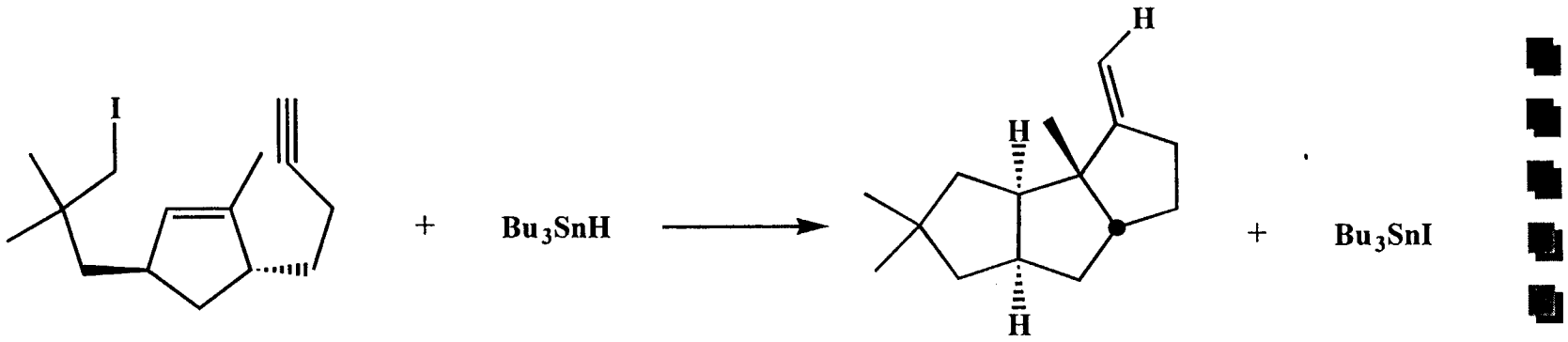
# The Separation Problem

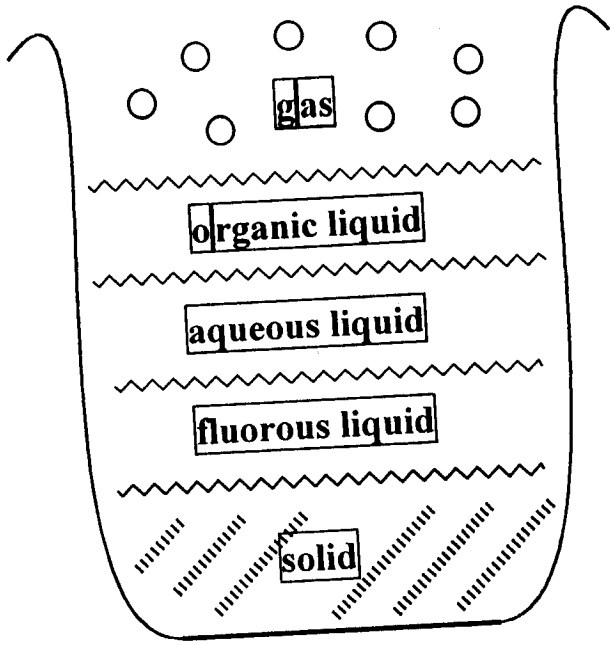
Substrate + Reagent $\xrightarrow{\text{reaction}}$ Product + Reagent–byproduct

*Problem:* organic product components cannot be separated by "workup" techniques



# Workup-Level Purifications

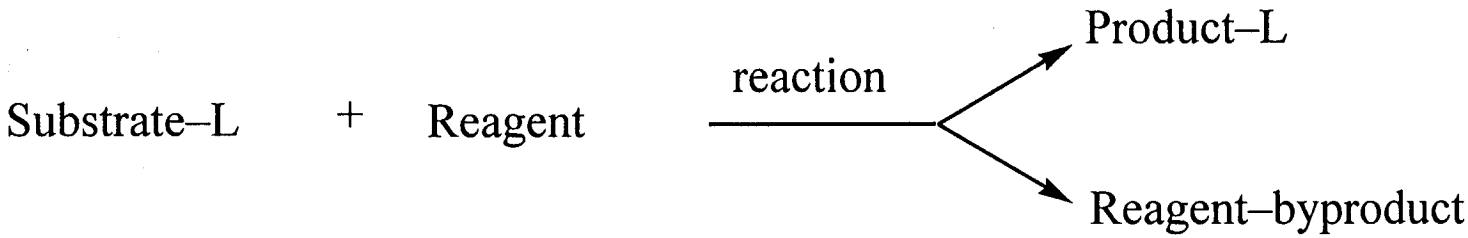
## Separation by evaporation, extraction, filtration




**Strategic Purification Goal**: Design each step of a (library) synthesis such that the products of the reaction separate into a different phase from everything else in the reaction mixture.

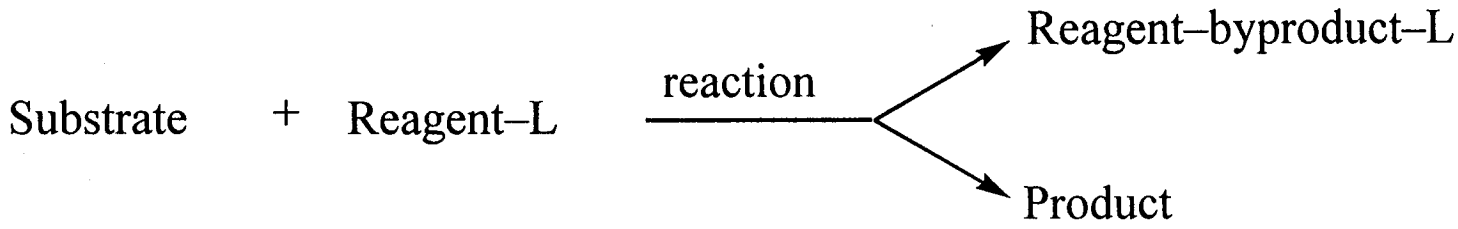
*Angew. Chem., Int. Ed. Eng.*, **1998**, *37*, 1175.

# Phase Labeling—Substrate



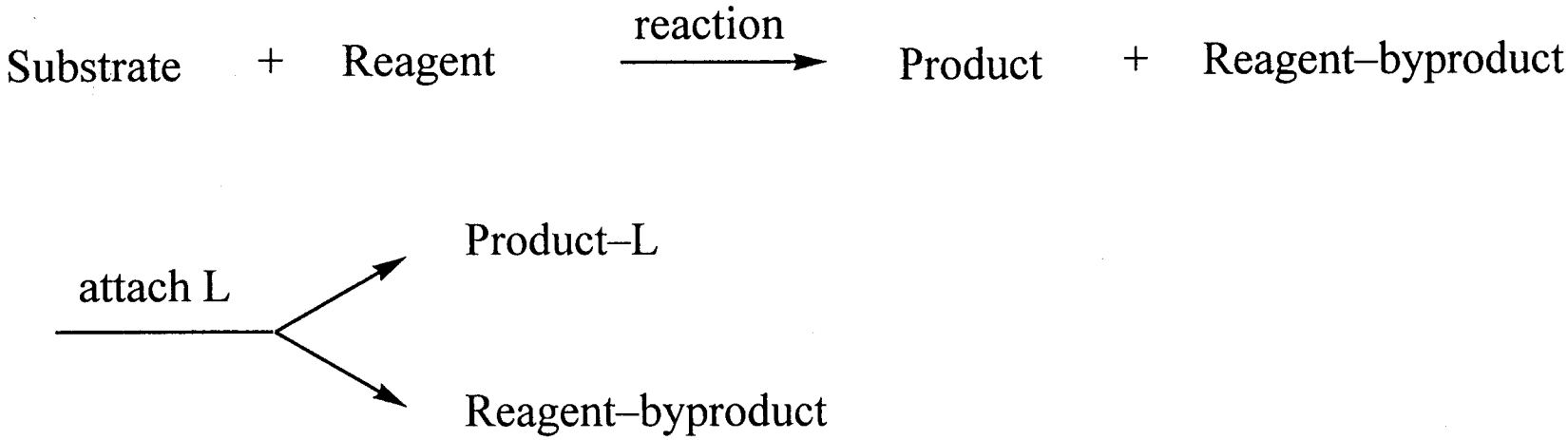

- Attach label (L)
- Conduct reaction
- Apply workup that sorts by L

# Phase Labeling—Reagent




- Attach label (L)
- Conduct reaction
- Apply workup that sorts by L

# Phase Switching



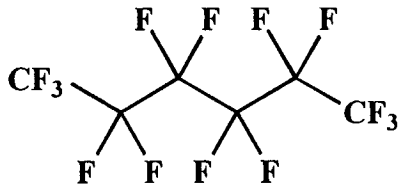

- Conduct reaction
- Attach label (L)
- Apply workup that sorts by L

# Matching Labels and Techniques

| Phase Label | Phase | Separation Technique |
|---|---|---|
| none | organic | evaporation, extraction, filtration |
| ionizable group | water | liquid-liquid or solid phase extraction |
| insoluble polymer | solid | filtration |
| soluble polymer | solid | precipitation-filtration |
| highly fluorinated group | fluorous | liquid-liquid or solid phase extraction |

# The "Fluorous" Phase

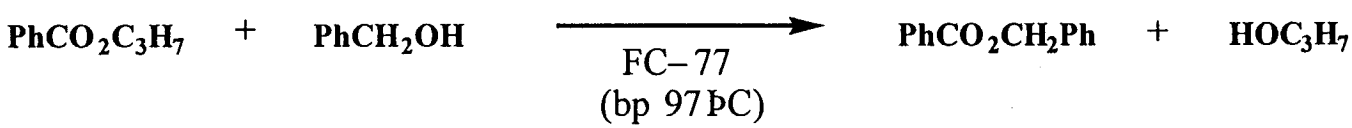
Perfluorocarbons are not miscible in many organic solvents or water




= $C_6F_{14}$

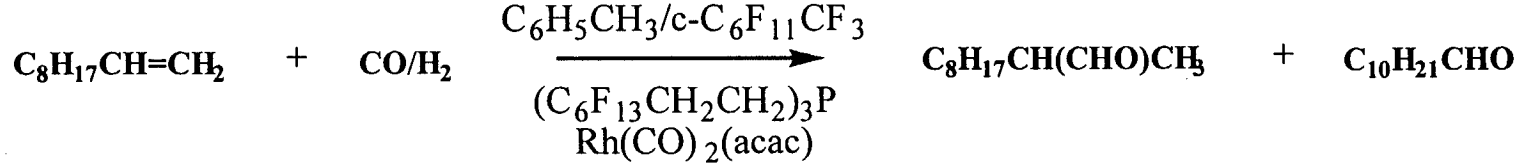
- FC-72™ (perfluorohexane)
  - 1 gal (4 L) - $390
  - FW = 338
  - bp - 56 ÞC
  - d - 1.8
- Features
  - stable and non-toxic
  - easily recycled
  - many other related solvents available
- Problem
  - nothing is soluble in FC-72!

# Fluorous Biphasic Reactions




- alcohol separates in a "Dean-Stark" trap
- product separates from FC– 77 on cooling

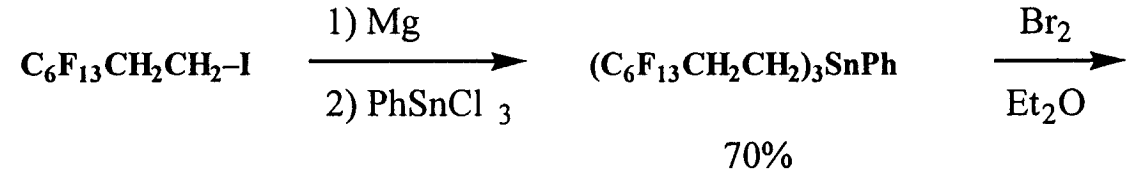
Zhu, *Synthesis* **1993**, 954.

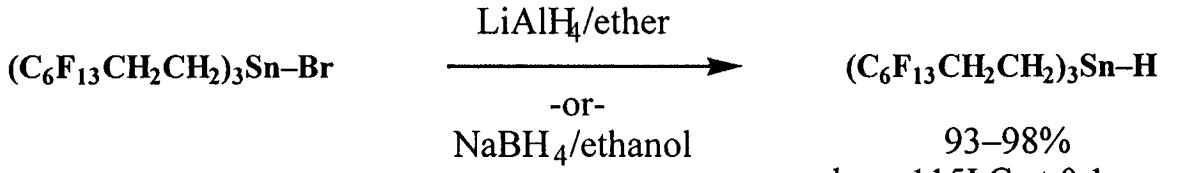



- two phase reaction
- catalyst in fluorous phase can be reused

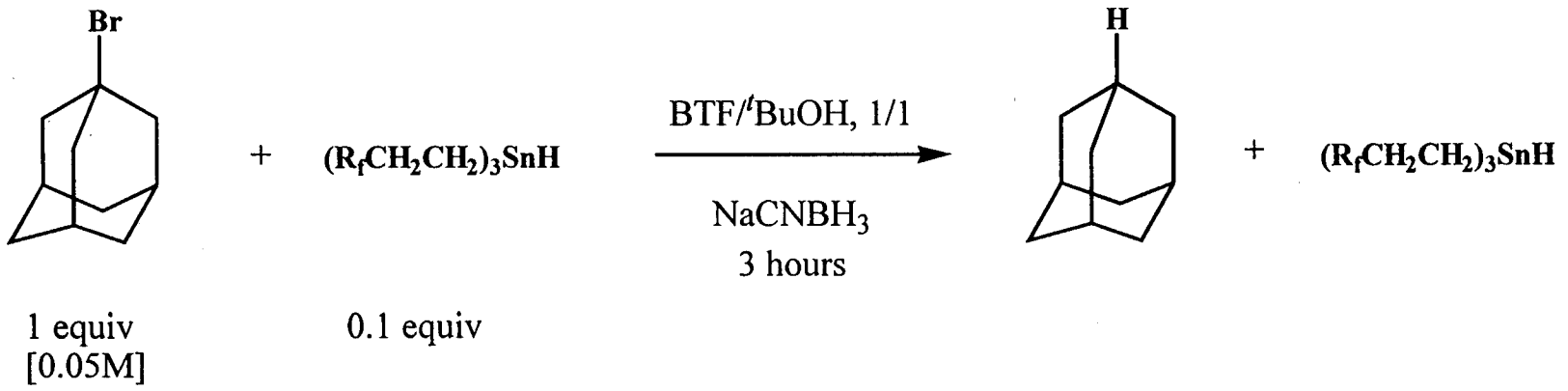
Horváth and Rábai, *Science* **1994**, *266*, 72.

# Synthesis of a Fluorous Tin Hydride



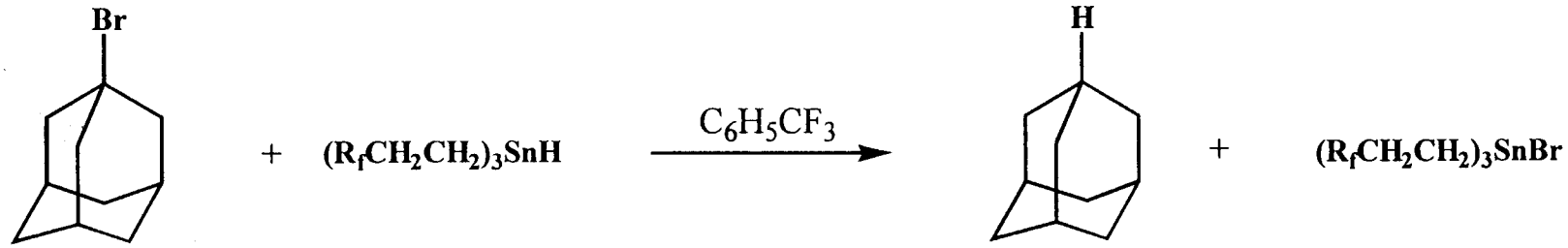



# A Catalytic Procedure



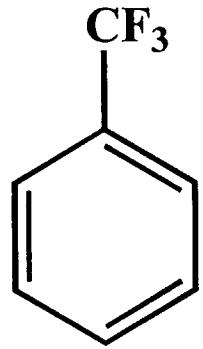

- purification by three-phase extraction
  - adamantane extracted into organic layer,
    - 100% GC yield, 92% isolated yield
  - tin extracted into $C_6F_{11}CF_3$; recovered in >95% yield
  - borohydride salts extracted into the water layer
- five recycles were conducted with recovered tin
- as little as 1% tin can be used

# Reduction with a Fluorous Tin Hydride

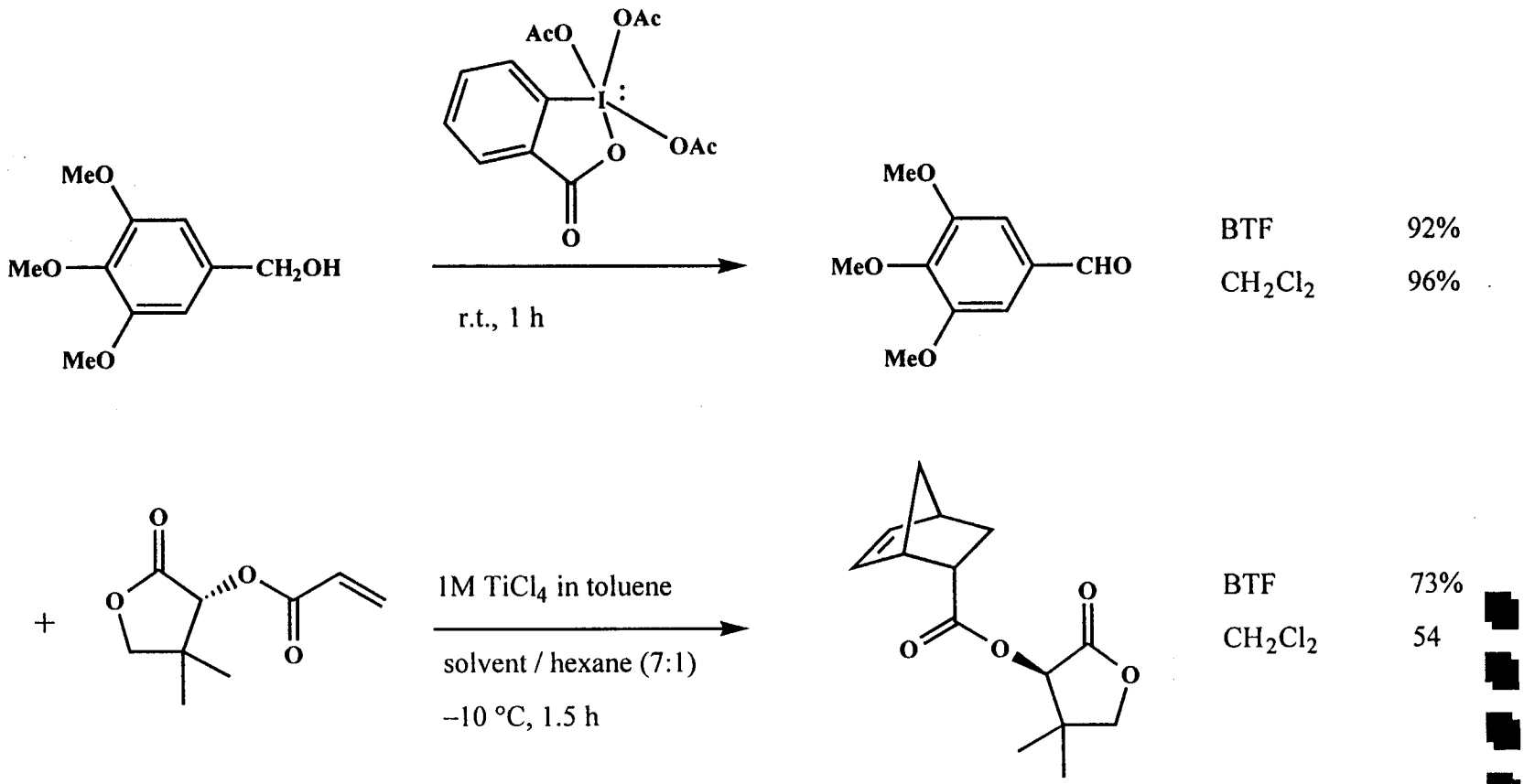



- 99% GC yield
- workup by FC-72/$CH_2Cl_2$ extraction

- Benzotrifluoride (BTF): a "Hybrid Solvent"
  - trifluoromethylbenzene, α,α,α–trifluorotoluene
  - sold as Oxsol®2000 By OxyChem
  - bp = 102ÞC, mp –29ÞC
  - miscible with many organic and fluorous solvents
  - an organic solvent that dissolves fluorous components

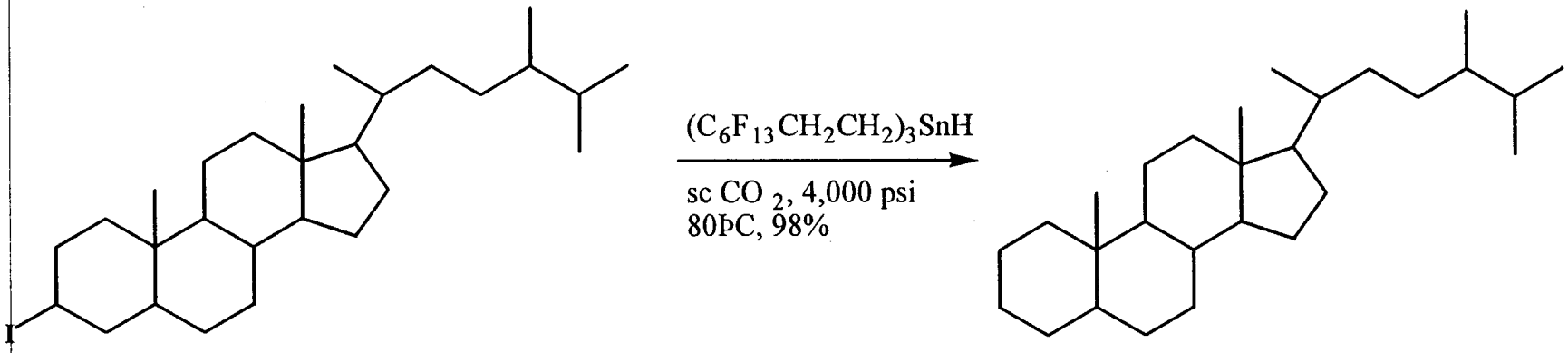


# BTF: A Substitute for $CH_2Cl_2$



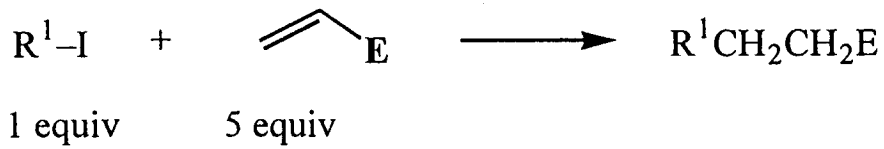

- Other reactions: acylation, tosylation, silylation, Swern oxidation, selenoxide oxidation/elimination, Mukaiyama, Sakurai, Friedel-Crafts reactions

# Reductions in Supercritical $CO_2$




Hadida, S.; Super, M. S.; Beckman, E. J.; Curran, D. P. *J. Am. Chem. Soc.* **1997**, *119*, 7406.

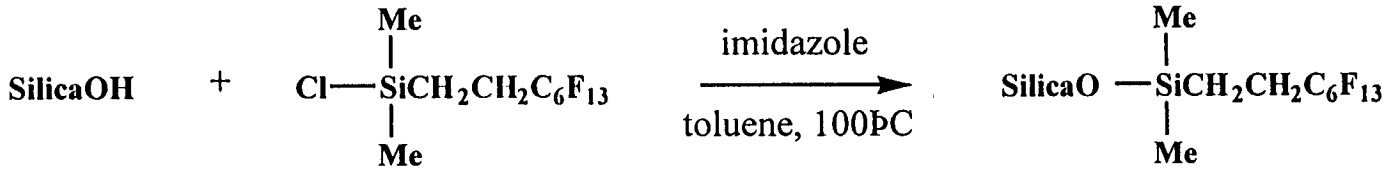
# Library Synthesis with a Fluorous Reagent



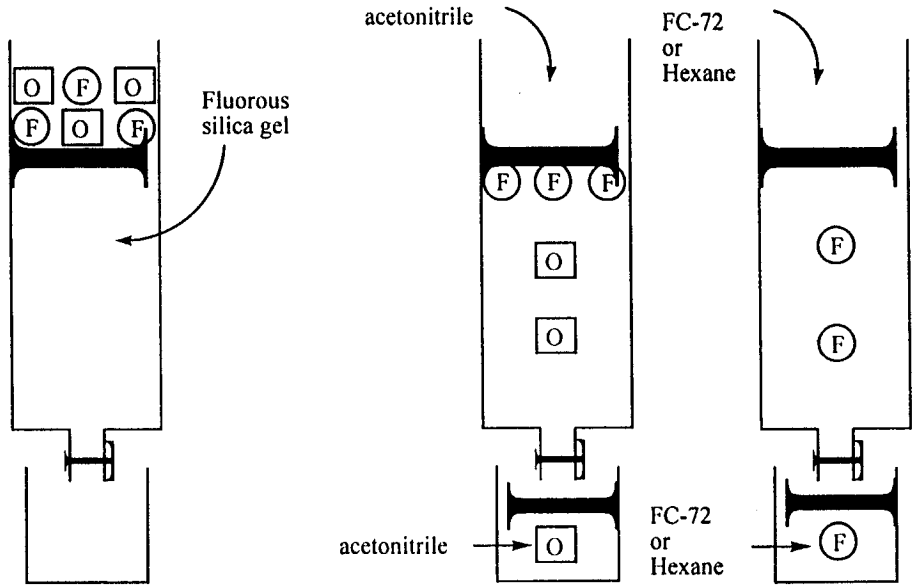

| $R^1$ : E | CN | $CO_2Me$ | COMe |
|---|---|---|---|
| $C_{15}H_{31}$ | 72% | 92% | 67% |
| *c*-$C_6H_{11}$ | 75% | 65% | 75% |
| Ad | 89% | 94% | 78% |

- excess alkene removed by evaporation
- inorganics in water (discarded)
- tin hydride in fluorous (reused)
- product in organic, 97-99% GC purity

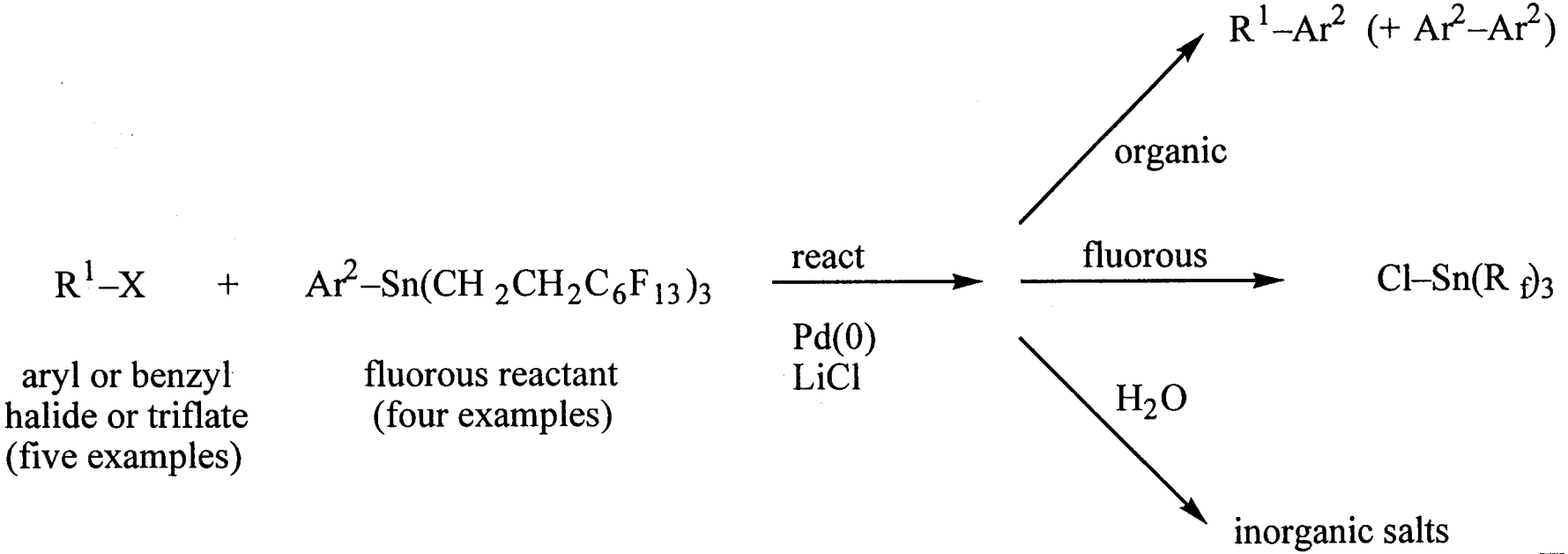
# Fluorous Reverse Phase Chromatography




- Commercial Analytical Columns: Fluofox®, ChromegaBond®



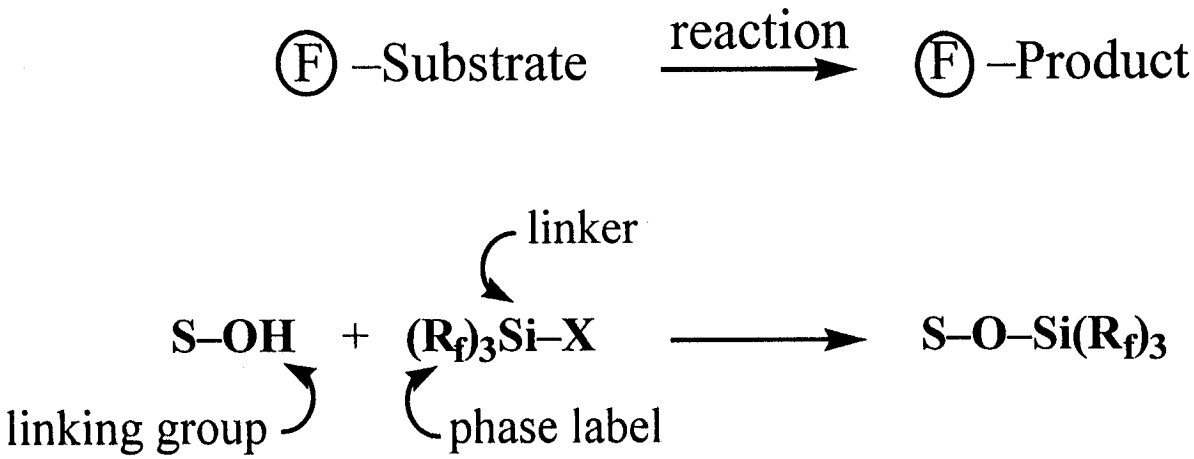
# Fluorous Reagents: The Stille Coupling




- > 15 examples, most yields 80-90%
- tin chloride recovered in 96% yield, reused
- excess tin reagent in fluorous phase
- symmetric byproduct (5-10%) *not* separated by extraction

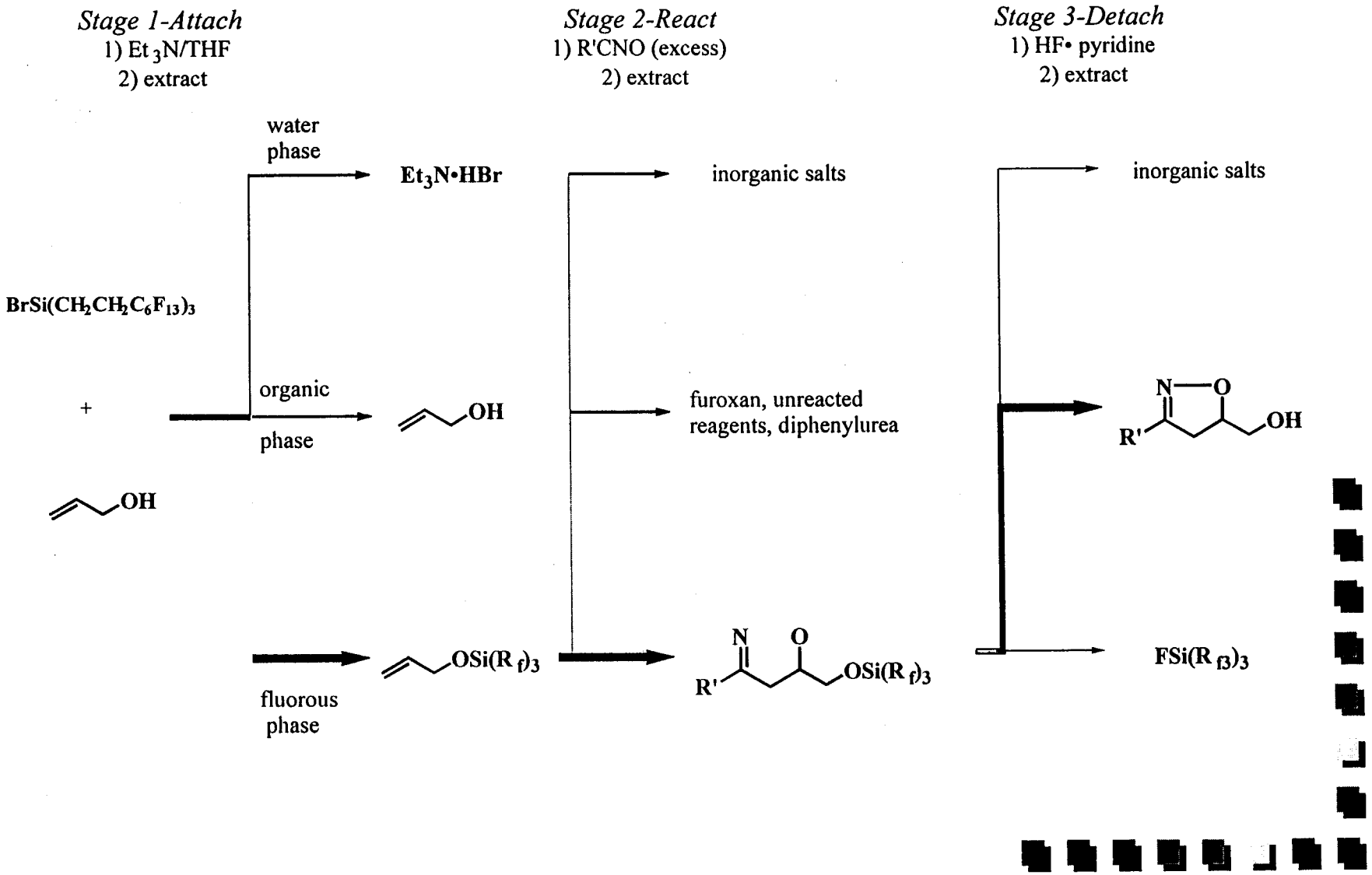
# Fluorous Synthesis

## A Strategic Alternative to Organic Synthesis and Solid Phase Synthesis

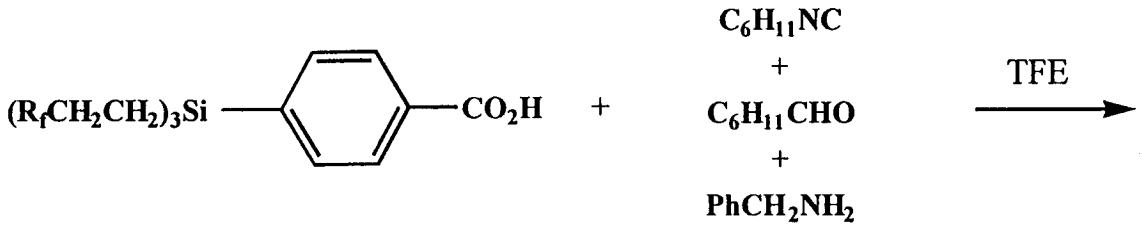



Studer, et al. *Science* **1997**, *275*, 823.

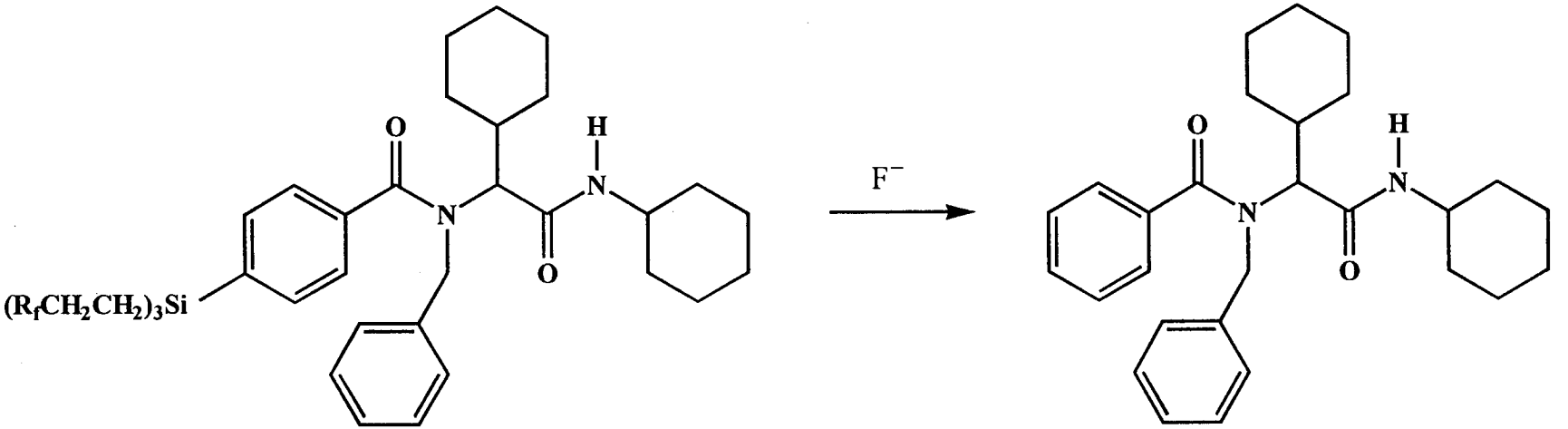
# Fluorous Synthesis: A Demonstration



# The "Flugi" Reaction



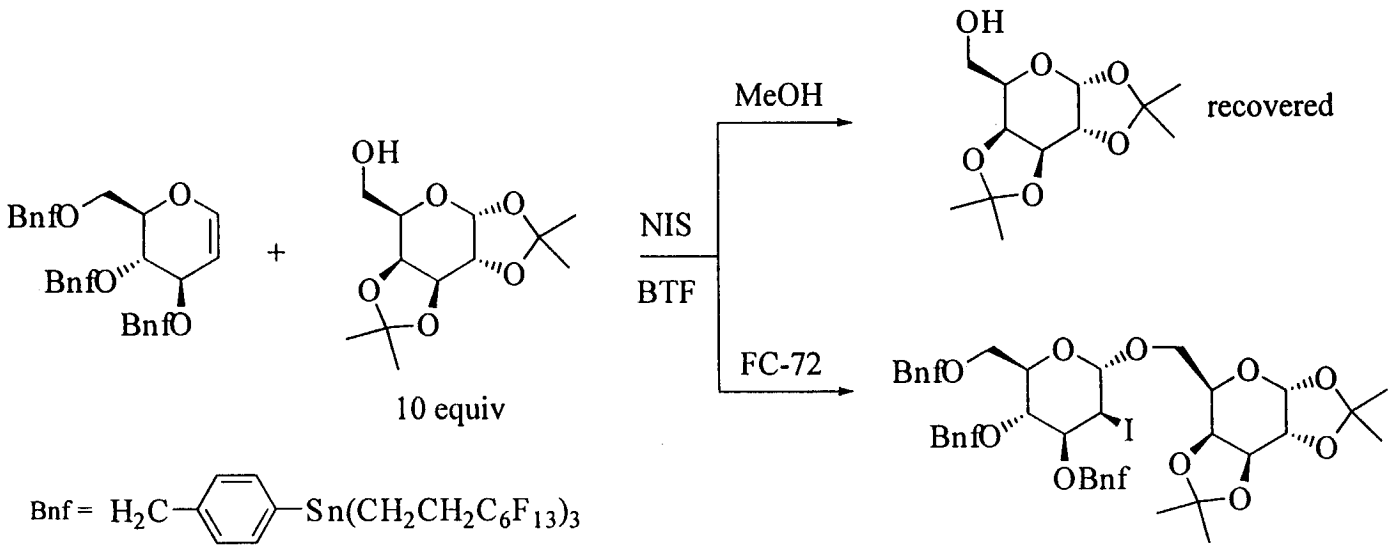

$R_f = C_{10}F_{21}$

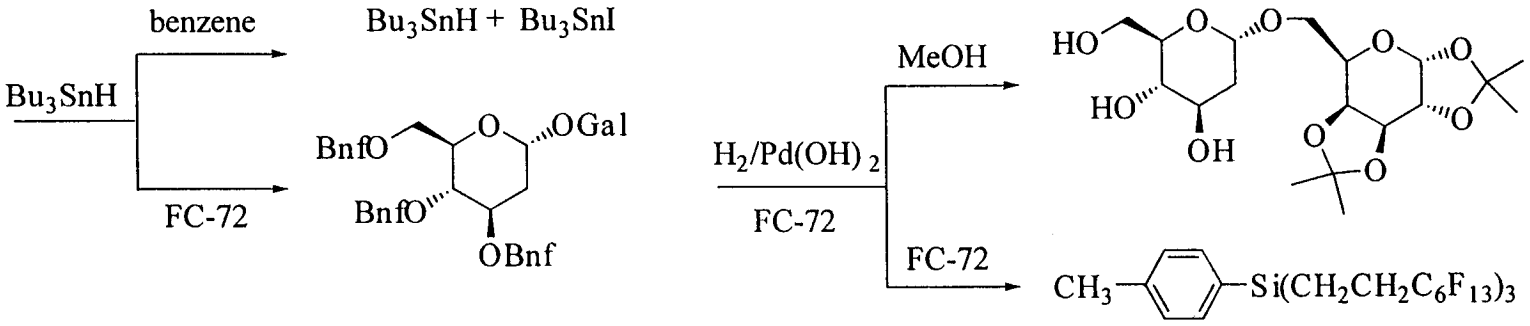



fluorous product, purified by 3-phase extraction

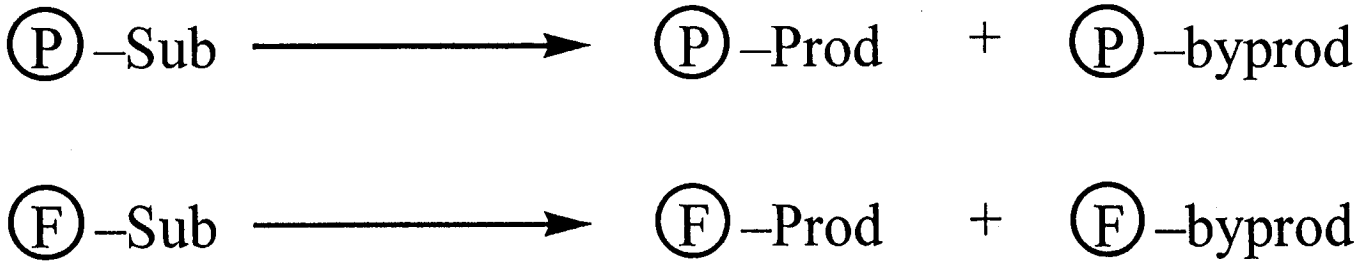
FW = 432
84% yield, >95% GC purity

# A Fluorous Disaccharide Synthesis



# The Achilles Heel of One Phase Methods

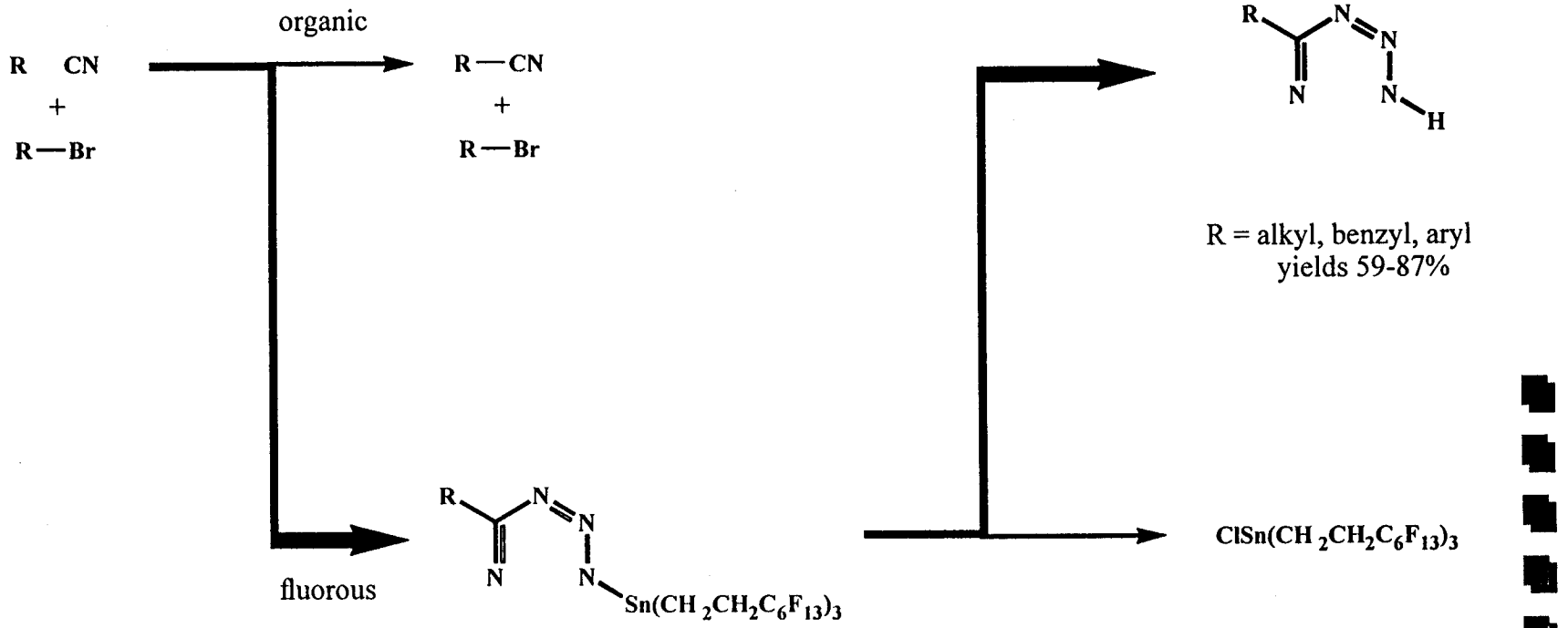



- Labeled products cannot be separated from labeled substrates or byproducts
- Quantitative yields based on substrate are required

# Fluorous Reagent/Label

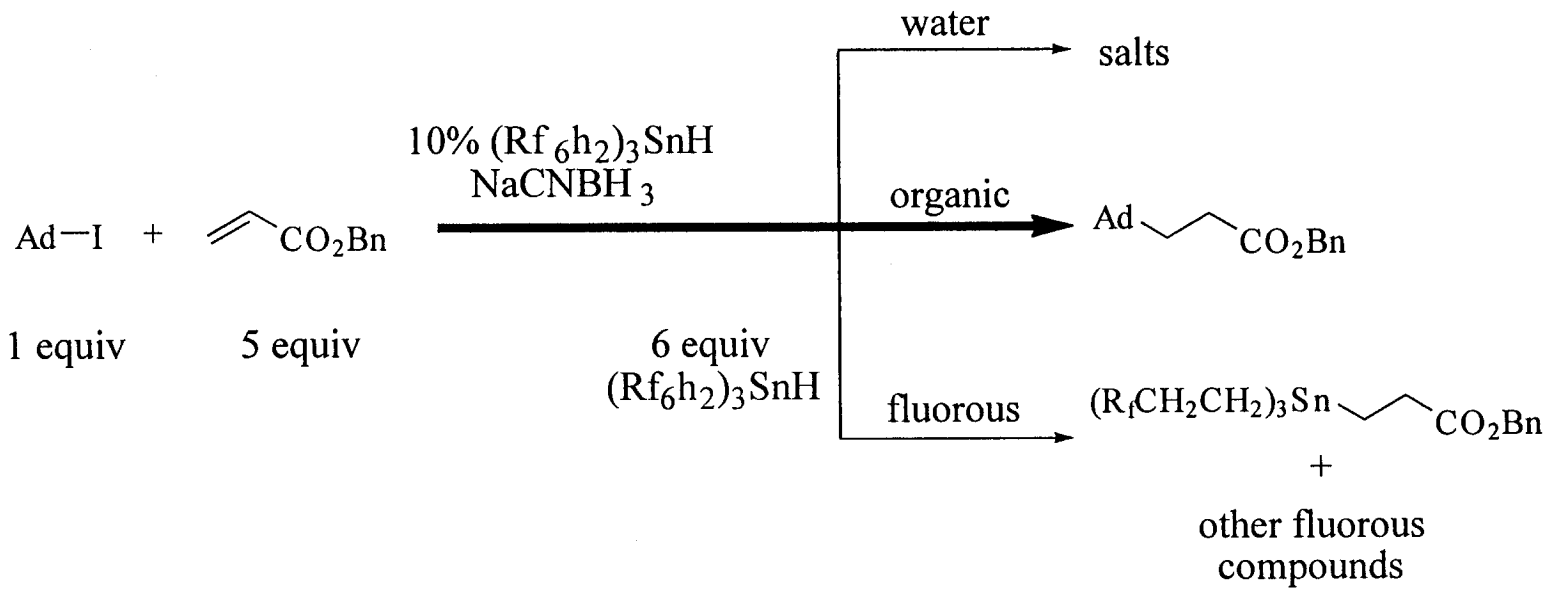
*Stage 1 Attact/React*
1) $(R_f)_3SnN_3$, BTF, 80 °C
2) extract

*Stage 2 Detach*
1) HCl
2) extract




R = alkyl, benzyl, aryl
yields 59-87%

# Fluorous Quenching



# Acknowledgements


- Co-workers
  - Dr. Sabine Hadida
  - Dr. Arimdo Studer
  - Dr. Masahide Hoshino
  - Dr. Mu He
  - Ms Ye Hua
  - Dr. Bruno Linclau
  - Ms. Sun-Young Kim
  - Mr. Zhiyong Luo
- Support
  - NIH
  - NSF
  - Parke-Davis
  - CombiChem
  - OxyChem
  - Merck
  - Bayer
  - Hewlett-Packard