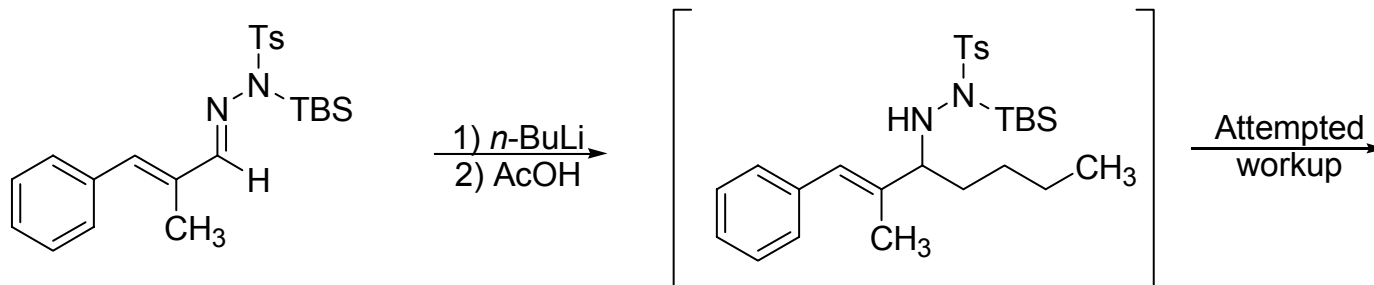Brosse, N.; Pinto, M. F.; Jamart-Gregoire, B. *J. Chem. Soc. Perkin Trans, 1*, **1998**, 3685-3688.

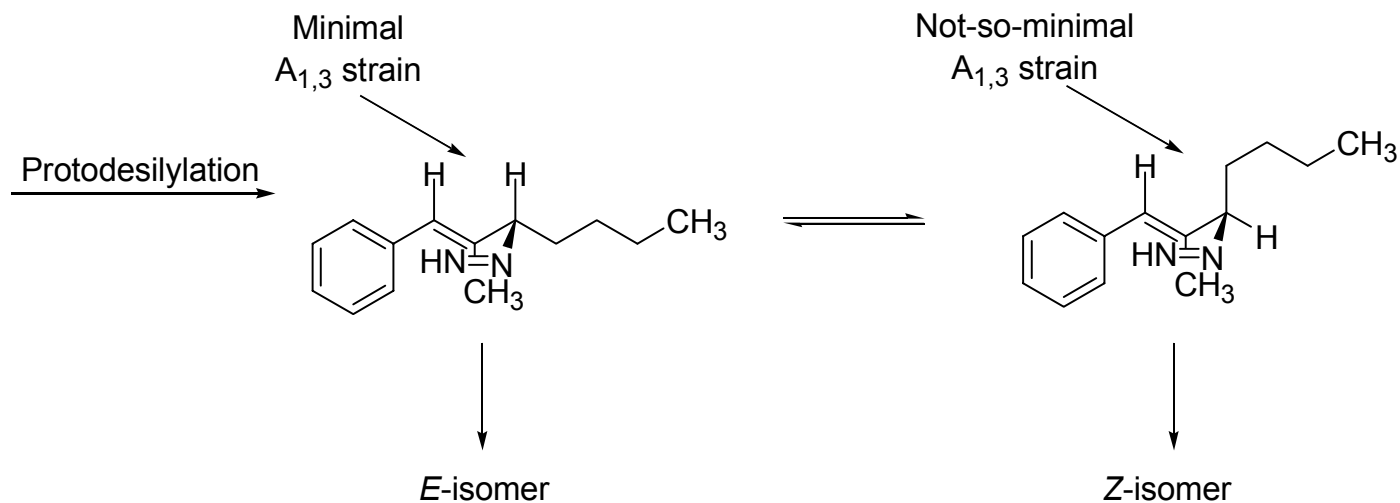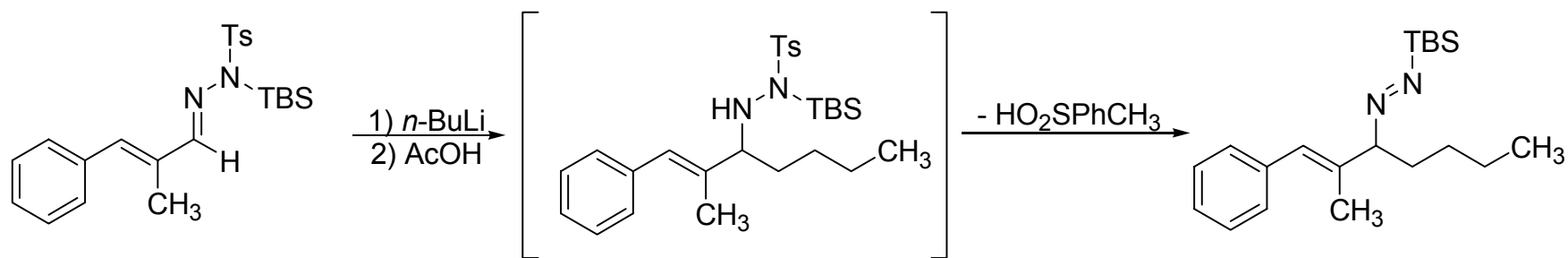# The Beginning of the Myers TBS-Tosylhydrazones

A one-pot hydrazone preparation is followed by conversion to an *E* olefin with overall apparent olefin migration. Note that prior to silylation, the tosylhydrazone typically undergoes 1,4-addition of organolithiums rather than 1,2-addition.

TsNHNH$_2$, THF, RT

TBSOTf, NEt$_3$, THF, -78 °C

(in one pot)

1) *n*-BuLi, THF, -78 °C
2) AcOH, CF$_3$CH$_2$OH, -20 °C

+

E : *Z* = 12:1

Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208-8210.

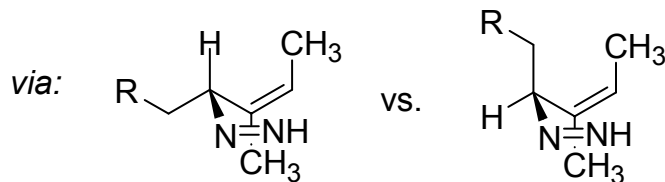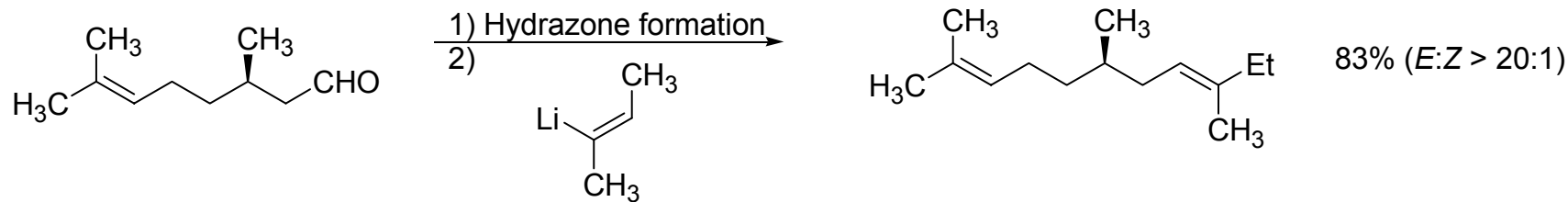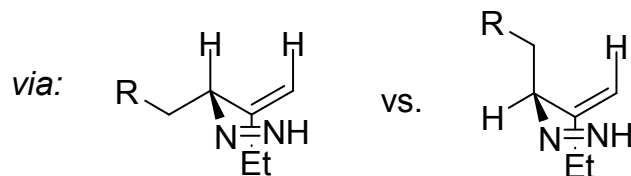# So what's the mechanism? Not this one!

Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208-8210.

The More Likely Mechanism

Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208-8210.
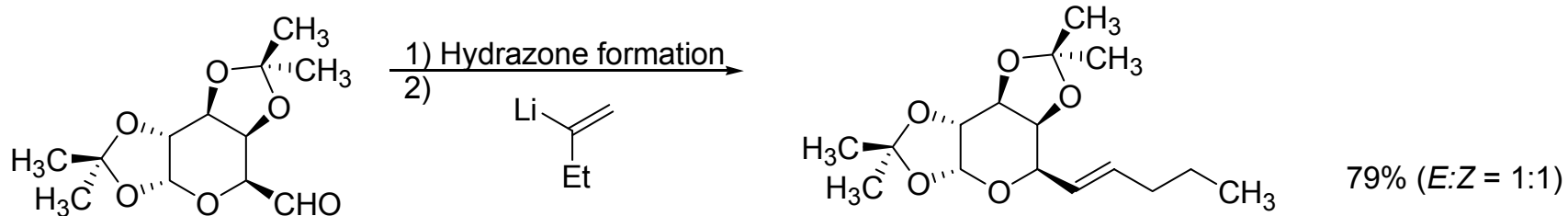
And Some Examples

Where $A_{1,3}$ strain begins to diminish, $A_{1,2}$ strain can start taking over:

Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208-8210.
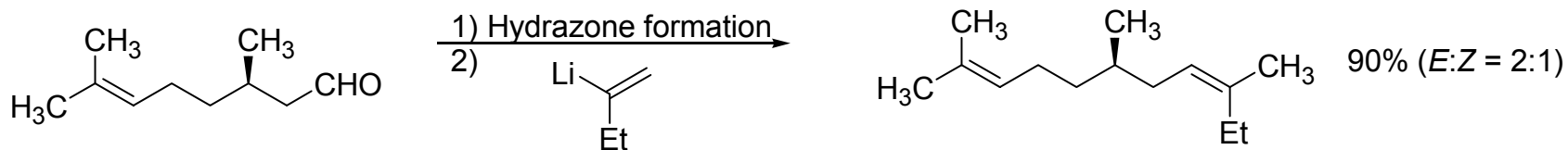
And a Few Hindered Cases

Importantly, no racemization occurs with nonracemic aldehyde precursors.

81% (*E:Z* >20:1)

86% (*E:Z* >20:1)

79% (*E:Z* = 1:1)

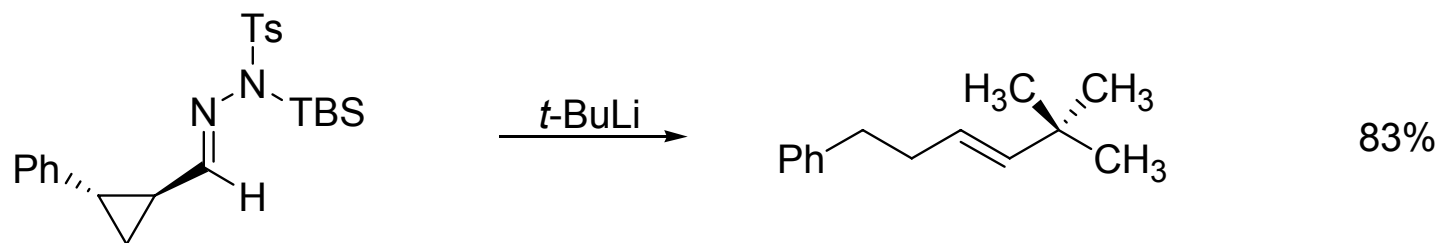Myers, A. G.; Kukkola, P. J. *J. Am. Chem. Soc.* **1990**, *112*, 8208-8210.
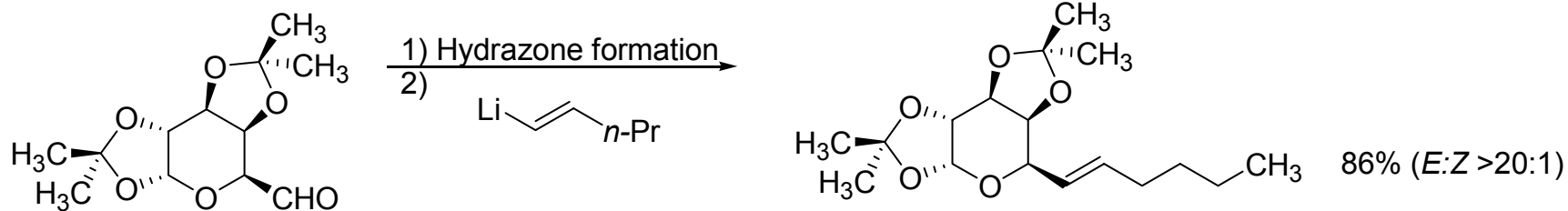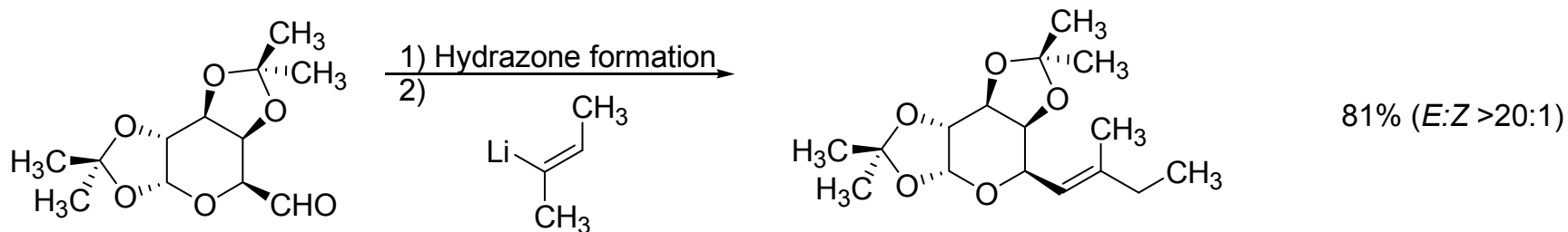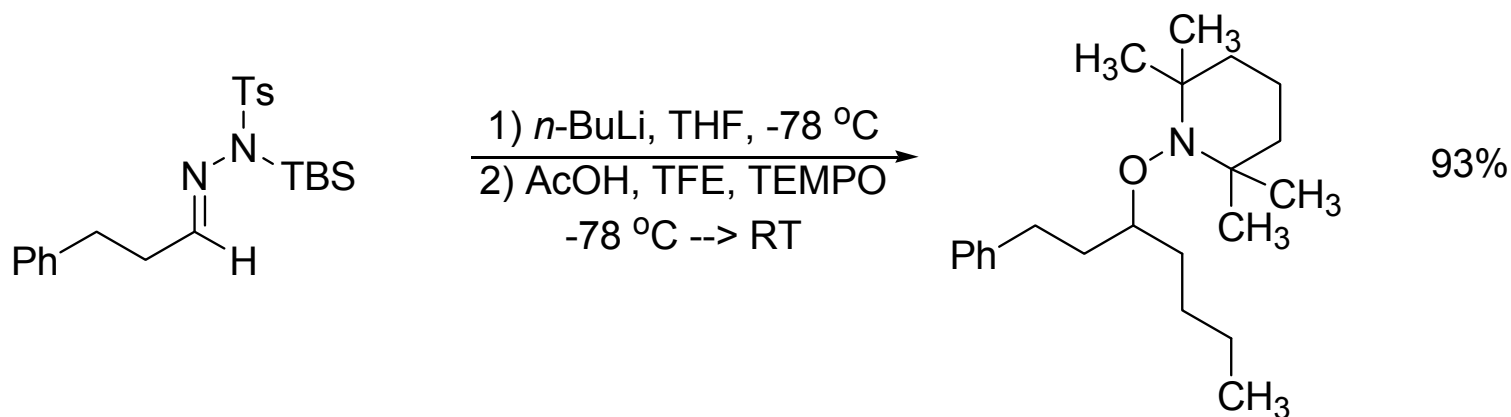
How About Some Saturation?

If both the hydrazone and the lithium reagent are saturated, then you can get a nice, reductive coupling for a net C-C (sp^3-sp^3) bond formation.

Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891-8892.
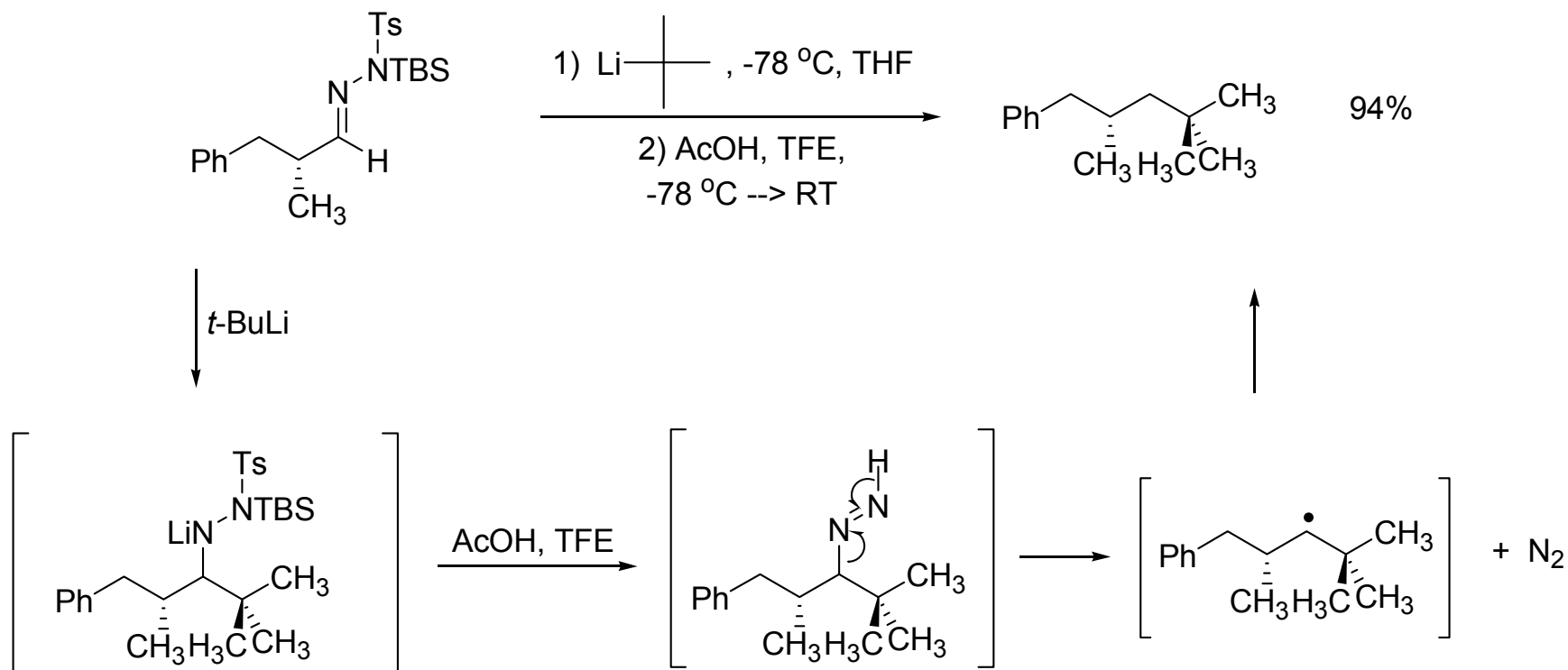
Evidence for Those Radicals…

…comes from TEMPO trapping and fragmentation of a cyclopropyl group.

1) *n*-BuLi, THF, -78 °C
2) AcOH, TFE, TEMPO
-78 °C --> RT

93%

t-BuLi

83%

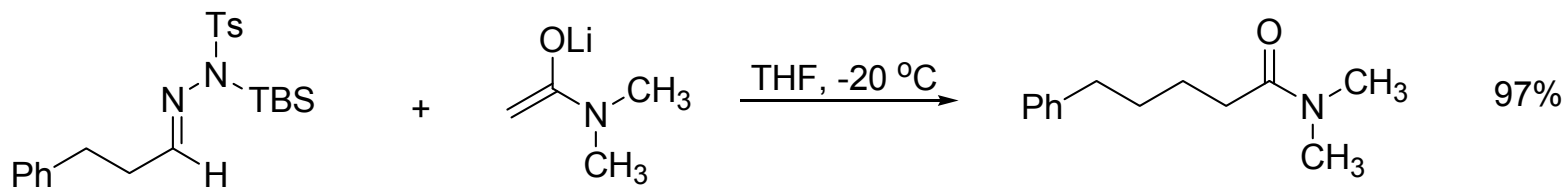Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891-8892.
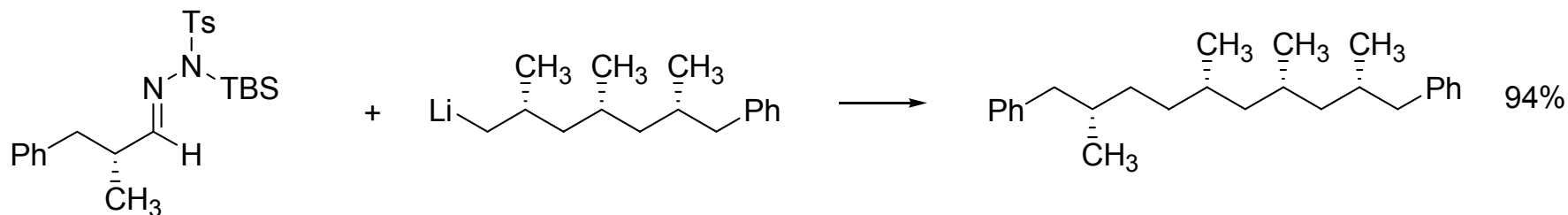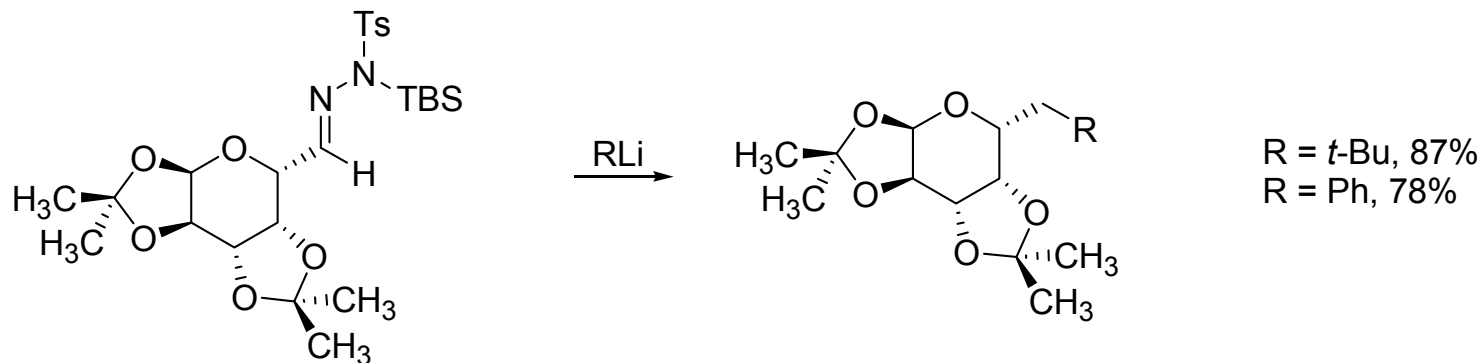
But There Can Be Competition for Radical vs. [1,5] H-Shift Pathways

As with the previous olefin coupling, when pendant unsaturation is appropriately positioned within the molecule, the [1,5] H-shift can be operative (and is preferred).

Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891-8892.
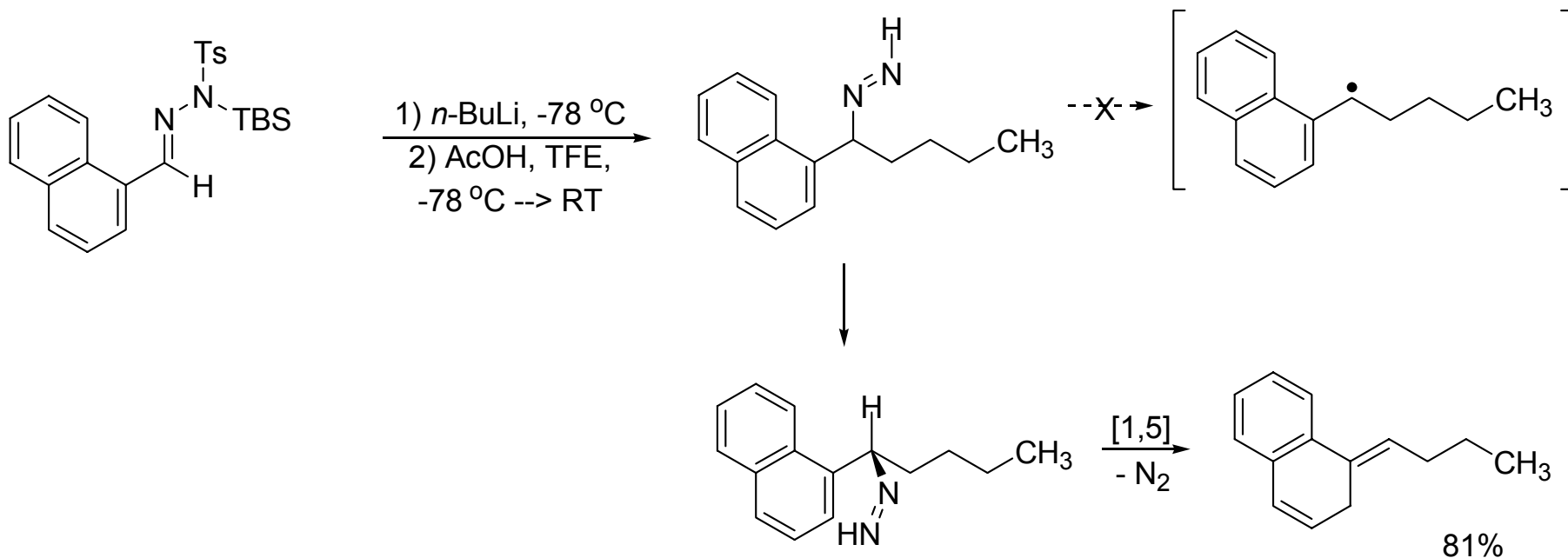
Some Examples of the Reductive Coupling

R = *t*-Bu, 87%
R = Ph, 78%

94%

THF, -20 °C

97%

Even an amide enolate is basic enough for this protocol, but lithium acetylides and Grignard reagents are not.

Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891-8892.
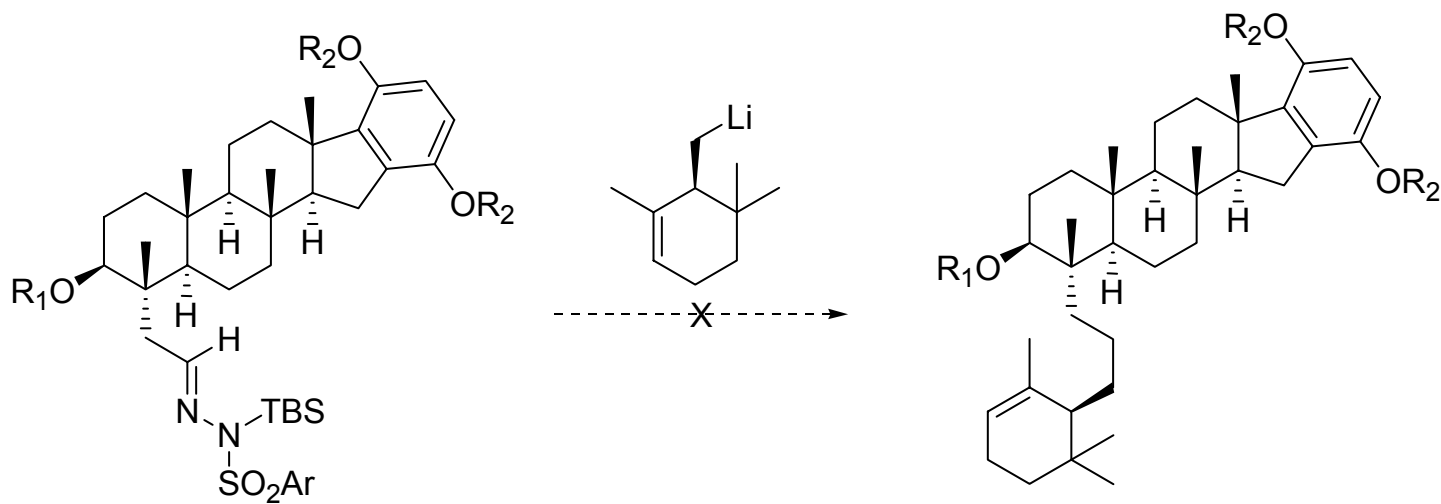
Some *Limitations* of the Reductive Coupling

Very bulky nucleophiles work OK, but the reaction does suffer when bulky hydrazones are used. Fortunately, a solution to the problem is available.

39%

+

52%

95%
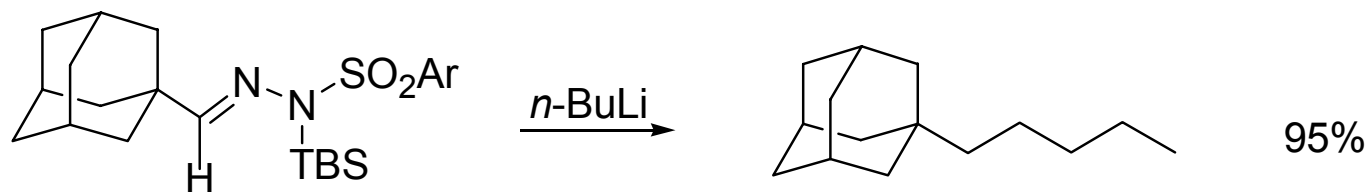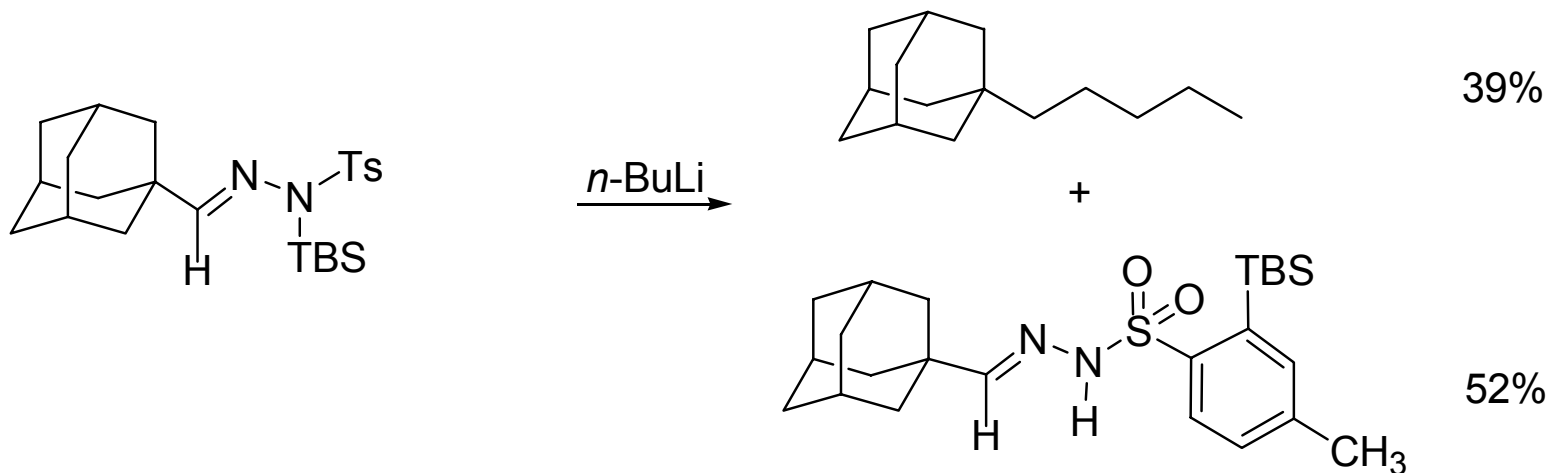
Ar = 2,4,6-triisopropylbenzene

Myers, A. G.; Movassaghi, M. *J. Am. Chem. Soc.* **1998**, *120*, 8891-8892.

An Example from the World of Synthesis

A late-stage usage of Myers' coupling chemistry was planned as shown below.
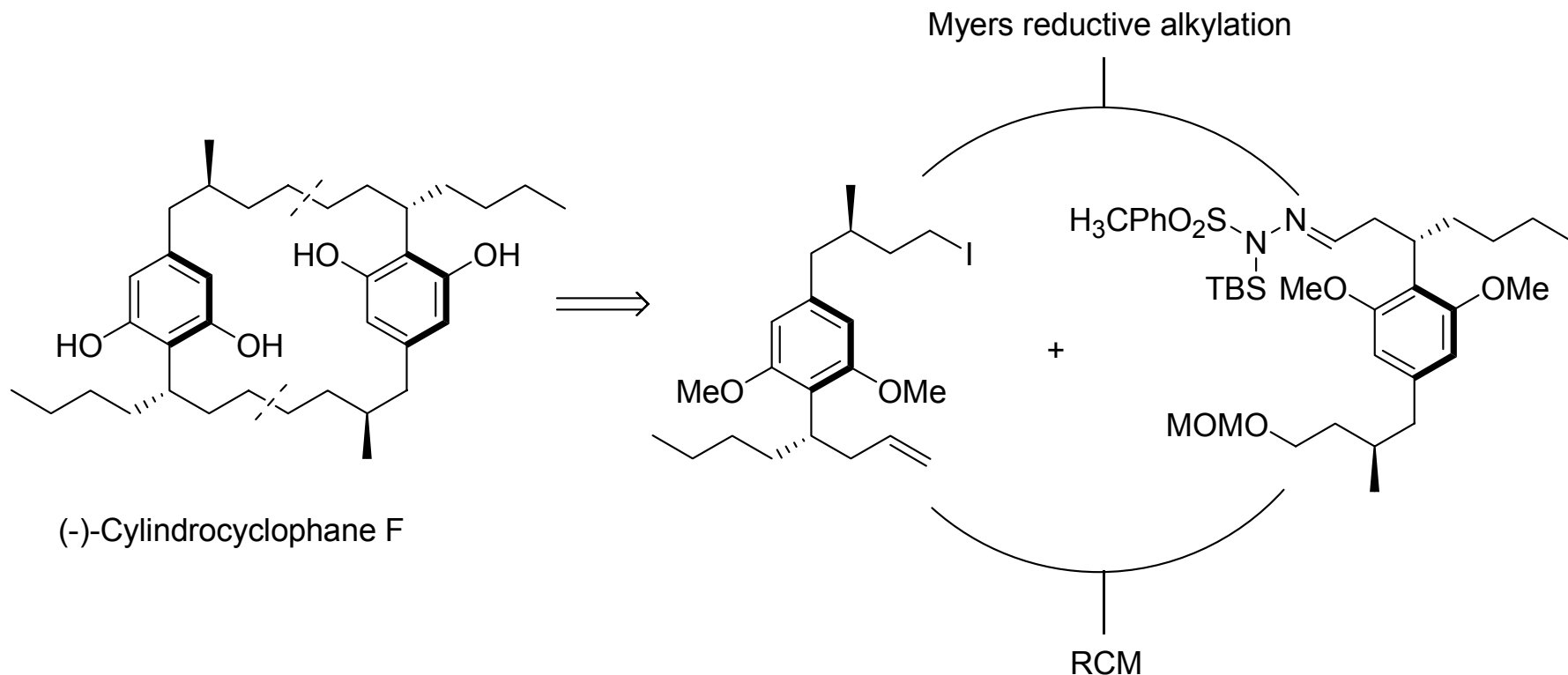Unfortunately, it failed in this case, and a lengthier route was needed.

Ar = ?
R$_1$ = TBS, R$_2$ = Me

R$_1$ = TBS, R$_2$ = Me
R$_1$ = H, R$_2$ = SO$_3$Na, Adociasulfate 1

Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206-7.

And Another!

Myers reductive alkylation

RCM

(-)-Cylindrocyclophane F

In the forward direction, this transformation, along with MOM deprotection, proceeded in a combined 73% yield. Subsequent RCM and further deprotections led nicely to the natural product.

Smith, A. B.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **1999**, *121*, 7423-4.
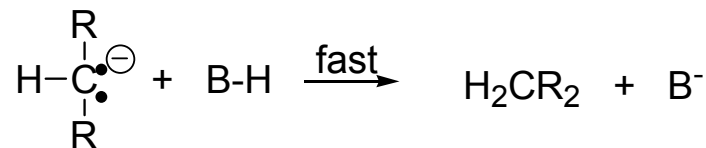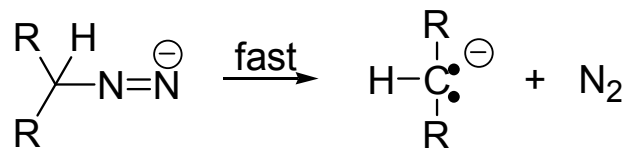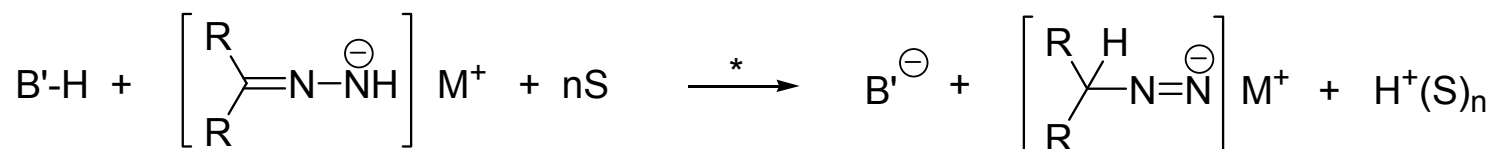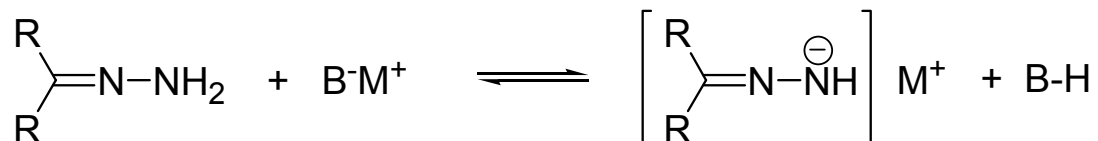
Wolff-Kishner Revisited
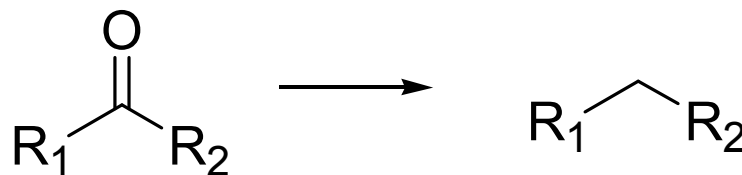
In the original procedure (1911), preformed hydrazones were added to hot, solid KOH, or heated with NaOEt in EtOH in a sealed tube at 160-200 °C. The most common modification now in use is the Huang-Minlon version, which calls for heating the carbonyl compound with hydrazine and alkali in a high-boiling ethereal solvent at ~ 200 °C. Obviously, milder conditions for this classic transformation would be of value.
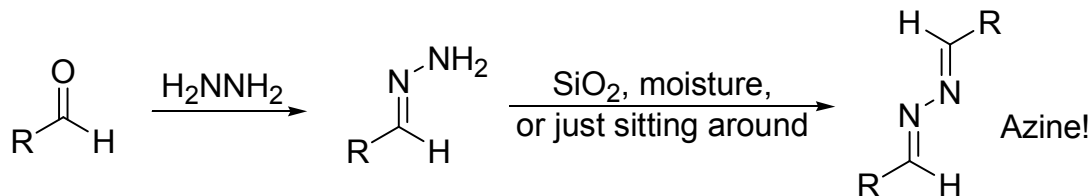
Kishner, N. *Zh. Russ. Fiz.-Khim. O-va., Chast. Khim.* **1911**, *43*, 582.
Huang-Minlon. *J. Am. Chem. Soc.* **1946**, *68*, 2487.

The Mechanism

Szmant, H. H. *Angew. Chem. Int. Ed.* **1968**, 7, 120-128.
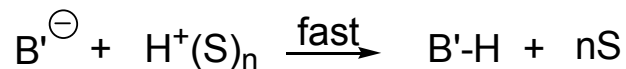
More Woes of the Traditional Wolff-Kishner

A major drawback of the Wolff-Kishner reduction is the competitive formation of the azine byproduct. This is particularly problematic for aldehyde hydrazones, with many hydrazones having lifetimes only on the order of several hours. Since silyl groups are often "proton surrogates," using a TBS-protected hydrazone instead would seem to be a good idea, but these compounds are not formed as easily as one might think:

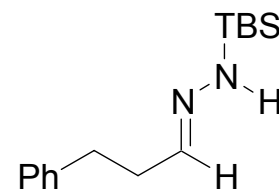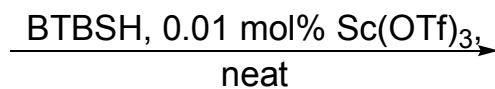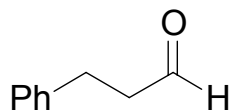Bode, K.; Klingebiel, U. *Adv. Organomet. Chem.* **1996**, *40*, 1.
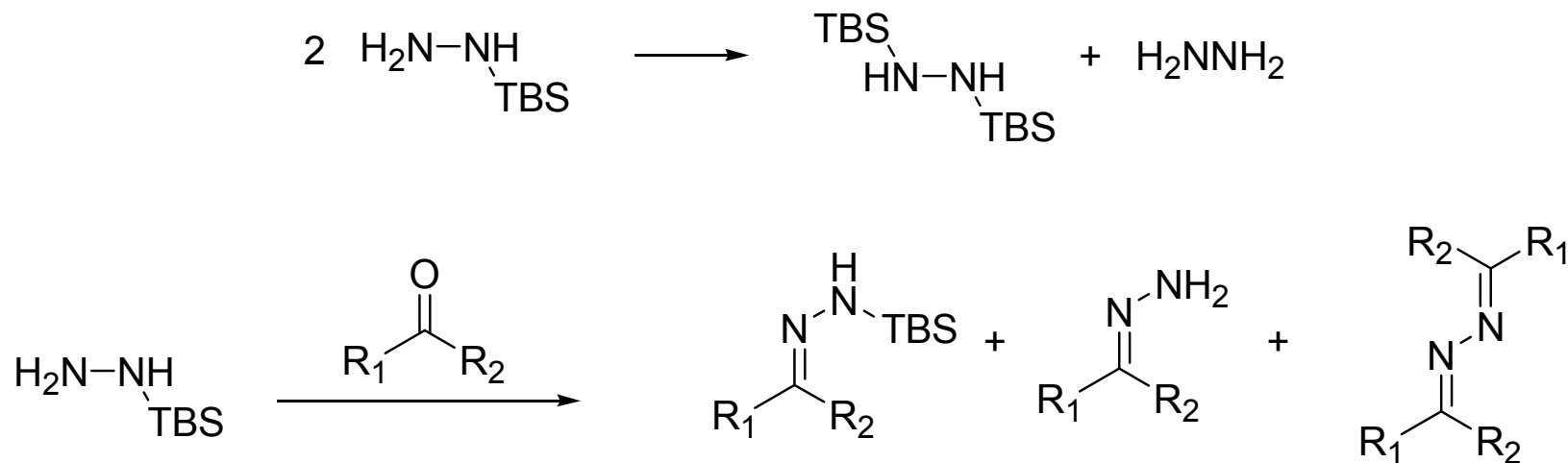
The More TBS the Merrier: A Simple Alternative
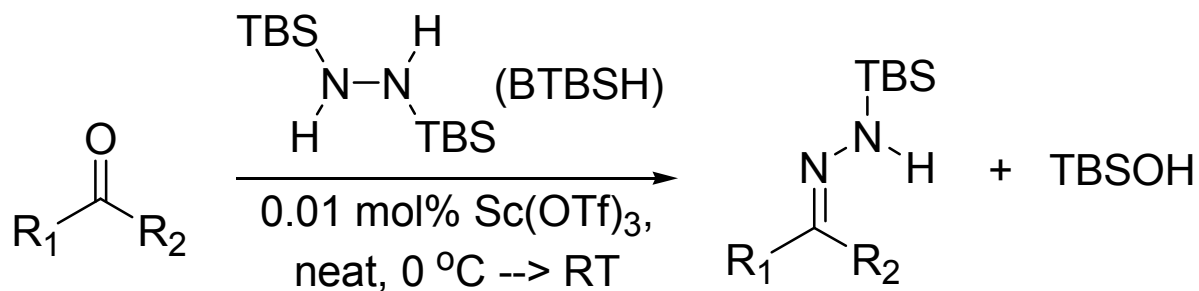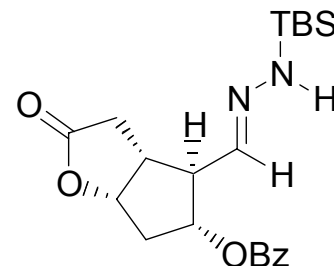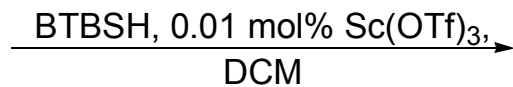

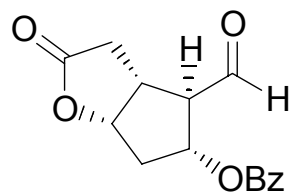
- BTBSH is *less* nucleophilic than TBS-hydrazine, but $Sc(OTf)_3$ compensates for this.
- The TBSOH byproduct formed is less nucleophilic than the H_2O produced when TBS-hydrazine is employed, thereby preventing self-hydrolysis of the hydrazine.
- BTBSH is *not* prone to disproportionation like the TBS-hydrazine.
- TBSOH is volatile enough to be removable under vacuum, and excess BTBSH doesn't affect later chemistry, so purification after this step is usually unnecessary.
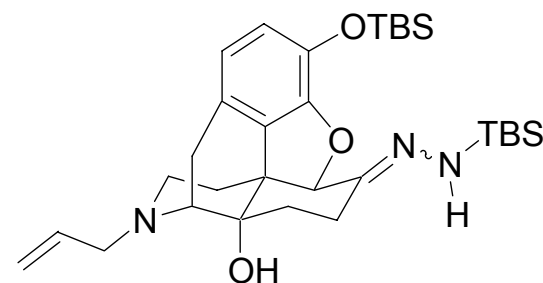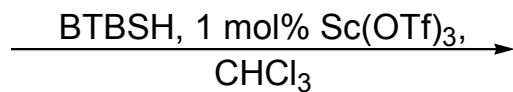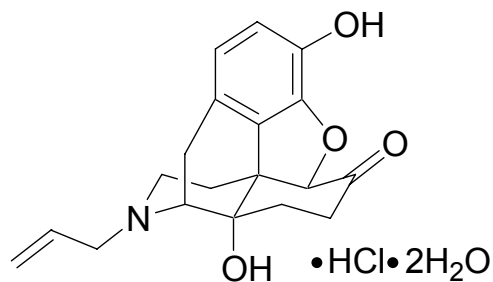- **The product hydrazones are indefinitely stable when properly stored.**

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.

A Few Examples

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.
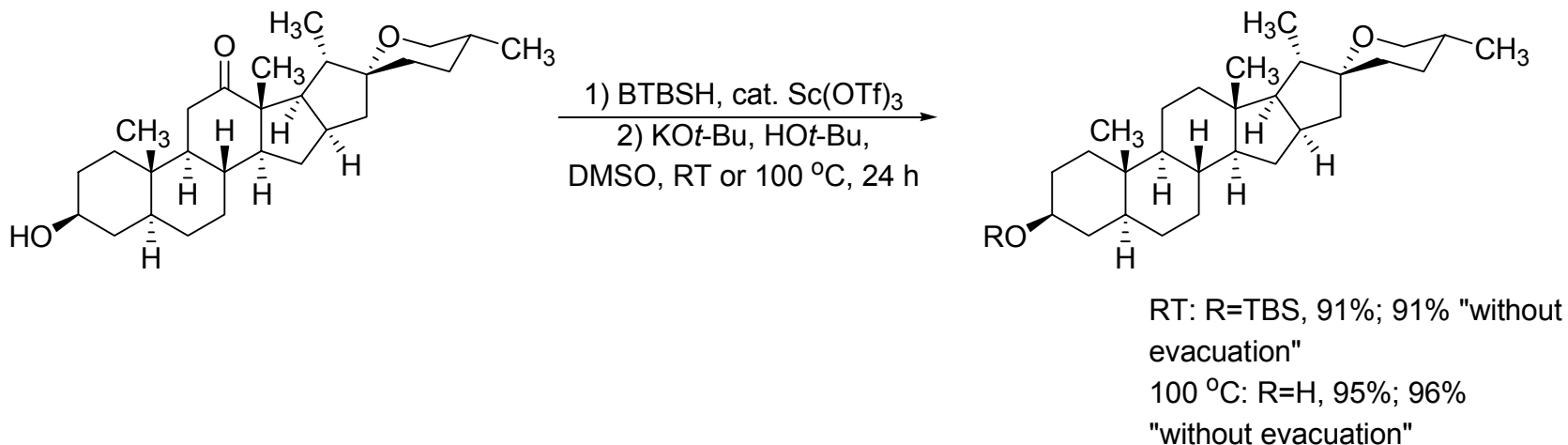
And Now: A Modified Wolff-Kishner Reduction

PhO—C₆H₄—CHO
1) BTBSH, cat. Sc(OTf)₃
2) KOt-Bu, HOt-Bu, DMSO, 100 °C, 24 h
→ PhO—C₆H₄—CH₃
92%; 96% "without evacuation"

PMP—CH₂CH₂—C(O)CH₃
1) BTBSH, cat. Sc(OTf)₃
2) KOt-Bu, HOt-Bu, DMSO, RT, 24 h
→ PMP—CH₂CH₂CH₂—CH₃
94%; 93% "without evacuation"

1) BTBSH, cat. Sc(OTf)₃
2) KOt-Bu, HOt-Bu, DMSO, RT or 100 °C, 24 h

RT: R=TBS, 91%; 91% "without evacuation"
100 °C: R=H, 95%; 96% "without evacuation"

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.
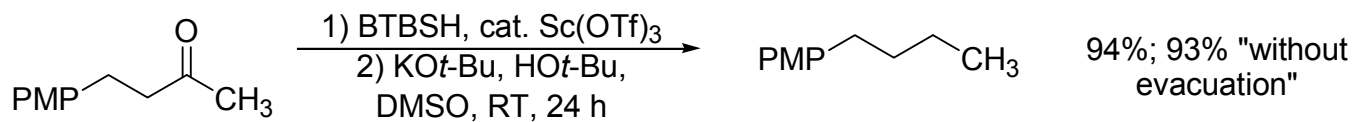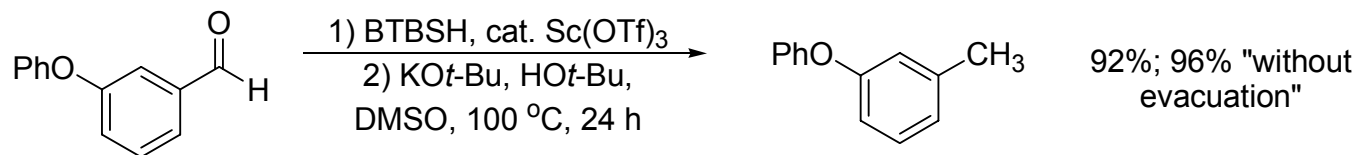
What About A Direct Comparison?
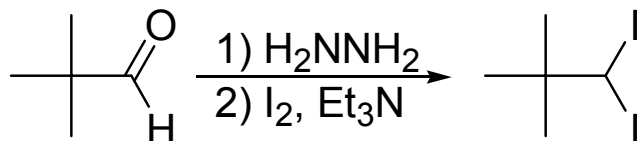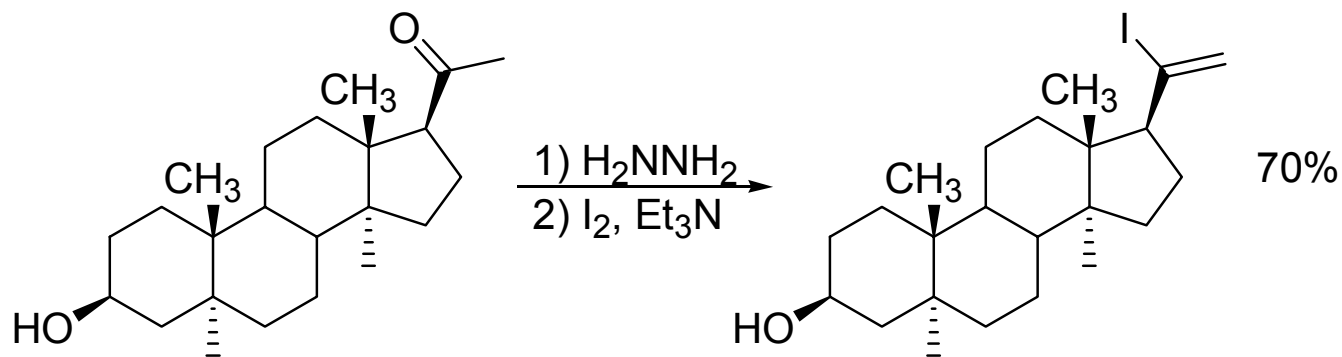
In this complex setting, the modified conditions gave a yield ~15%
higher than the traditional Wolff-Kishner conditions.
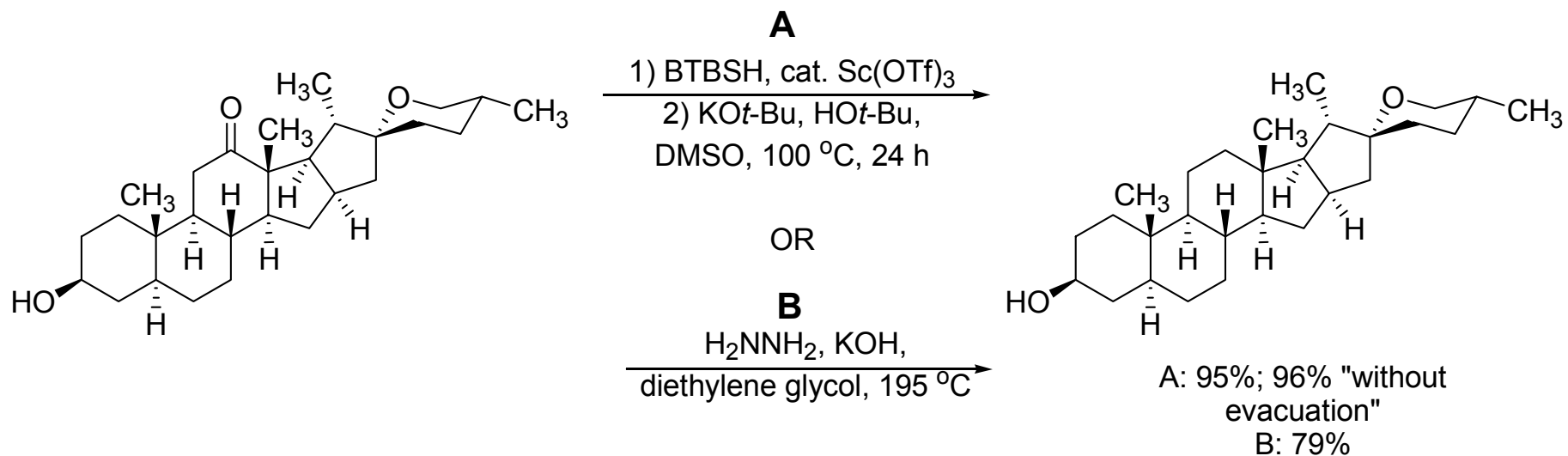
A
1) BTBSH, cat. Sc(OTf)$_3$
2) KO*t*-Bu, HO*t*-Bu,
DMSO, 100 ^{o}C, 24 h

OR

B
H$_2$NNH$_2$, KOH,
diethylene glycol, 195 ^{o}C

A: 95%; 96% "without
evacuation"
B: 79%

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.

Iodides, Anyone?

$$\text{1) H}_2\text{NNH}_2 \quad \text{2) I}_2, \text{Et}_3\text{N}$$

70%

Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962,** 470-476.
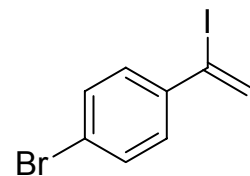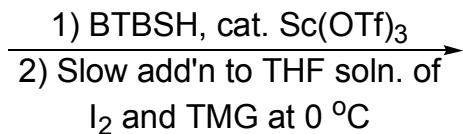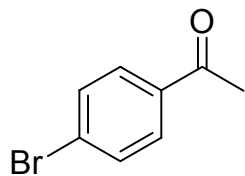
A Useful Mechanistic Dichotomy
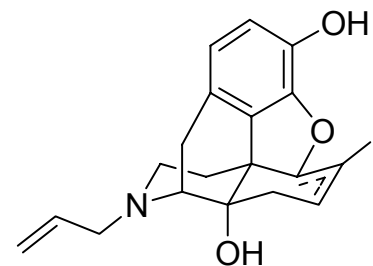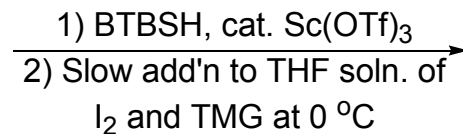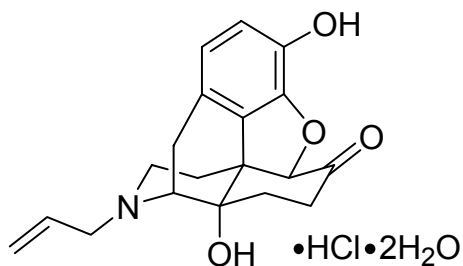
Here's a mechanistic picture for their formation:
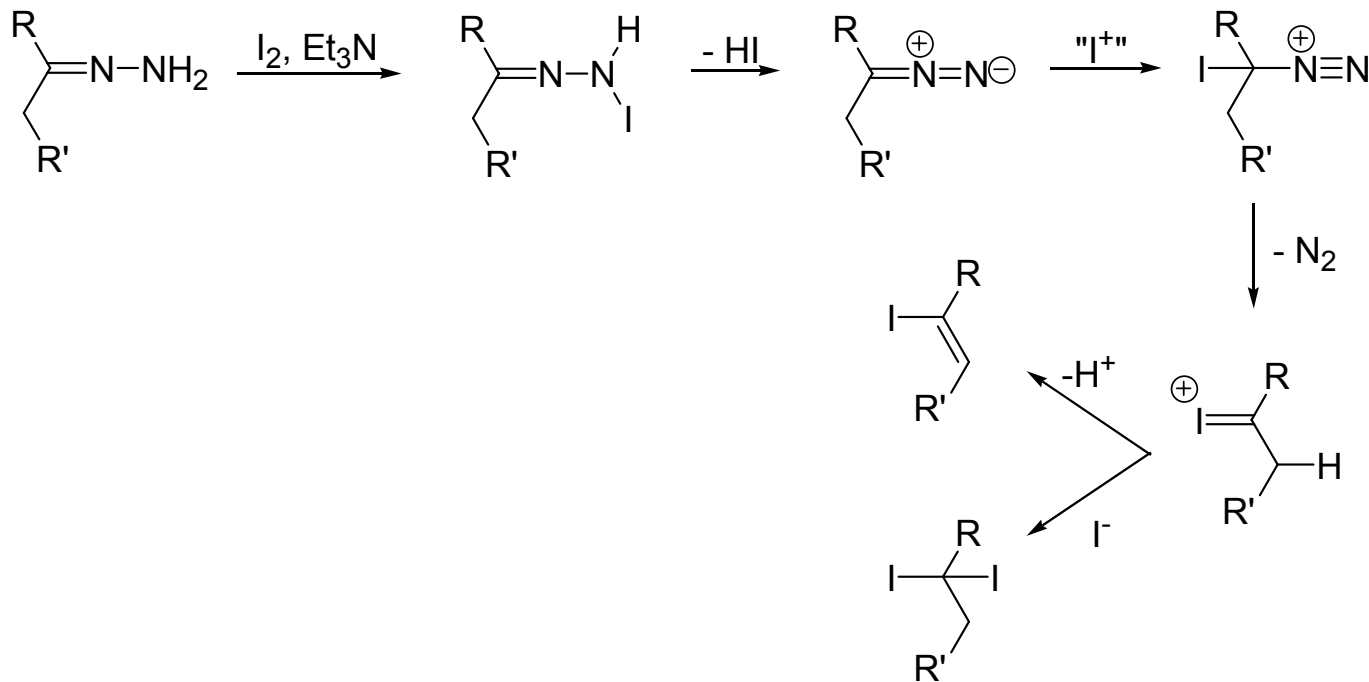
Depending on the availability of β-hydrogens, either vinyl iodides or *gem*-diiodides (or mixtures) are obtainable.

Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962,** 470-476.

More Bang for the Buck for the TBS Hydrazones

If the TBS hydrazones work for Wolff-Kishner reactions, then why not for the Barton iodide reactions?
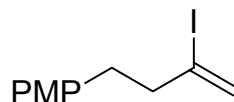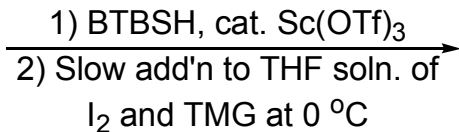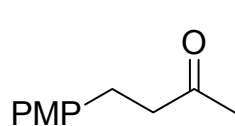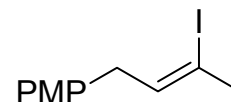

1) BTBSH, cat. Sc(OTf)$_3$
2) Slow add'n to THF soln. of I$_2$ and TMG at 0 °C

85%

1) BTBSH, cat. Sc(OTf)$_3$
2) Slow add'n to THF soln. of I$_2$ and TMG at 0 °C

84%

tetrasub. : trisub. = 57:43

1) BTBSH, cat. Sc(OTf)$_3$
2) Slow add'n to THF soln. of I$_2$ and TMG at 0 °C

71%

62 : 17 : 21

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.
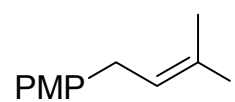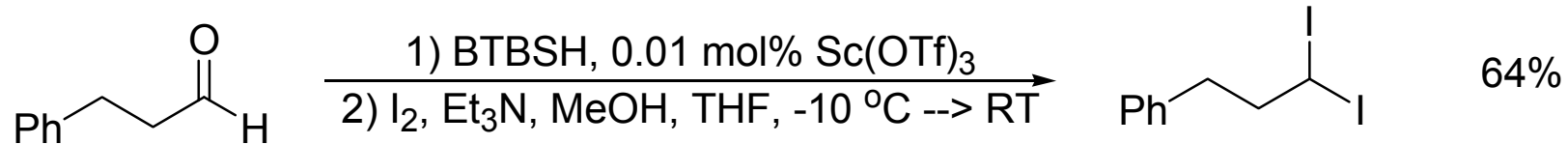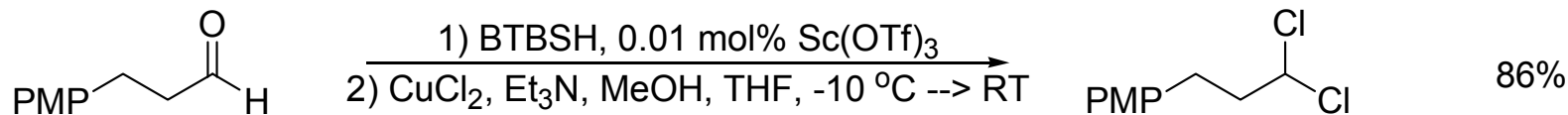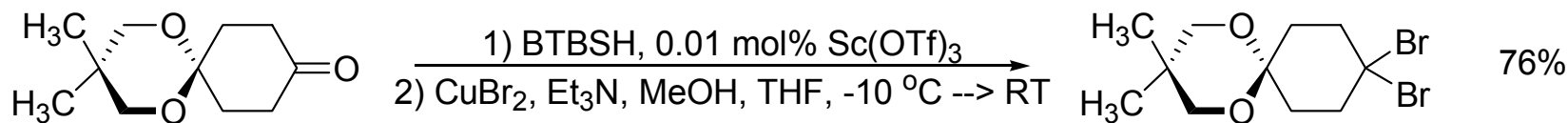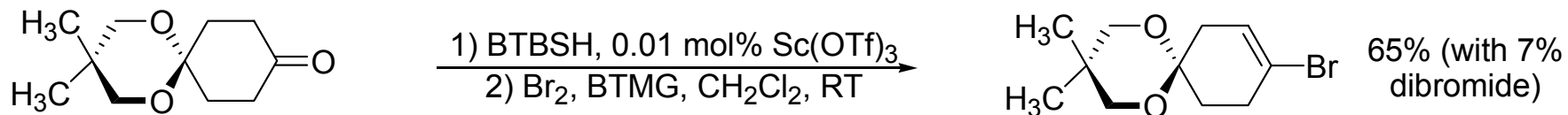
As for the *Gem*-Diiodides…

These reactions are serviceable as well, even where competitive vinyl iodide formation is possible.

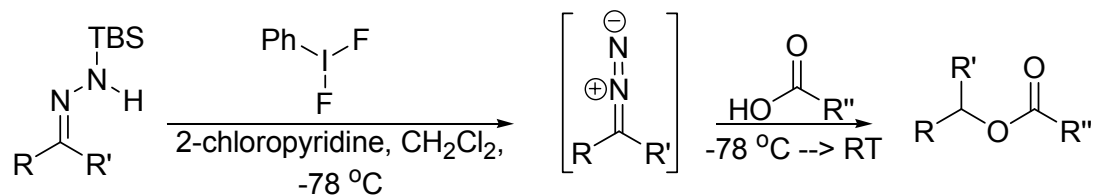1) BTBSH, 0.01 mol% Sc(OTf)$_3$

2) I$_2$, Et$_3$N, MeOH, THF, -10 °C --> RT

64%

1) BTBSH, 0.01 mol% Sc(OTf)$_3$

2) I$_2$, Et$_3$N, MeOH, THF, -10 °C --> RT

62%

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.
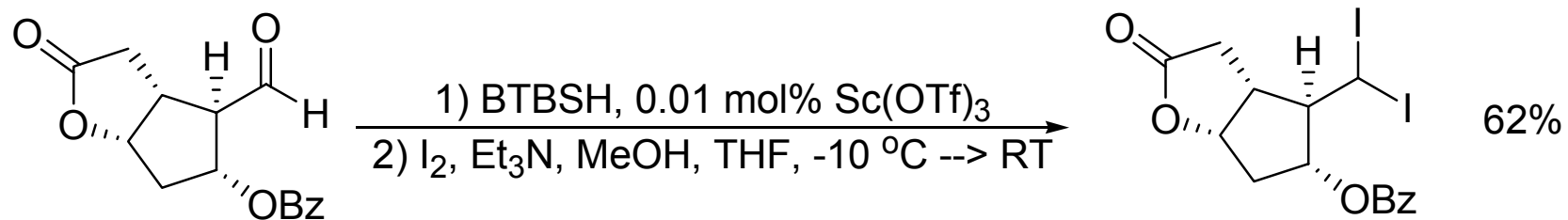
Other Halides Needn't Be Left Out!

Reaction 1:

1) BTBSH, 0.01 mol% Sc(OTf)$_3$
2) Br$_2$, BTMG, CH$_2$Cl$_2$, RT

65% (with 7% dibromide)

Reaction 2:

1) BTBSH, 0.01 mol% Sc(OTf)$_3$
2) CuBr$_2$, Et$_3$N, MeOH, THF, -10 °C --> RT

76%

Reaction 3:

1) BTBSH, 0.01 mol% Sc(OTf)$_3$
2) CuCl$_2$, Et$_3$N, MeOH, THF, -10 °C --> RT
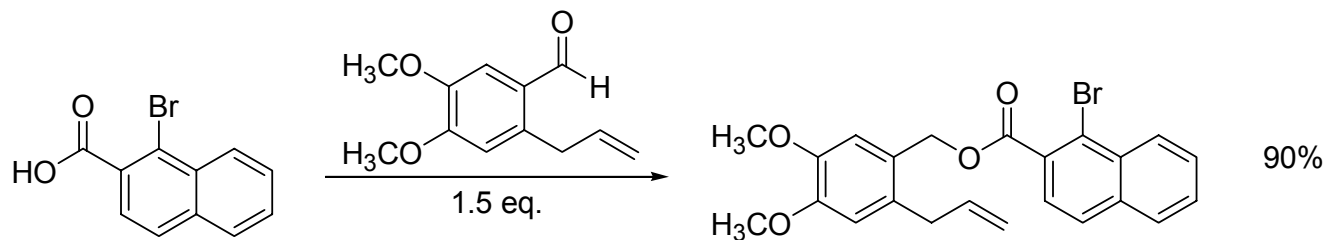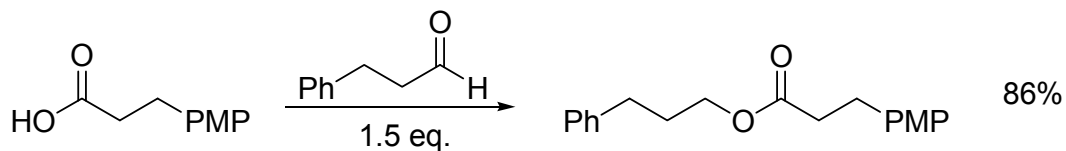
86%

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 5436-5445.

And for Something Completely Different…

Esterification with in-situ generated diazoalkanes!

Two simple examples:

86%

90%

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222-12223.

And Finally, A Few More Examples

84%

82%

53%

Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222-12223.