“Click” Chemistry, a New Approach to Familiar Reactions

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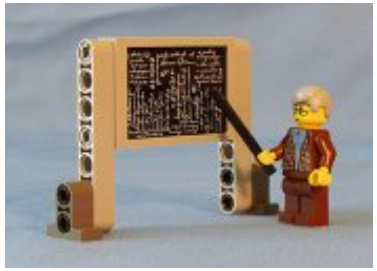
January 26, 2005

“Click” Chemistry?

- As defined by K. B. Sharpless
  - “‘Click’ chemistry…a set of powerful, virtually 100% reliable, selective reactions for the rapid synthesis of new compounds *via* heteroatom links (C-X-C)…Click chemistry is integral now to all research within the Sharpless Lab.”



Borman, S. *C & En*. **2002**, *80(6)*, 29.

“Click” Chemistry?

- “Strategy for the rapid and efficient assembly of molecules with diverse functionality…enabled by a few nearly perfect reactions, it guarantees reliable synthesis of the desired products in high yield and purity…”
  - Brik, A.; Muldoon, J.; Lin, Y.; Elder, J. Goodsell, D. Olson, A.; Fokin, V.; Sharpless, B.; Wong, H. *Chem. Bio. Chem.* **2003**, *4*, 1246.

- “Designing powerful and selective reactions for an efficient synthesis of interesting compounds and combinatorial libraries through heteroatom links…” The Huisgen 1,3-dipolar cycloaddition of azides and alkynes is regarded as the ‘cream of the crop’ of concerted reactions…”
  - Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett*. **2003**, *5*, 1753.

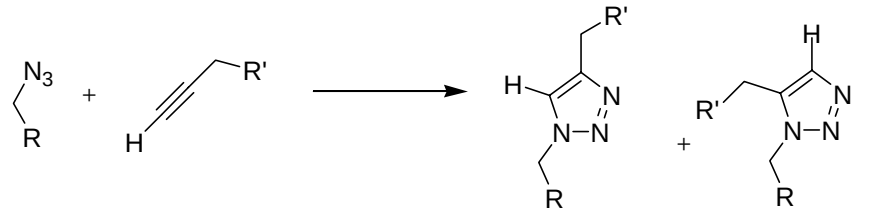
- “Synthetic appeal…high yields, simple reaction conditions, tolerance of oxygen and water, and simple product isolation...”
  - Helms, B.; Mynar, J; Hawker, C.; Frechet, J. *J. Am. Chem. Soc*. **2004**, *126*, 15020.

Classes of “Click” Reactions

- Nucleophilic opening of highly strained rings
  - S_N2 ring opening reactions
  - Epoxides, aziridines, cyclic sulfates, cyclic sulfamidates, aziridinium ions

- “Protecting Group” Reactions
  - Reversible carbonyl chemistry
  - Acetals, ketals and their aza-analogs

- Cycloaddition Reactions
  - Hetero Diels-Alder, 1,3 dipolar cycloadditions involving heteroatoms



1,4 triazole 1,5 triazole

Kolb, H.; Finn, M.; Sharpless, B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

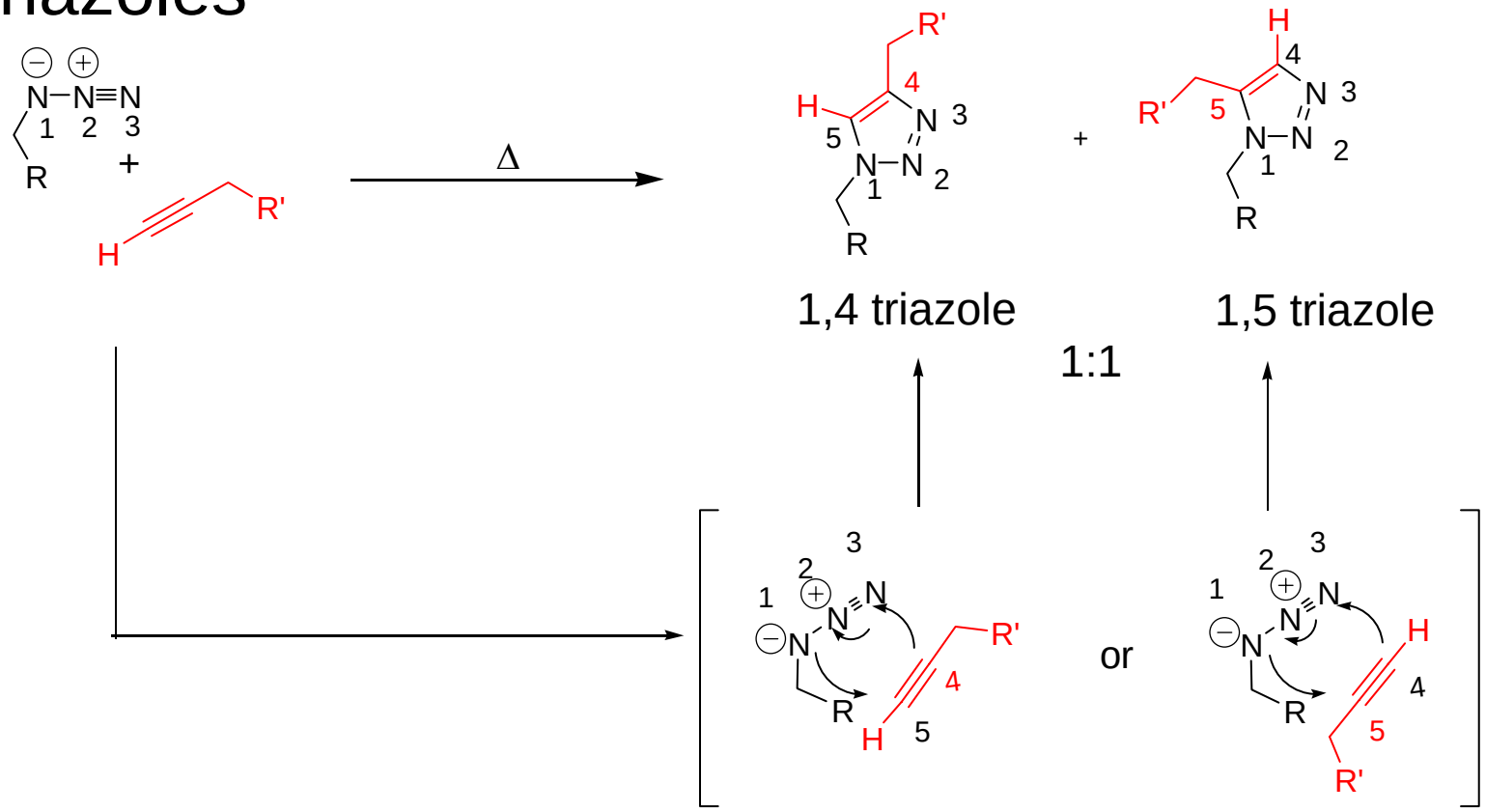
Applications of Triazoles

- Agricultural
  - Fungicides
  - Herbicides
  - Antimicrobial
- Industrial
  - Photostabilizers
  - Fluorescent whiteners
  - Optical brightening agents
  - Corrosion retardants
- Medicinal
  - Cytostatic
  - Virostatic
  - Antiinflamatory
- Macromolecules
  - Drug delivery
  - Nanoscale electronics
  - Oligonucleotides

Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.

Huisgen's [1,3] Dipolar Cycloaddition

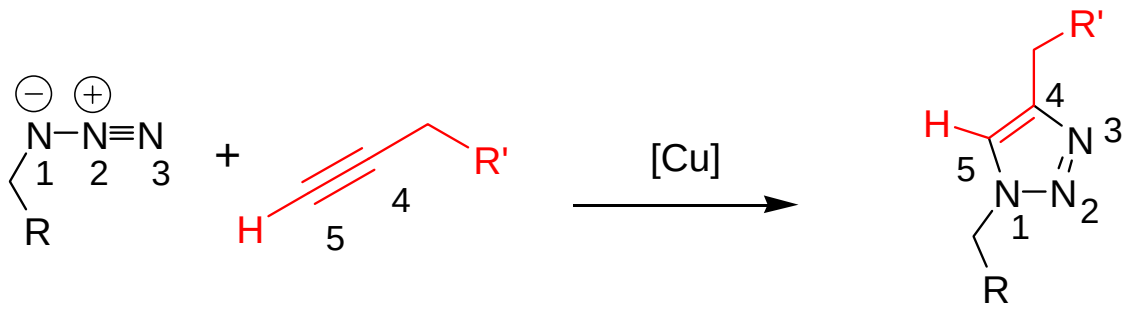
- Cycloaddition between azides and acetylenes to form triazoles



Huisgen, R. 1984. 1,3-dipolar cycloaddition- Introduction, survey, mechanism. In: Padwa, A.; ed. 1,3-dipolar Cycloaddition Chemistry (Vol. 1). Wiley. P. 1-176.

Regioselectivity of “Click” Chemistry

- Addition of Cu(I)-catalyst
  - “the champion “click” process…”

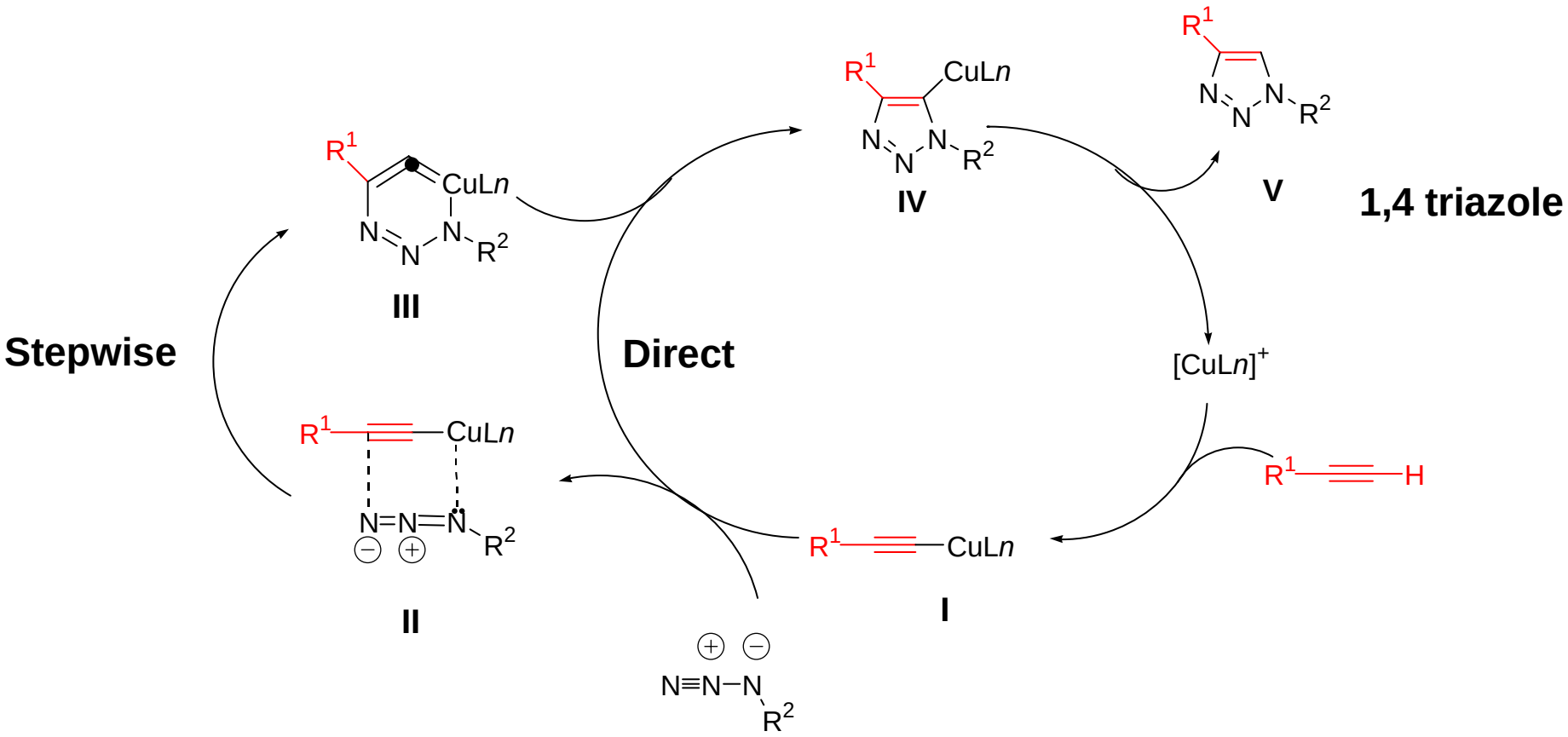


1,4 triazole

- Alkyne activation

Rostovtsev, V., Green, L., Fokin, V. Sharpless. B. *Angew. Chem Int. Ed*. **2002**, *41*, 2596.
Li, Z.; Seo, T.; Ju, J. *Tetrahedron. Lett*. **2004**, *45*, 3143.

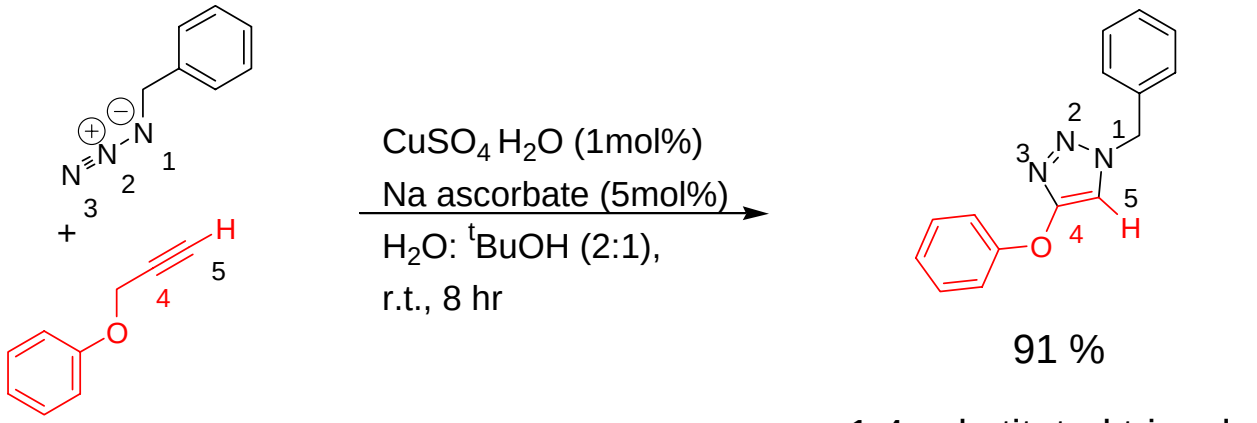
Proposed catalytic cycle for Cu(I)-catalyzed ligation



Rostovtsev, V.; Green, L.;Fokin, V;Sharpless. B. *Angew. Chem Int. Ed*. **2002**, *41*, 2596.
Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett*. **1975**, *16*, 4467.
Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.

Regioselectivity using Cu(I)

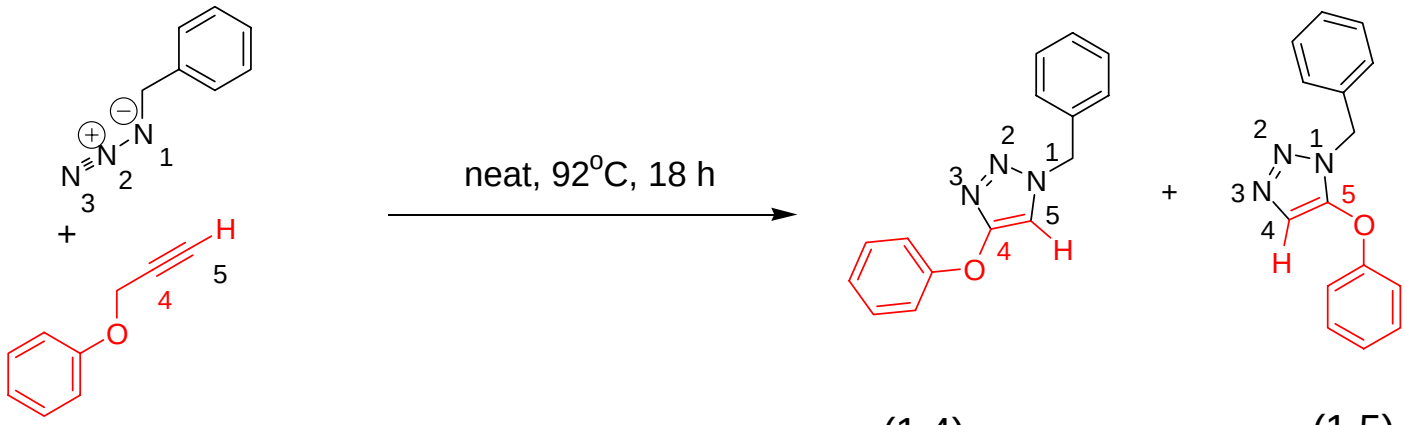
Cu catalyzed:



91 %

1,4 substituted triazole

Thermal:

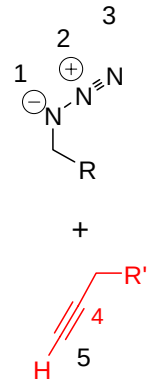


(1,4) (1,5)

1.6 : 1

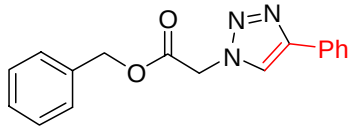
Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, B. *Angew. Chem Int. Ed*. **2002**, *41*, 2596.

Functional Group Tolerance

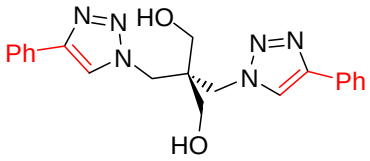


[0.25-0.5] M

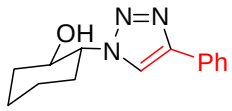
$CuSO_4$ (1mol%)
Na ascorbate (10 mol%)
H_2O: ^tBuOH
12-24 hr.



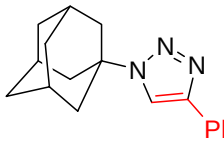
92 %



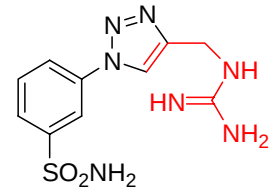
93%



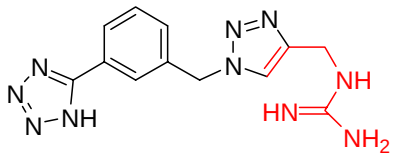
82%



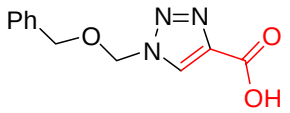
84 %



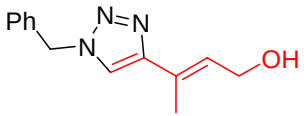
91 %



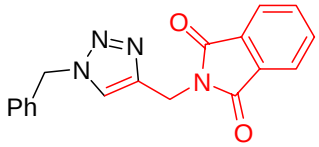
88 %



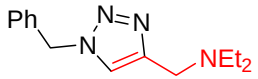
88 %



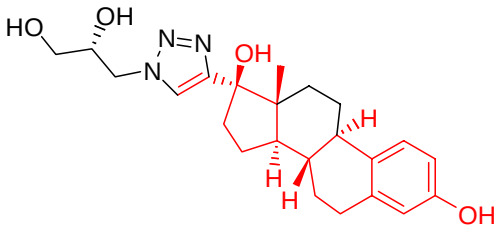
84 %



88 %



90 %



94 %

Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, B. *Angew. Chem Int. Ed*. **2002**, *41*, 2596.

Regioselectivity of “Click” Chemistry

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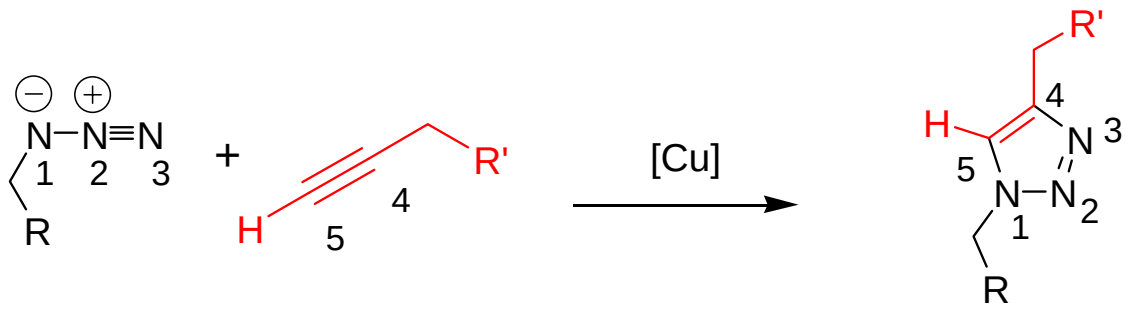

1,4 triazole

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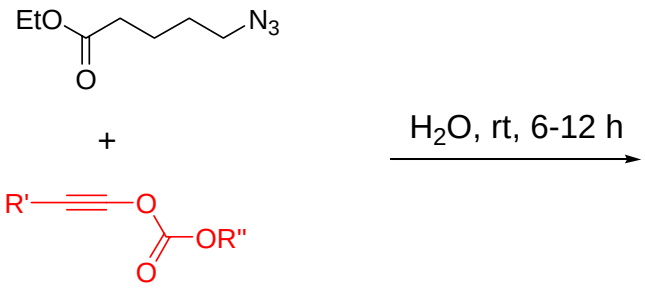
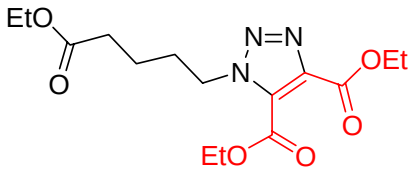
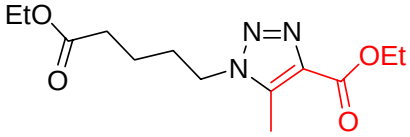
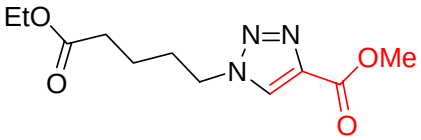
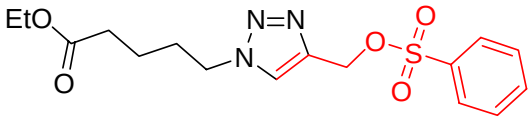
Li, Z.; Seo, T.; Ju, J. *Tetrahedron Lett*. **2004**, *45*, 3143.

Regioselectivity by Alkyne Activation



	no [Cu]	CuCl (0.1eq.), 1 h
	81%	N/A
	94%	N/A
	82%	90%
	67%	85%

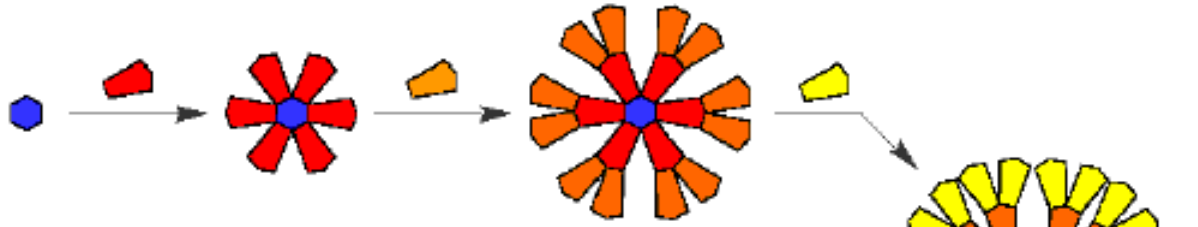
Li, Z.; Seo, T.; Ju, J. *Tetrahedron Lett*. **2004**, *45*, 3143.

“Click” Applications in Macromolecules

- Dendrimer Synthesis
- Solid Support Chemistry
  - SPOS
  - SPPS
- DNA functionalization

Dendrimer Synthesis

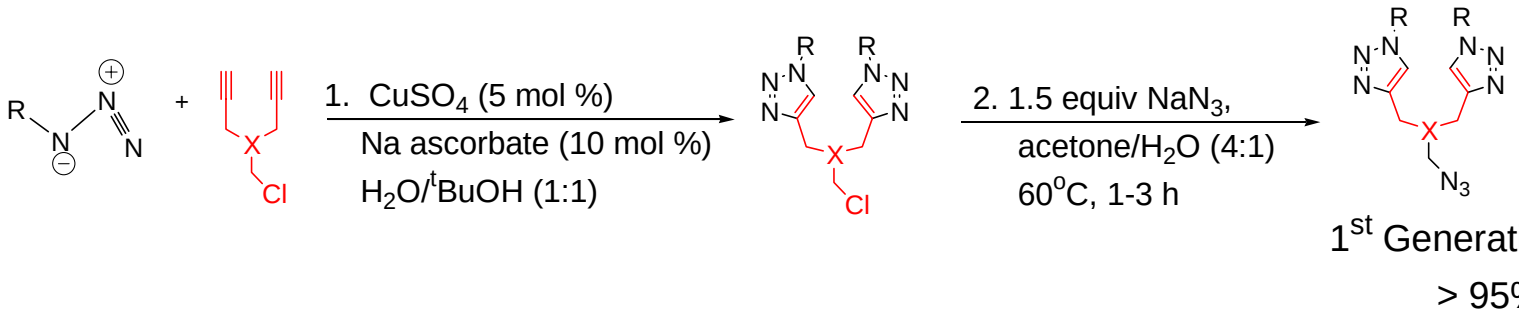
Divergent-Growth

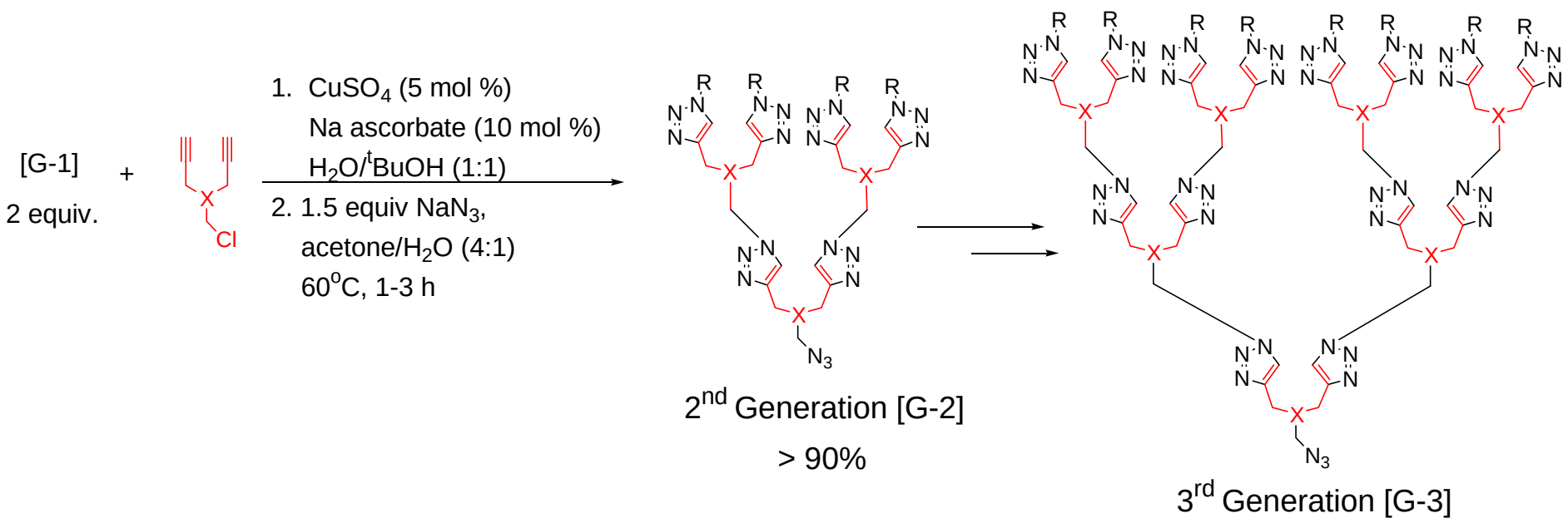


Convergent-Growth

Tomalia, I. *Polymer J.* **1985**, *17*, 117.
Frechet, J.; Hawker, C. *J. Amer. Chem. Soc.* **1990**, *112*, 7638.

Dendrimer Synthesis

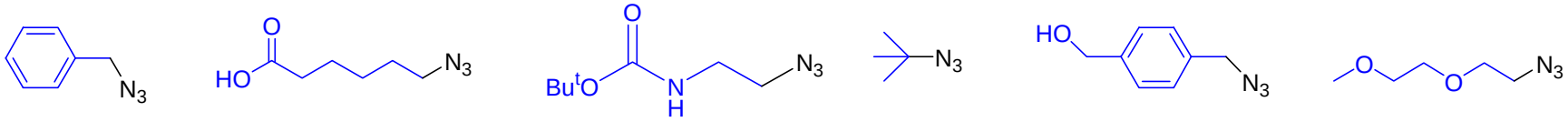




Wu, P.; Feldman, A.; Nugent, A.; Hawker, C.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J.; Sharpless, B.; Fokin, V. *Angew. Chem. Int. Ed*. **2004**, *43*, 3928.

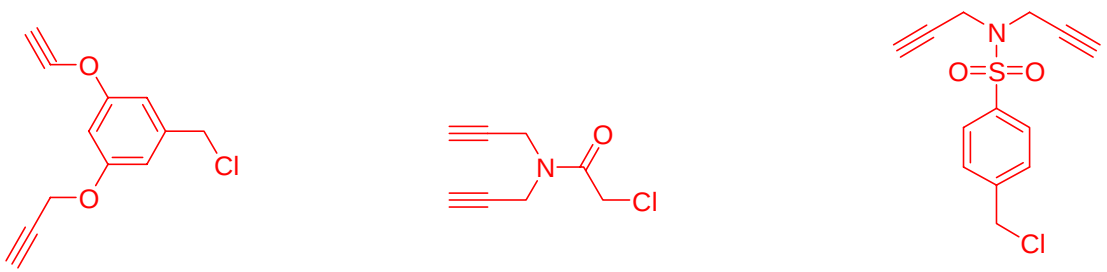
Dendrimer Synthesis

Azides:

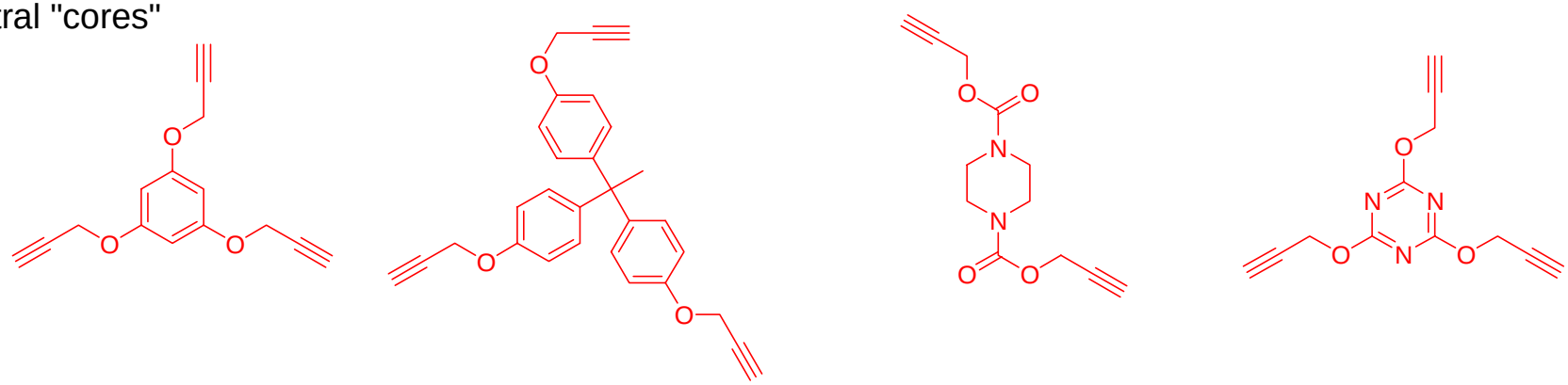


Alkynes:

branching "cores"

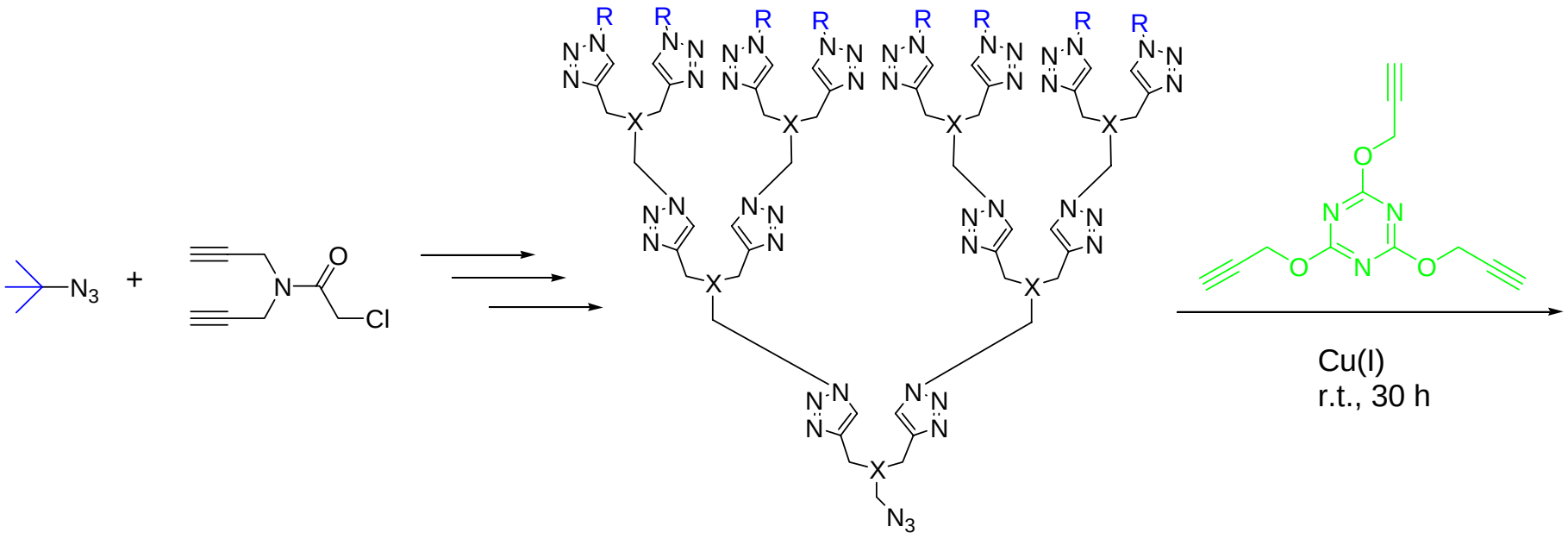


Central "cores"



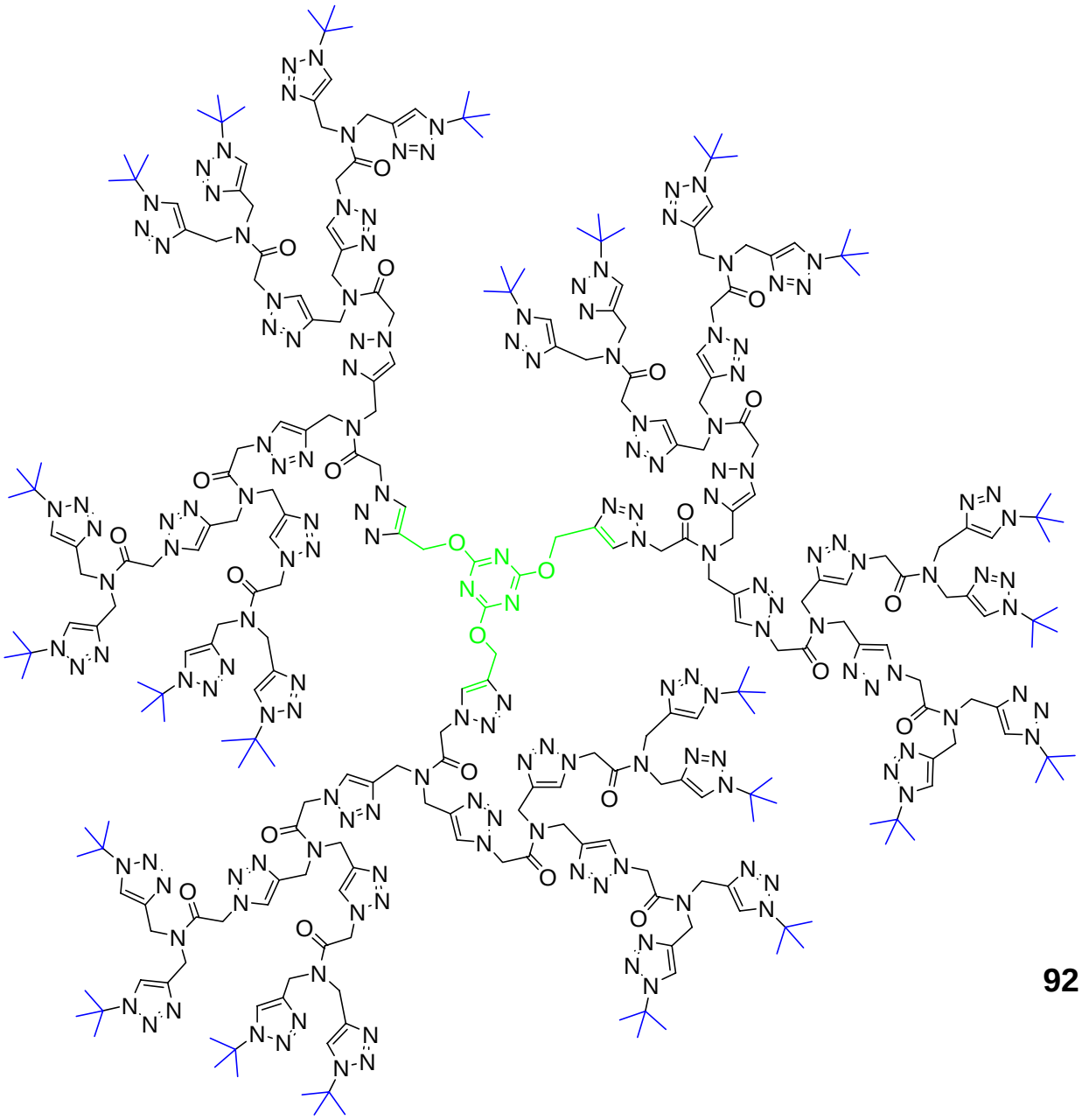
Dendrimer Synthesis

- 4th generation dendrimer synthesis



3rd Generation [G-3]

Wu, P.; Feldman, A.; Nugent, A.; Hawker, C.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J.; Sharpless, B.; Fokin, V. *Angew. Chem. Int. Ed*. **2004**, *43*, 3928.



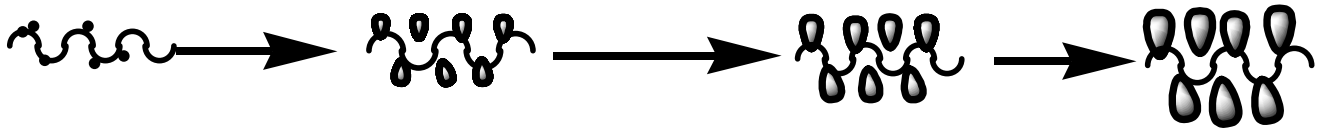
92 % yield

Wu, P.; Feldman, A.; Nugent, A.; Hawker, C.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J.; Sharpless, B.; Fokin, V.
Angew. Chem. Int. Ed. **2004**, *43*, 3928.

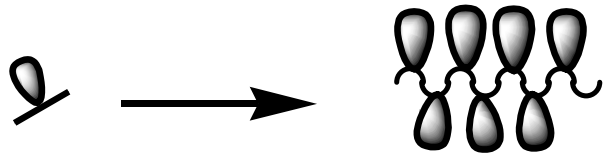
Dendronized linear polymers

- Three main pathways
  - I “grafting-to”

  - II “grafting-from”

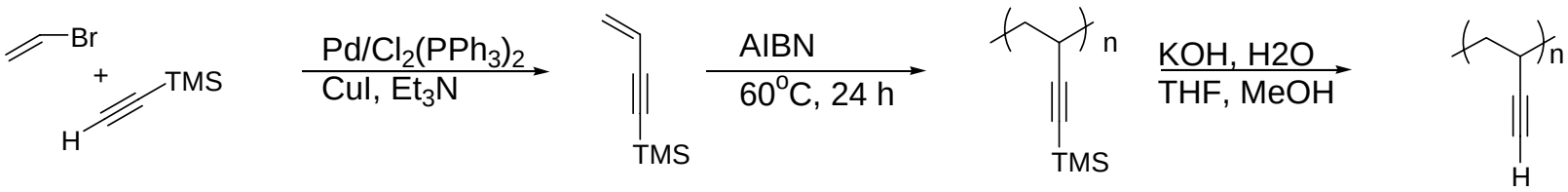


  - III incorporate dendrons into the monomer

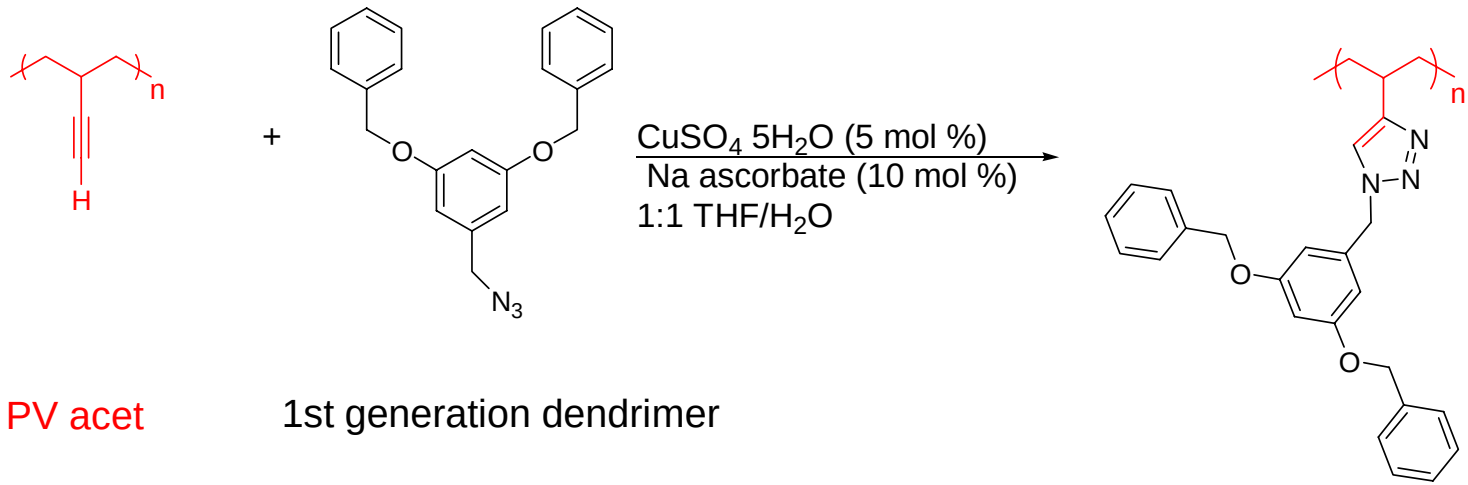


Helms, B.; Mynar,J; Hawker, C.; Frechet, J. *J. Am. Chem. Soc*. **2004**, *126*, 15020.

Dendronized linear polymers



poly vinylacetylene
(PV acet)



PV acet

1st generation dendrimer

Quantitative yield

Ochiai, B.; Tomalia, I.; Endo, T. *Macromol. Chem. Phys*. **2001**, *202*, 3099.
Helms, B.; Mynar, J.; Hawker, C.; Frechet, J. *J. Am. Chem. Soc*. **2004**, *126*, 15020.

“Click” Applications in Macromolecules

- Dendrimer Synthesis
- Solid Support Chemistry
  - SPOS
  - SPPS
- DNA functionalization

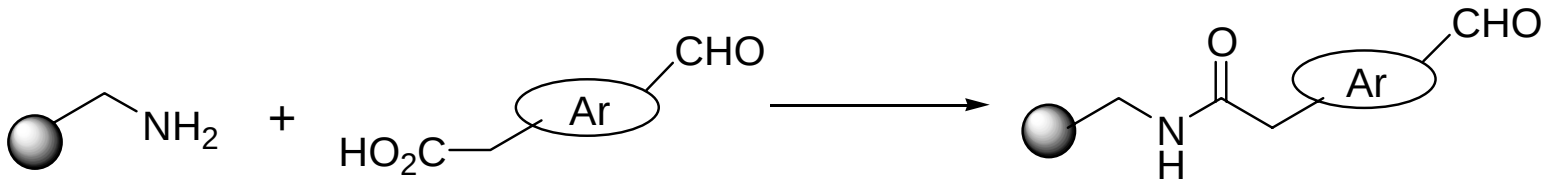
“Click” Chemistry Using a Solid Support

- Solid Phase Organic Synthesis (SPOS)

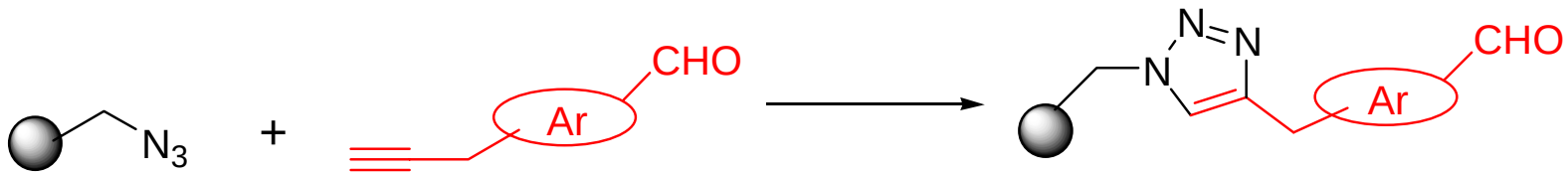
- Solid Phase Peptide Synthesis (SPPS)

SPOS: Solid Phase Organic Synthesis

BAL Resin:

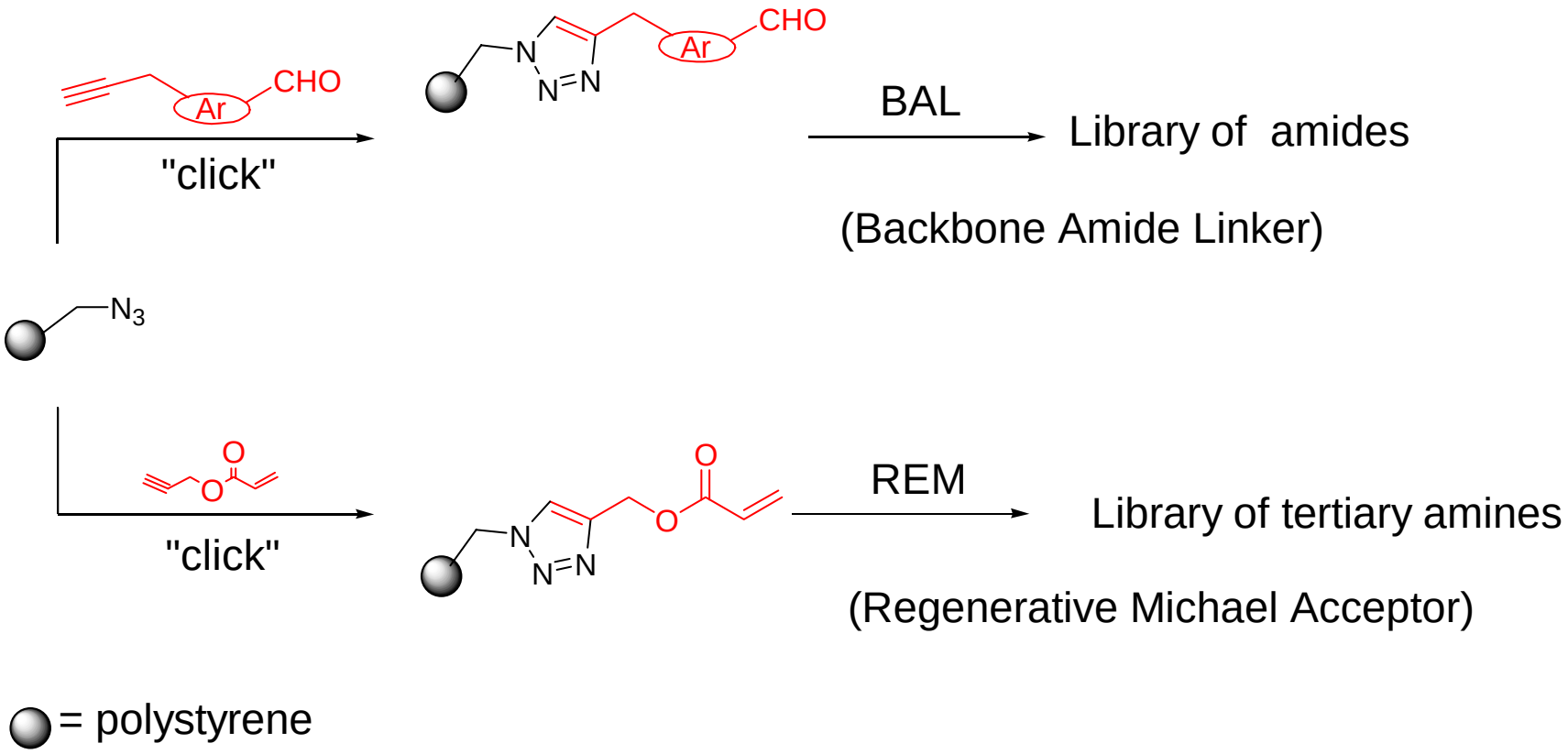


"Click" Resin



Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett*. **2003**, *5*, 1753.

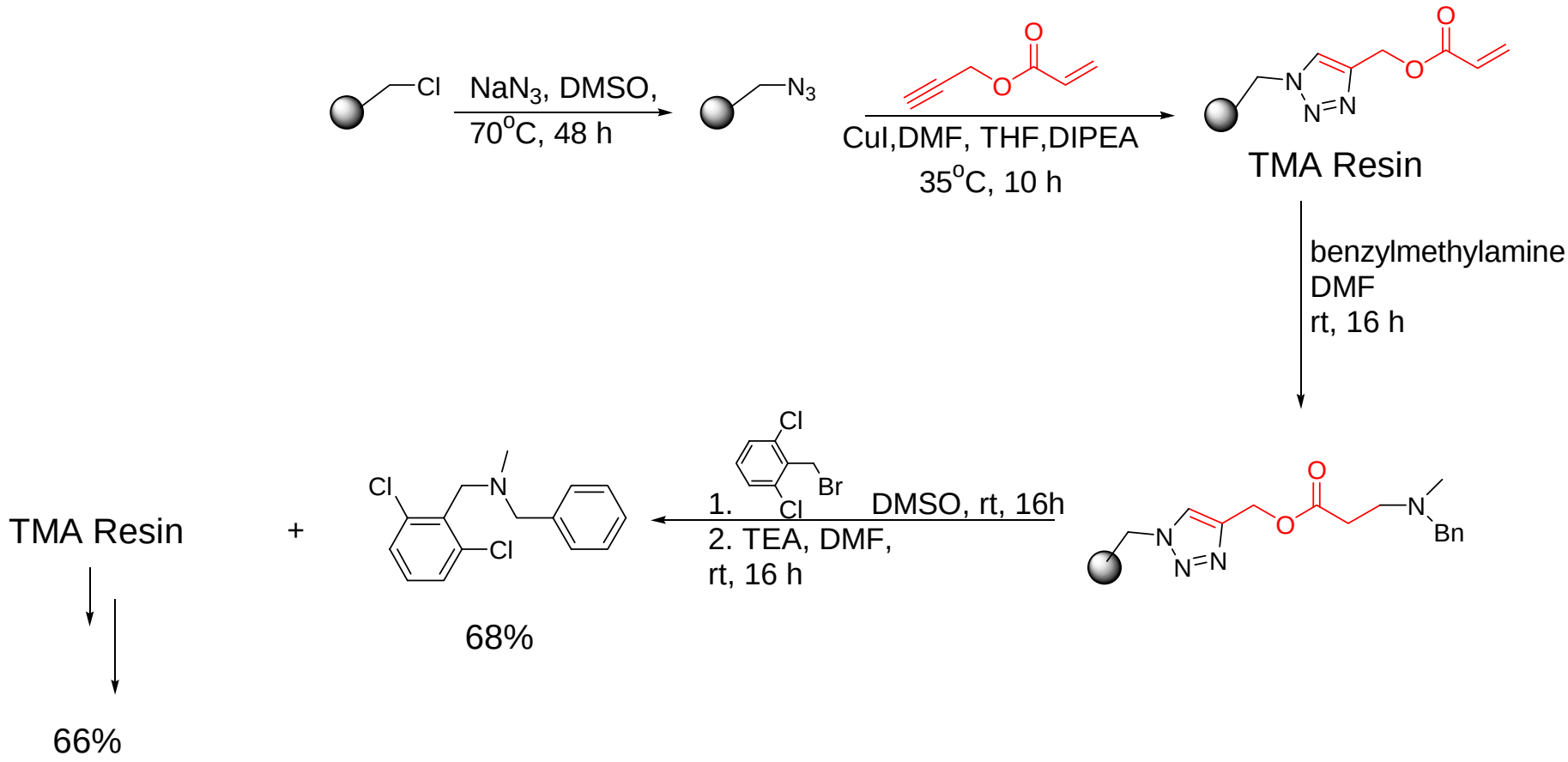
SPOS: Library of Tertiary Amines



Lober, S.; Gmeiner, P. *Tetrahedron*, **2004**, *60*, 8699.

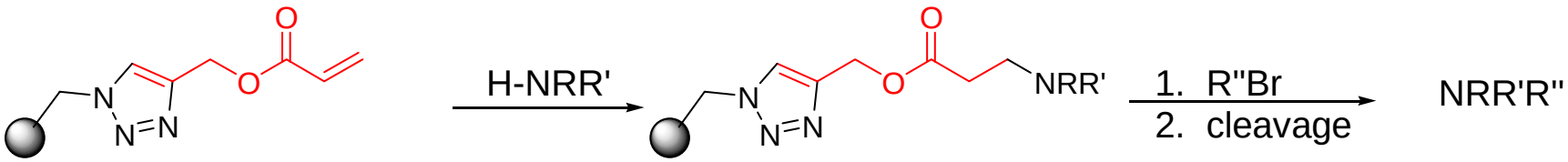
SPOS: Library of Tertiary Amines

- Triazolylmethyl acrylate (TMA) Resin



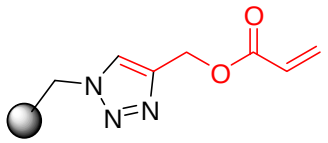
Lober, S.; Gmeiner, P. *Tetrahedron*, **2004**, *60*, 8699.

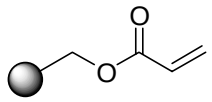
- Parallel synthesis: TMA & REM Resins

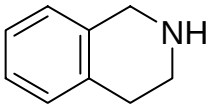


TMA Resin

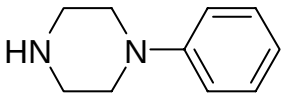
a-e







tetrahydro-isochinoline

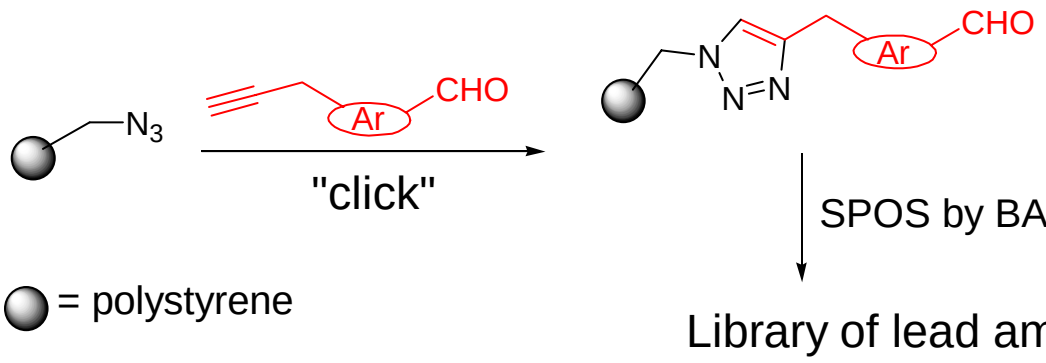


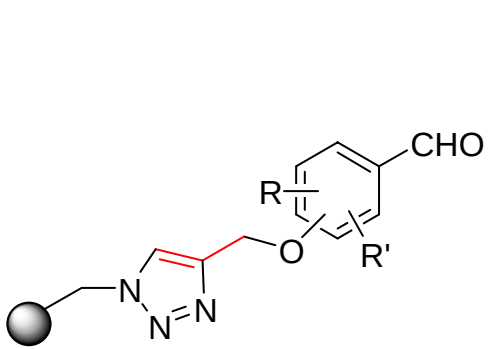
N-phenyl piperazine

	NRR'	R''	TMA yield (purity)	REM yield (purity)
a	Tetrahydro-isochinoline	Allyl	82 (95)	88 (>90)
b	Tetrahydro-isochinoline	*p*-Nitrobenzyl	77 (92)	63 (>90)
c	Tetrahydro-isochinoline	CH_2CO_2Me	75 (92)	73 (>90)
d	N-Phenyl-piperazine	Allyl	79 (93)	75 (>90)
e	N-Phenyl-piperazine	*p*-Nitrobenzyl	53 (91)	47 (>90)

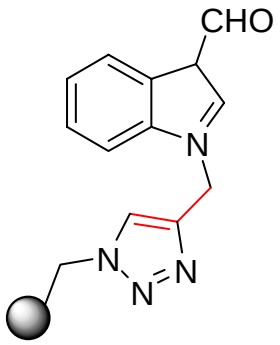
Lober, S.; Gmeiner, P. *Tetrahedron*, **2004**, *60*, 8699.

SPOS: Selective Receptor Ligands





FAMT



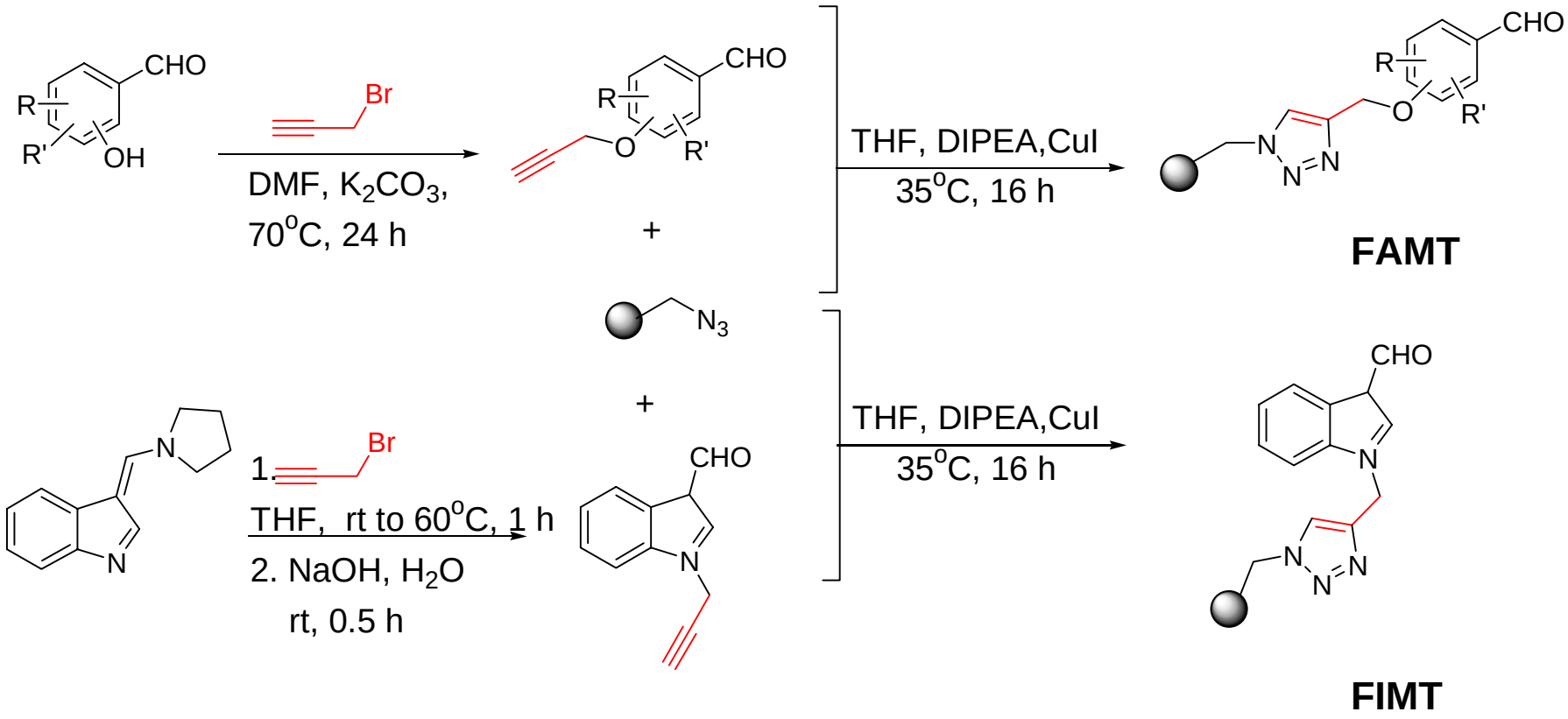
FIMT

FAMT: Formyl Aryloxy Methyl Triazole

FIMT: Formyl Indole Methyl Triazole

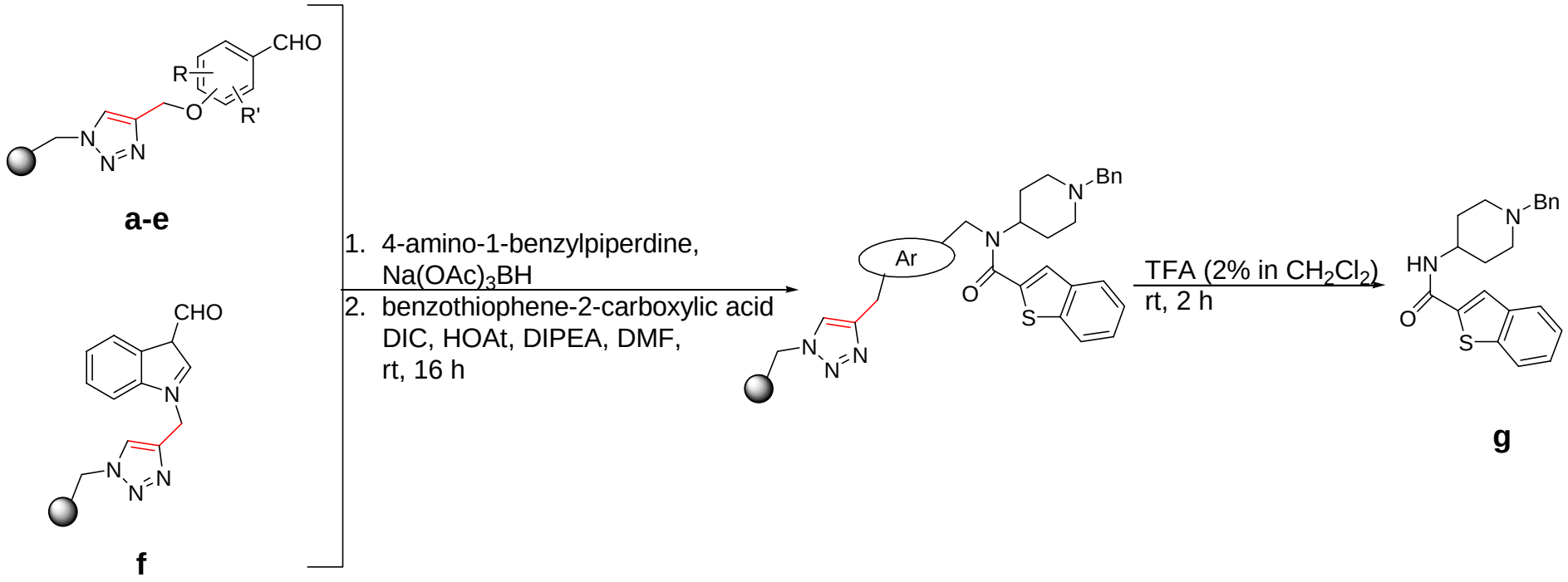
Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett*. **2003**, *5*, 1753.

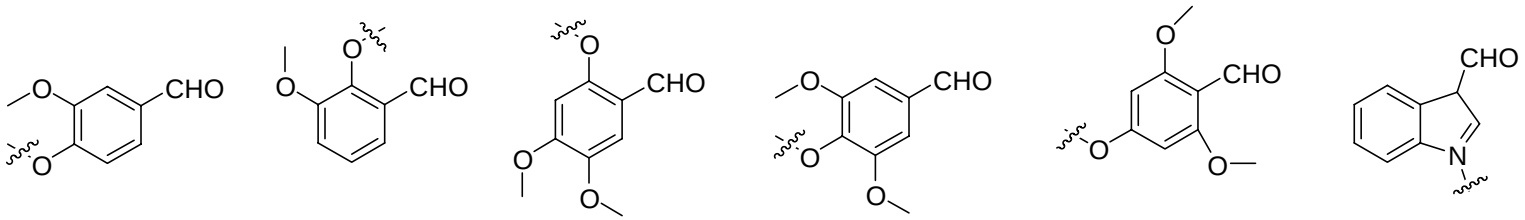
SPOS: Selective Receptor Ligands



Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett*. **2003**, *5*, 1753.

SPOS: Selective Receptor Ligands

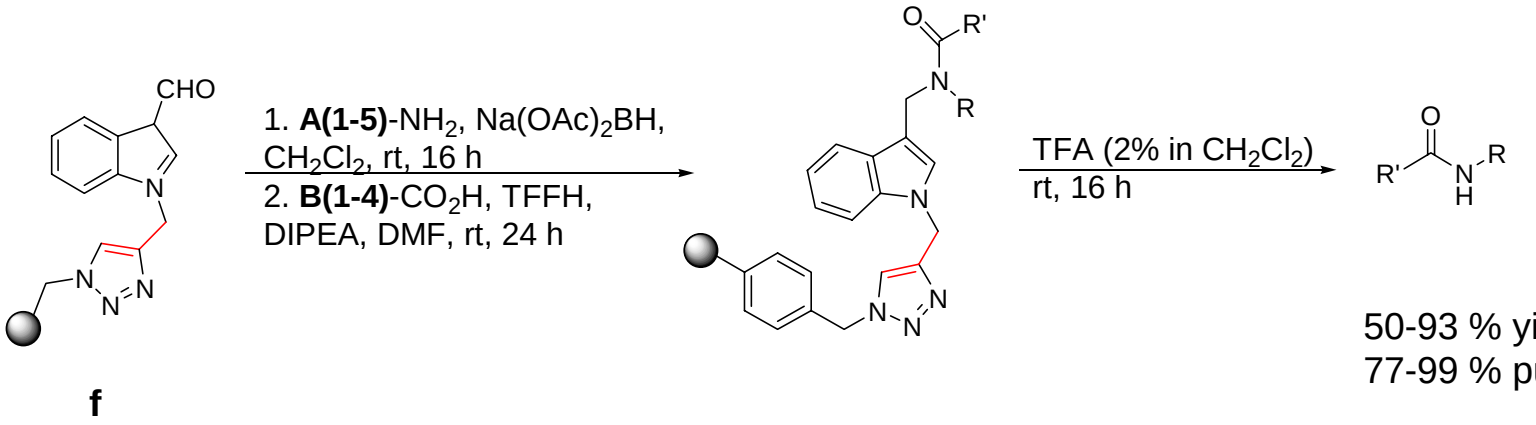




	a	b	c	d	e	f
Yield (purity) of **g**	**6 (>95)**	**9 (>95)**	**94 (>95)**	**9 (>95)**	**67 (>95)**	**94 (>95)**

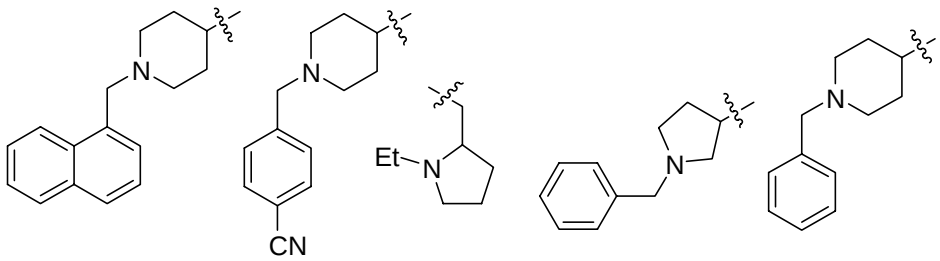
Lober, S.; Rodriguez-Loaiza, P.; Gmeiner, P. *Org. Lett*. **2003**, *5*, 1753.

Preparation of Amide Library using FIMT Resins



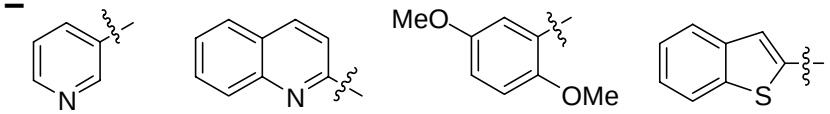
f

R =



A1 **A2** **A3** **A4** **A5**

R' =



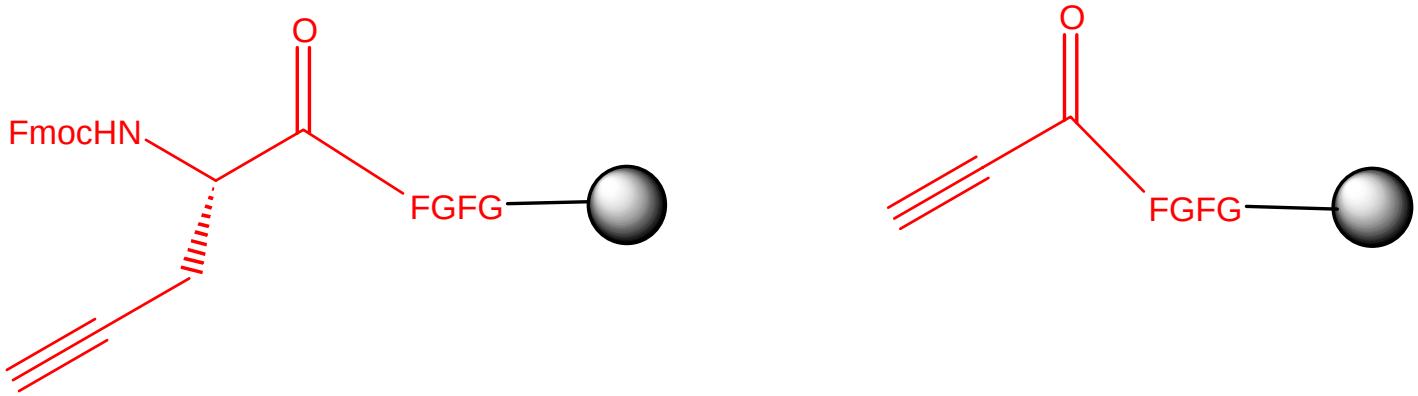
B1 **B2** **B3** **B4**

	B1	B2	B3	B4
A1	55% (85%)	92% (94%)	90% (94%)	73% (85%)
A2	50% (77%)	91% (98%)	88% (97%)	74% (91%)
A3	58% (90%)	93% (93%)	93% (93%)	78% (95%)
A4	53% (90%)	90% (96%)	53% (96%)	72% (95%)
A5	60% (97%)	90% (99%)	60% (99%)	74% (99%)

“Click” Applications in Macromolecules

- Dendrimer Synthesis
- Solid Support Chemistry
  - SPOS
  - SPPS
- DNA functionalization

SPPS: Cu(I) catalysis on Solid Support



FGFG=Phe-Gly-Phe-Gly

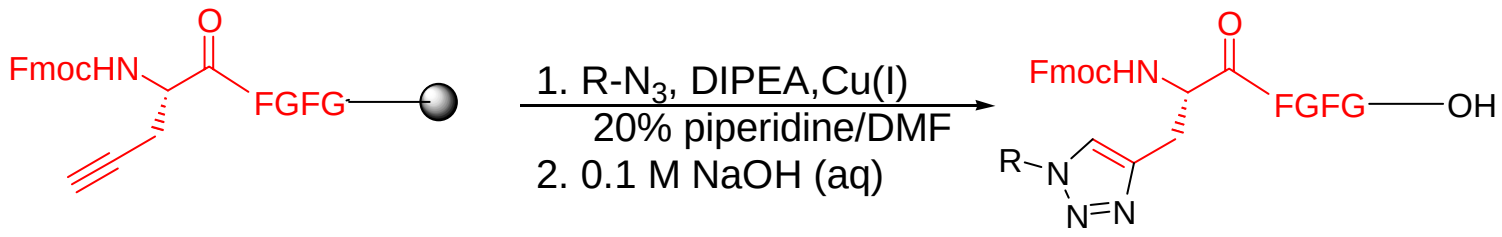
= HMBA-PEGA$_{800}$

Solvents: CHCN
CH_2Cl_2
THF
toluene
N,N-dimethylformamide
N-ethyldiisopropylamine

Quantitative conversions & purities: 75-95%

Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.

SPPS: Cu(I) catalysis on Solid Support

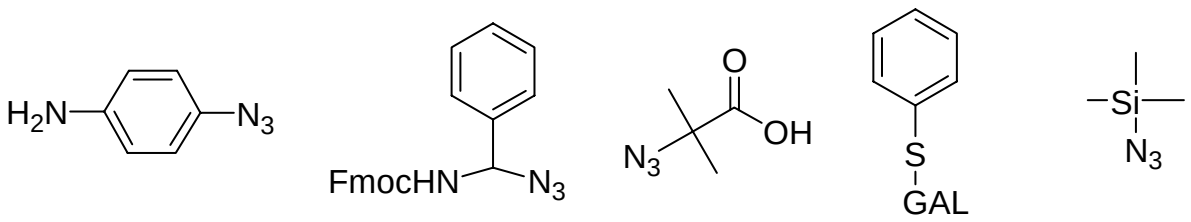


a-e

FGFG=Phe-Gly-Phe-Gly

● = HMBA-PEGA$_{800}$

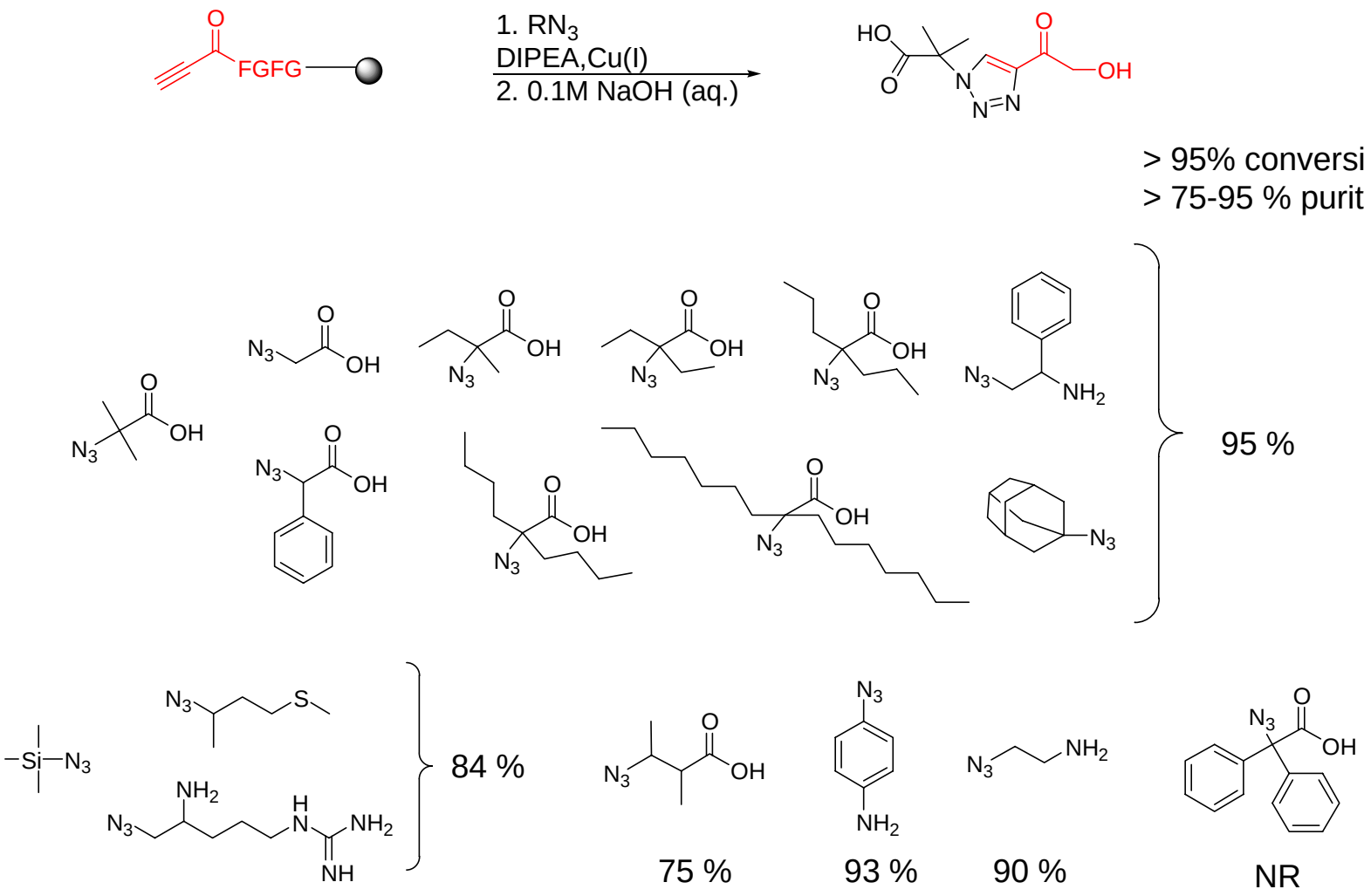
All conversions > 95%*



a	b	c	d	e
90%	79%	78%	75%	NR

Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.

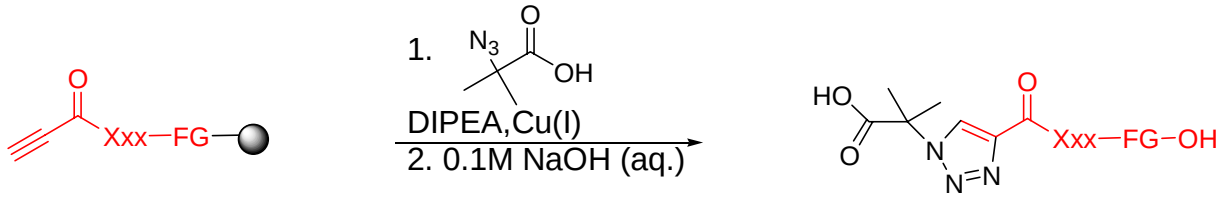
SPPS:Cu(I) catalysis on Solid Support



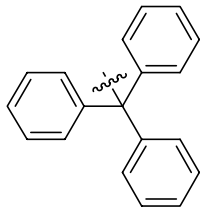
Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.

SPPS: Cu(I) catalysis on Solid Support

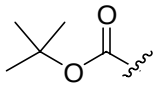
- Peptide Protecting Group Compatibility



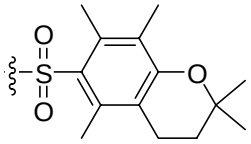
> 95% conversion



Triphenylmethyl (Trt)



t-Butyloxycarbonyl (Boc)



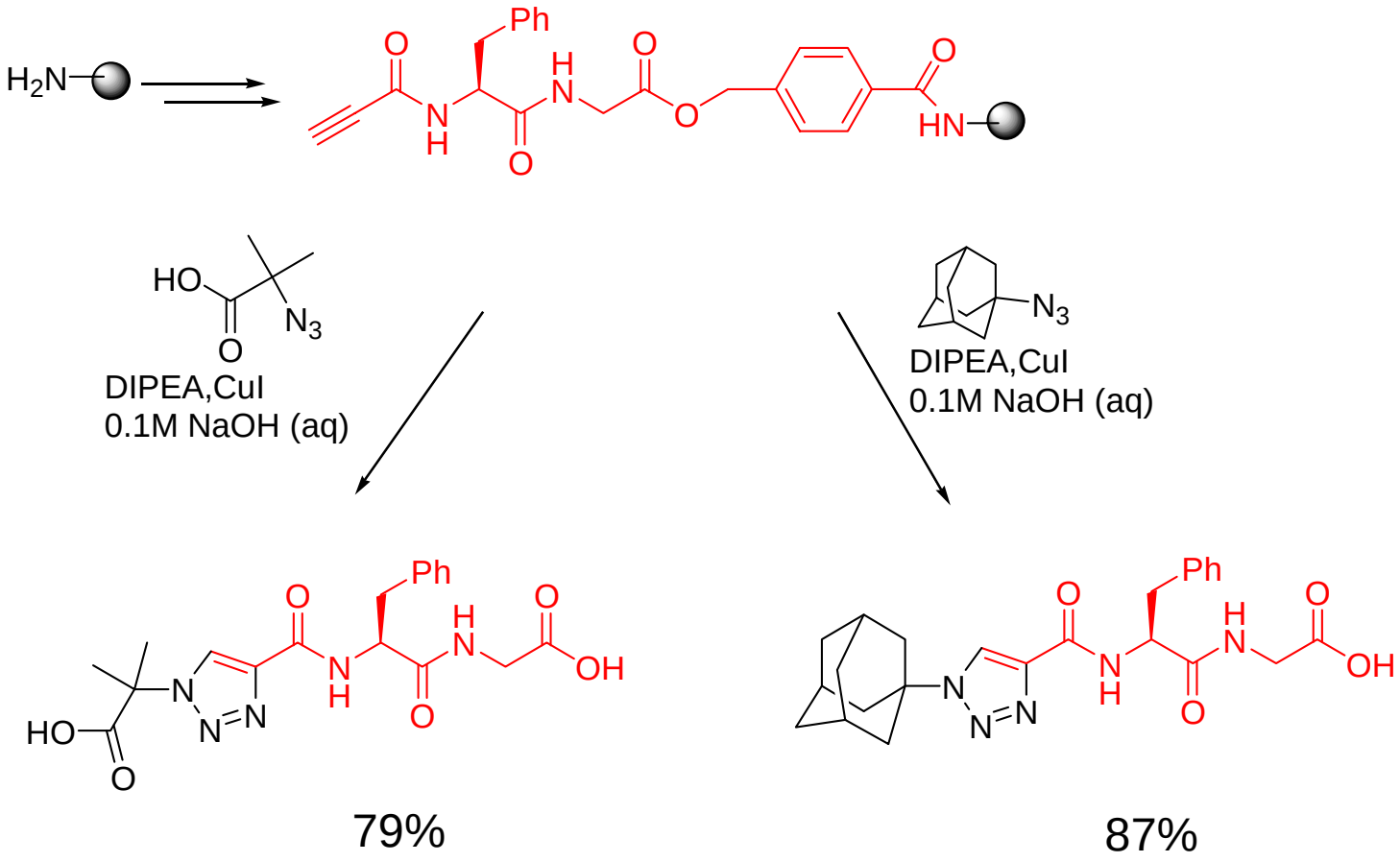
2,2,5,7,8-pentamethyl-chroman-6-sulphonyl (Pmc)

Xxx	% purity	Xxx	% purity
Ala	> 95	His(Trt)	80
Pro	> 95	Cys(Trt)	81
Thr(^{t}Bu)	> 95	Met	85
Tyr (^{t}Bu)	> 95	Lys(Boc)	> 95
Asp (^{t}Bu)	> 95	Trp(Boc)	> 95
Asn(Trt)	90	Arg(Pmc)	88

Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.

SPPS: Cu(I) catalysis on Solid Support

- Scale Up



Tornoe, C.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057.

“Click” Applications in Macromolecules

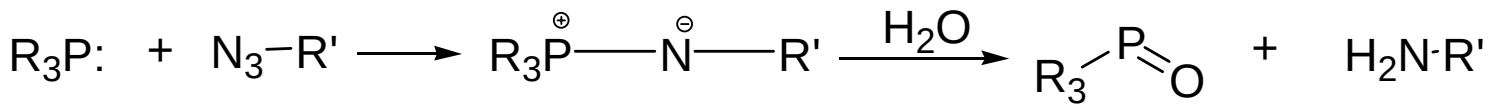
- Dendrimer Synthesis
- Solid Support Chemistry
  - SPOS
  - SPPS
- DNA functionalization

“Click” Chemistry in Biology

- Construction of fluorescent oligonucleotides for DNA sequencing
- Biological Inhibitors
- In-situ “Click” approach

DNA Sequencing

- Modified Oligonucleotides
- Introducing additional functional groups in DNA
  - Staudinger reaction

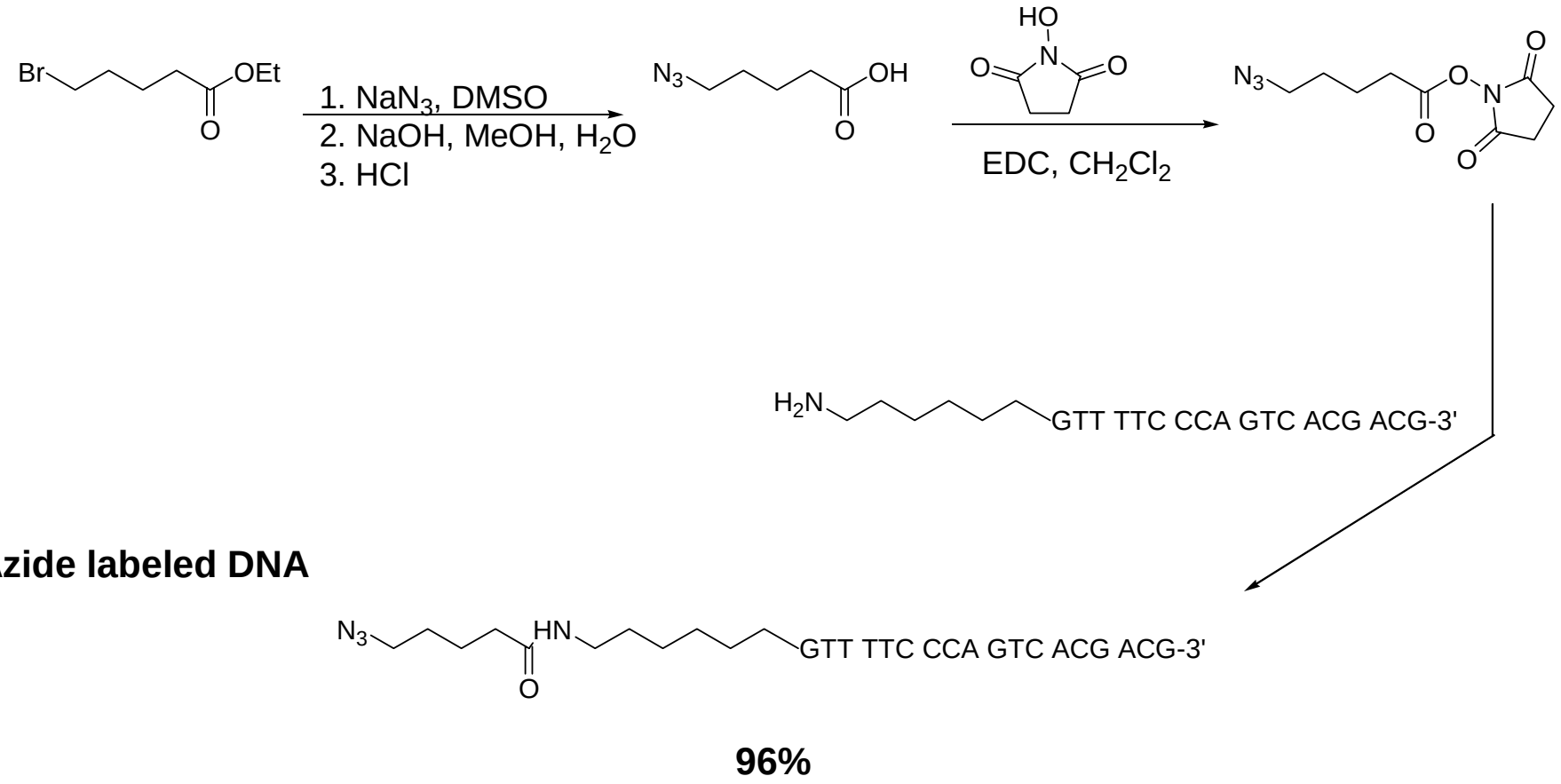


  - Limitations: aqueous conditions required hydrolyze intermediate aza-ylide

Seo, T.; Li, Z.; Ruparel H.; Ju J. *J. Org Chem*. **2003**, *68*, 609.
Saxon, E.; Bertozzi C. *Science,* **2002**, *287*, 2007.

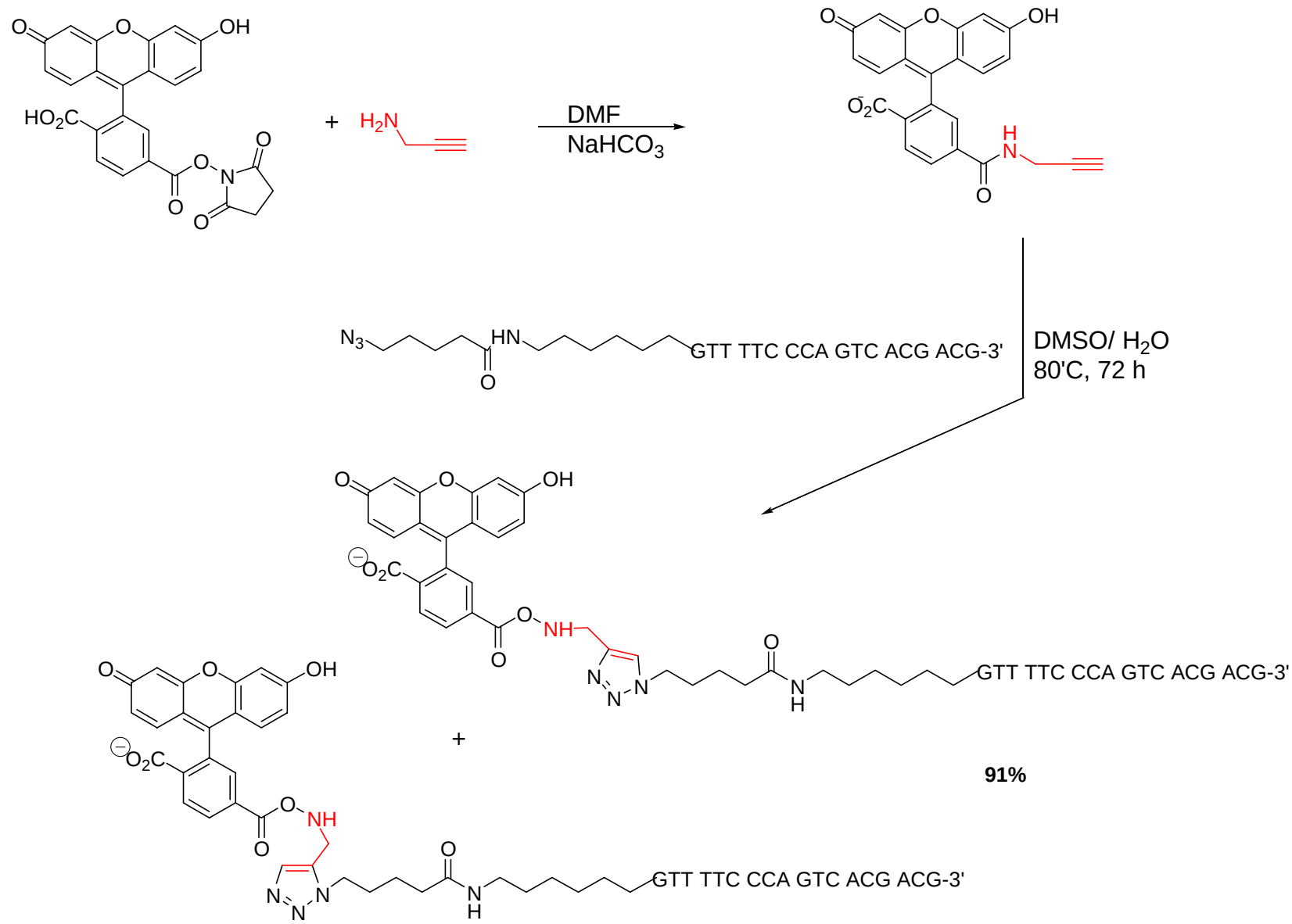
DNA Sequencing

- Fluorescent ss DNA sequencing



Seo, T.; Li, Z.; Ruparel H.; *J. Org Chem*. **2003**, *68*, 609.

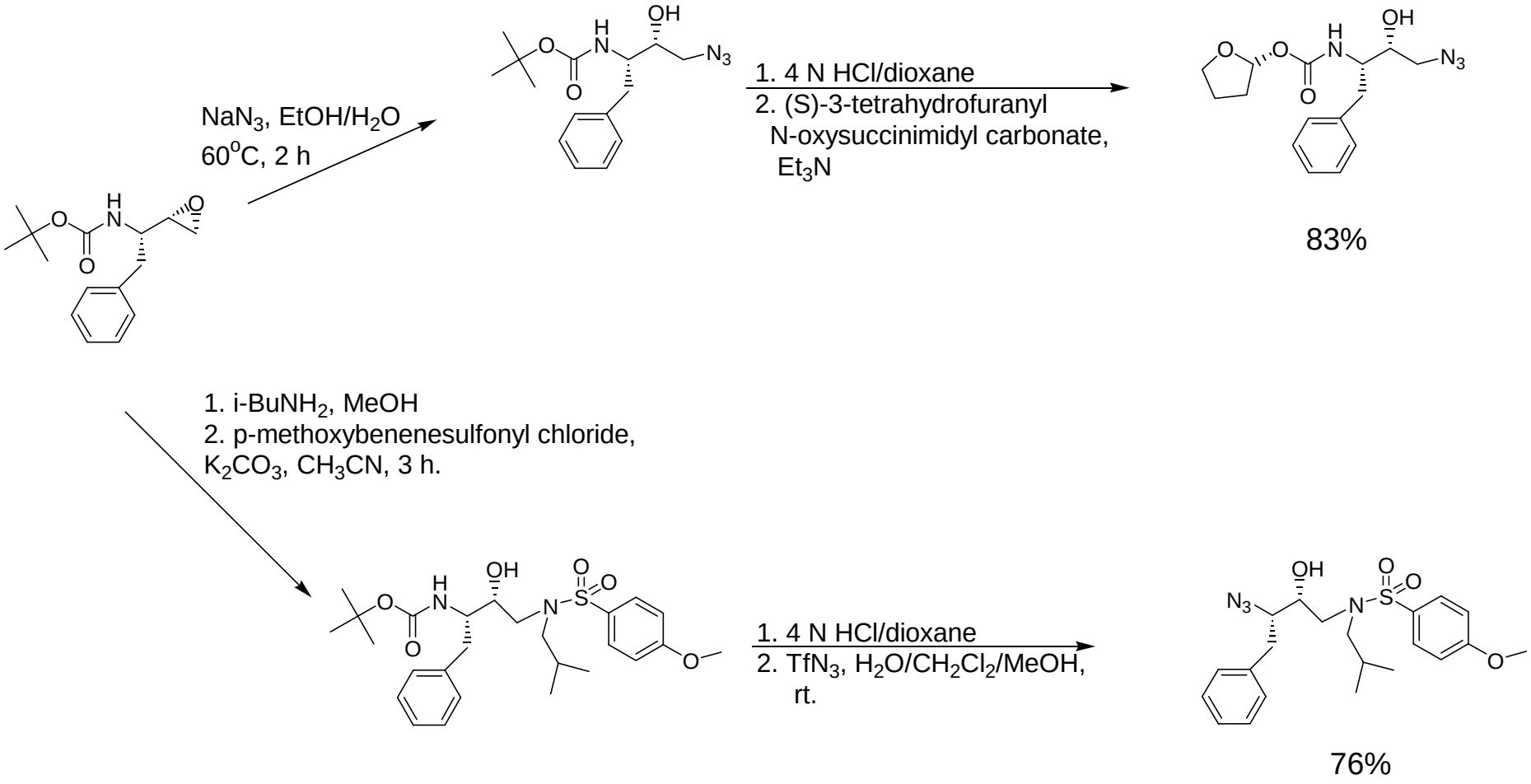
DNA Sequencing



Seo, T.; Li, Z.; Ruparel H.; *J. Org Chem*. **2003**, *68*, 609.

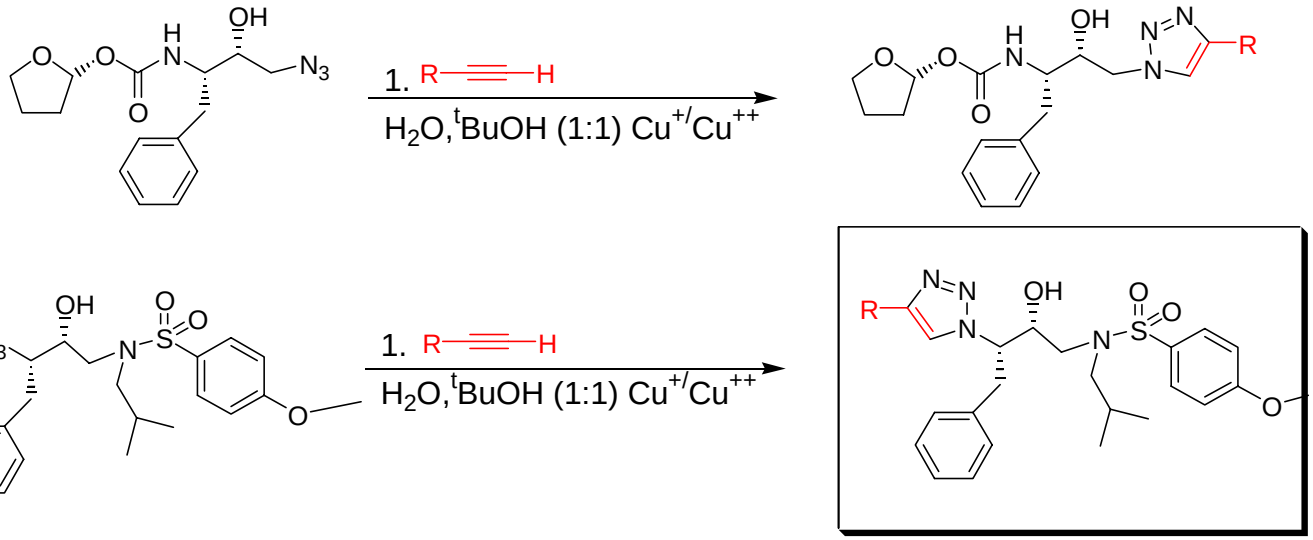
Biological Inhibitors

- HIV-1 protease (HIV-1 PR)

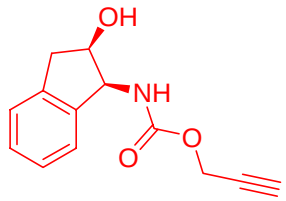


Brik, A.; Muldoon, J.; Lin, Y.; Elder, J. Goodsell, D. Olson, A.; Fokin, V.; Sharpless, B.; Wong, H. *Chem. Bio. Chem.* **2003**, *4*, 1246.

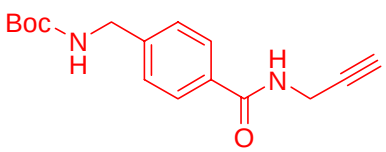
Biological Inhibitors



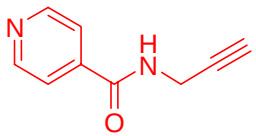
R=



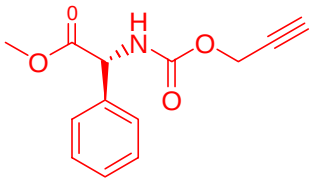
1



2



3



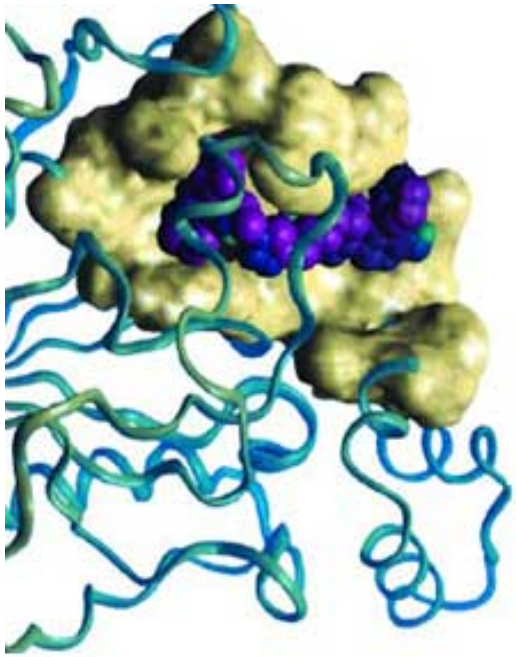
4

IC_{50} [nM]

Enzyme	1	2
HIV PR	6 +/- 0.5	13 +/- 0.5
V82F	19 +/- 1	24 +/- 1
G48V	39 +/- 1	17 +/- 1
V82A	46 +/- 2	52 +/- 2

Brik, A.; Muldoon, J.; Lin, Y.; Elder, J. Goodsell, D. Olson, A.; Fokin, V.; Sharpless, B.; Wong, H. *Chem. Bio. Chem.* **2003**, *4*, 1246.

In Situ “Click” Chemistry



IN SITU CLICK CHEMISTRY

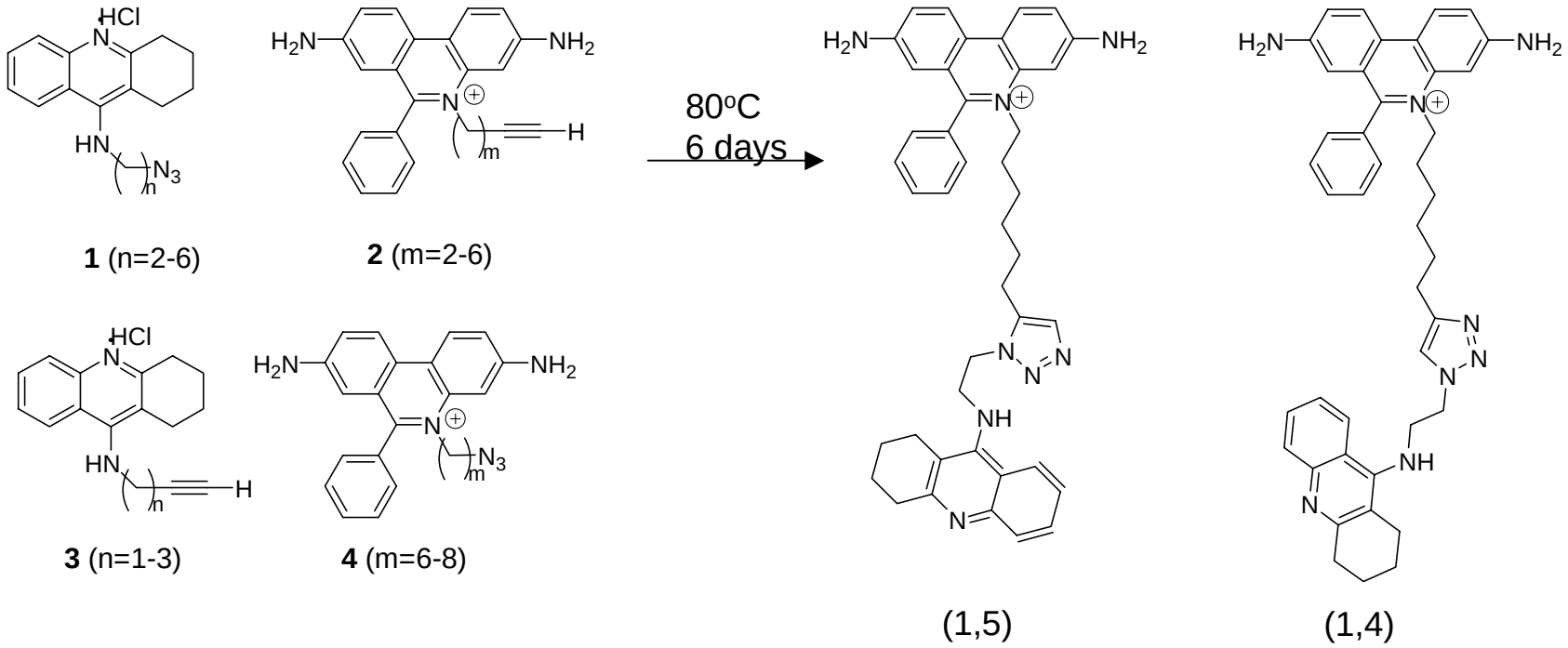
Templating strategy offers potential route to new drugs and other functional compounds

PERFECT FIT Model of acetylcholinesterase inhibitor.

Lewis, W.; Green, L.; Grynszpan, F.; Radic, Z.; Carlier, P.; Taylor, P.; Finn, M.; Sharpless, B. *Angew chemie. Int. Ed*, **2002**, *41*, 1054.

In-Situ “Click” Chemistry

- Enzyme Templating
  - Inhibitor for acetylcholinesterase



1 (n=2-6)

2 (m=2-6)

3 (n=1-3)

4 (m=6-8)

Lewis, W.; Green, L.; Grynszpan, F.; Radic, Z.; Carlier, P.; Taylor, P.; Finn, M.; Sharpless, B. *Angew chemie. Int. Ed*, **2002**, *41*, 1054.

Why “Click” Chemistry?

- Functional group tolerance
- Aqueous conditions
- Shorter reaction time
- High yield
- High purity
- Regiospecificity

Acknowledgments

- Dr. Jackson
- Dr. Borhan
- Dr. Odom
- Jackson & Miller Research Group