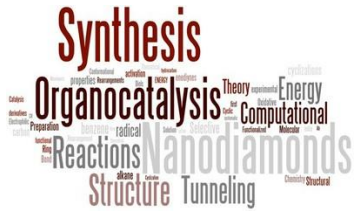


Chemoselective Building Blocks – Connecting Molecules without Protecting Groups

05.09.2014

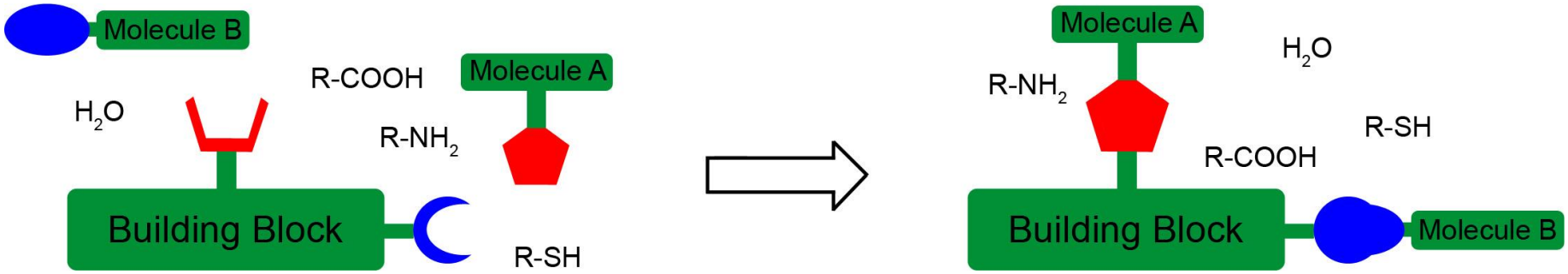
Institute of Organic Chemistry
Justus-Liebig University Giessen

Jan-Philipp Berndt

Chemoselective Building Blocks

Inspired by the concept of bioorthogonal reactions for modification of biomolecules

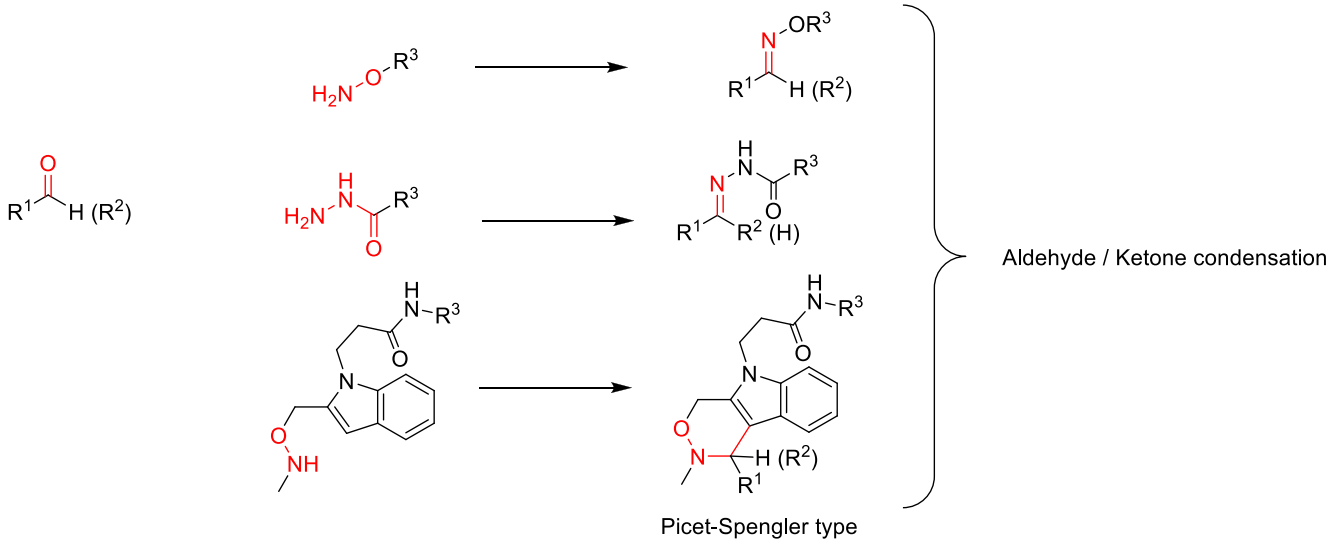
- no cross-reactivity with any of the naturally occurring functional groups (bioorthogonal)
- selective for the target
- stable in aqueous systems
- reaction should proceed in water

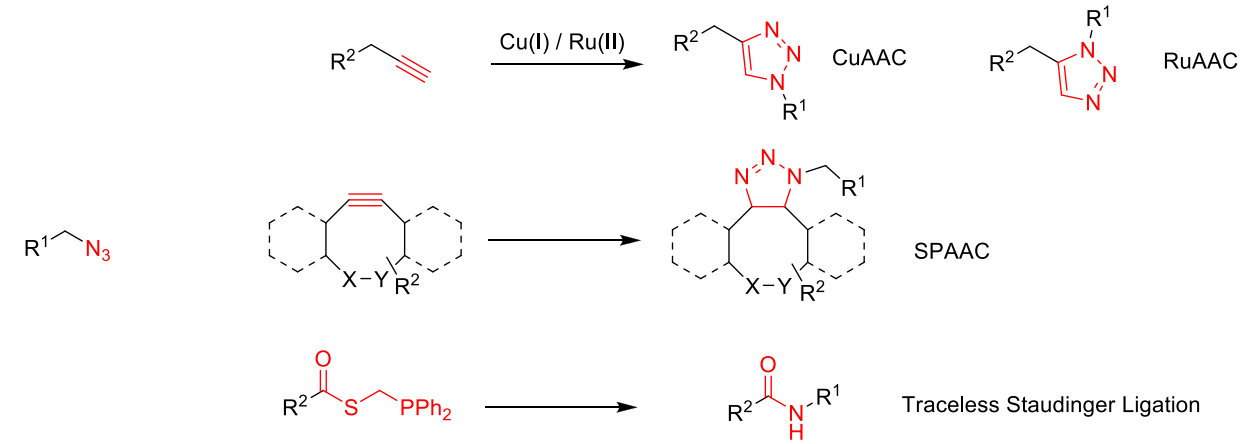


→ No protecting groups are necessary

Debets M.F., van Hest J.C.M., Rutjes P.J.T., *Org. Biomol. Chem.*, **2013**, *11*, 6439.

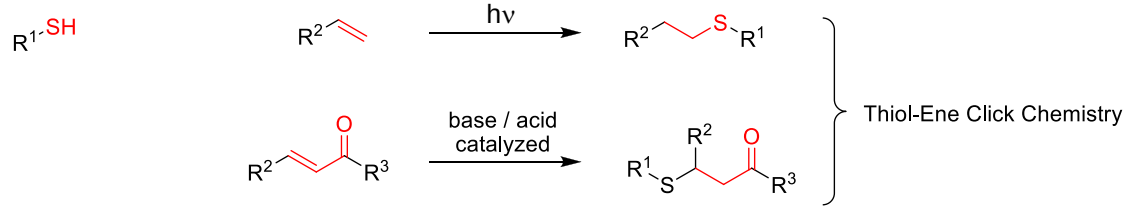
Chemoselective Groups

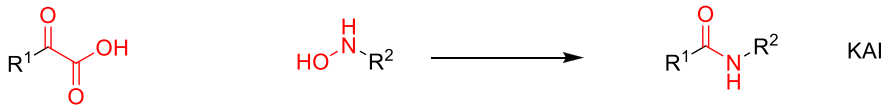


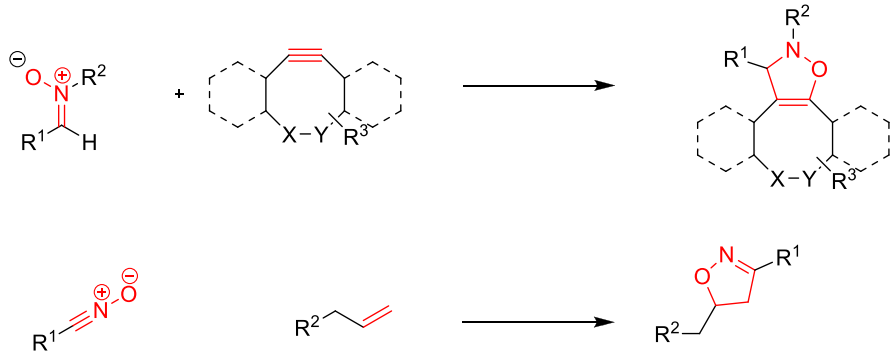


Nilsson B.L., Kiessling L.L., Raines R.T., *Org. Lett.,* **2000**, *2*, 1939. Saxon E., Armstrong J.I., Bertozzi C.R., *Org. Lett.,* **2000**, *2*, 2141.
Rostovtsev V.V., Green L.G., Fokin C.C., Sharpless K.B., *Angew. Chem. Int. Ed.*, **2002**, *41*, 2596.
Debets M.F., van Hest J.C.M., Rutjes P.J.T., *Org. Biomol. Chem.*, **2013**, *11*, 6439.

Chemoselective Groups







Many more cycloadditions…

Hoyle C.E., Bowman C.E., *Angew. Chem. Int. Ed.*, **2010**, *49*, 1540.
Pusterla I., Bode J.W., *Angew. Chem. Int. Ed.*, **2012**, *51*, 513.
Debets M.F., van Hest J.C.M., Rutjes P.J.T., *Org. Biomol. Chem.*, **2013**, *11*, 6439.

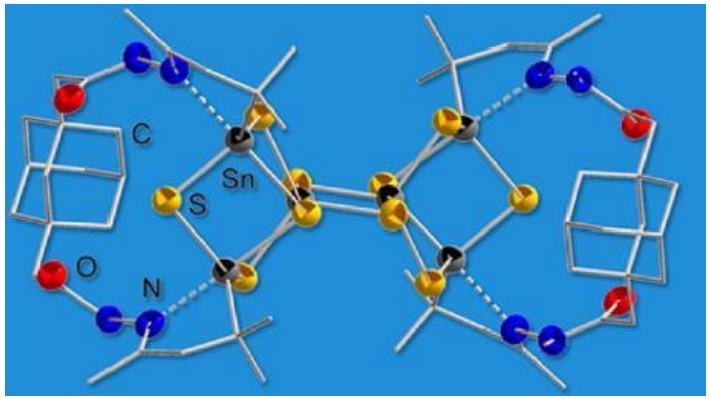
Functionalizing Sn/S-Clusters

LOEWE-Project - Block B3 → Modifying Peptides

↓

Functionalizing Sn/S-Cluster

- Functionalization can tune properties of chalcogenides
- Adamantane is a highly rigid and symmetric cage structure
  → Affecting of aggregation by introducing steric restrictions

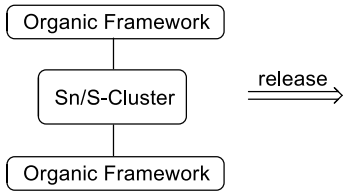


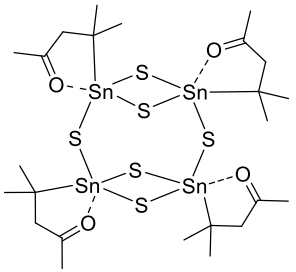
Catalysis

Conductivity

Thermoelectrica

Cytotoxic Agent?

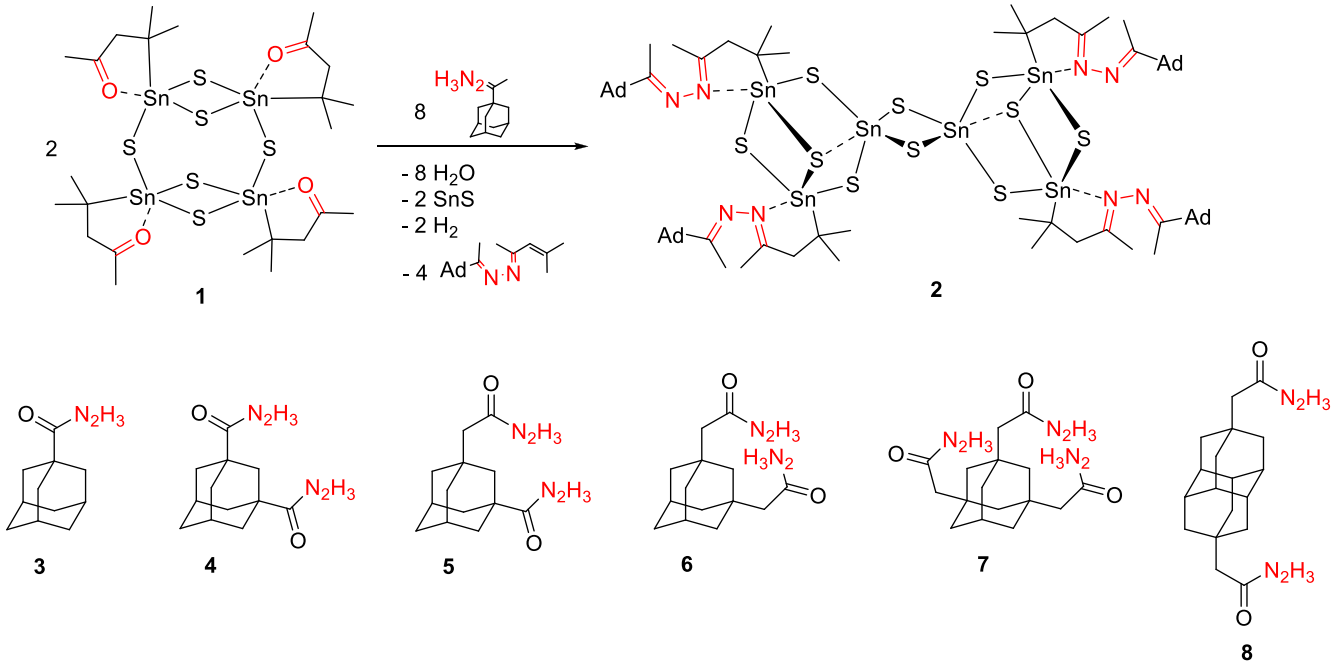




Zheng N., Bu X., Feng P., *Nature*, **2003**, *426*, 428.
Wang L., Wu T., Bu X., Zhao X., Zuo F., Feng P., *Inorg. Chem.*, **2013**, *52*, 2259.
Yuhas B.D., Smeigh A.L., Samuel A.P.S., Shim Y., Bag S., Douvalis A.P., Wasielewski M.R., Kanatzidis M.G., *J. Am. Chem. Soc.*, **2011**, *133*, 7255.

Functionalizing Sn/S-Clusters

Diamondoid-Functionalization



How to functionalize further the Cluster?

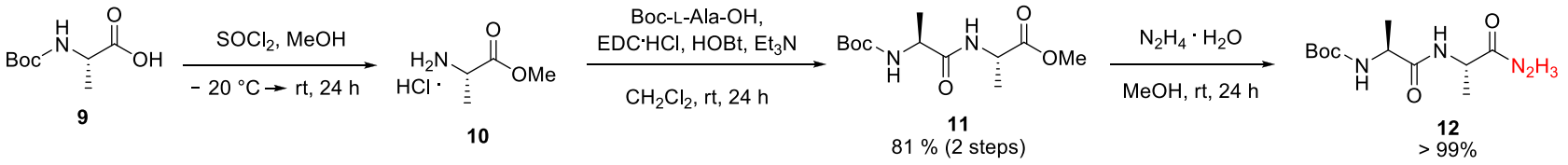
Functionalized hydrazides

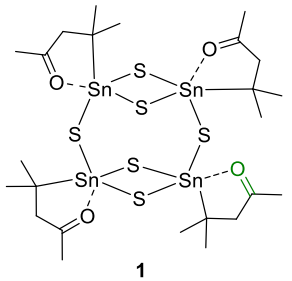
Postfunctionalization

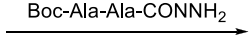
Barth B.E.K., Tkachenko B.A., Eußner J.P., Schreiner P.R., Dehnen S., *Organometallics*, **2014**, *33*, 1678.

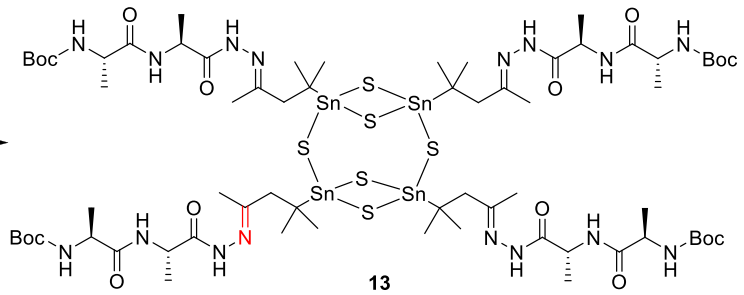
Functionalizing Sn/S-Clusters

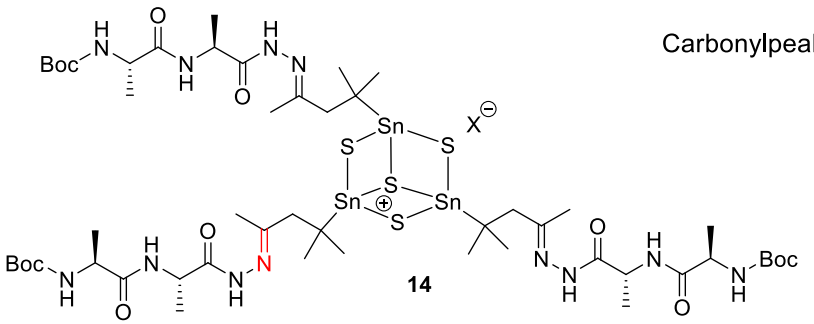
Functionalization with Peptides





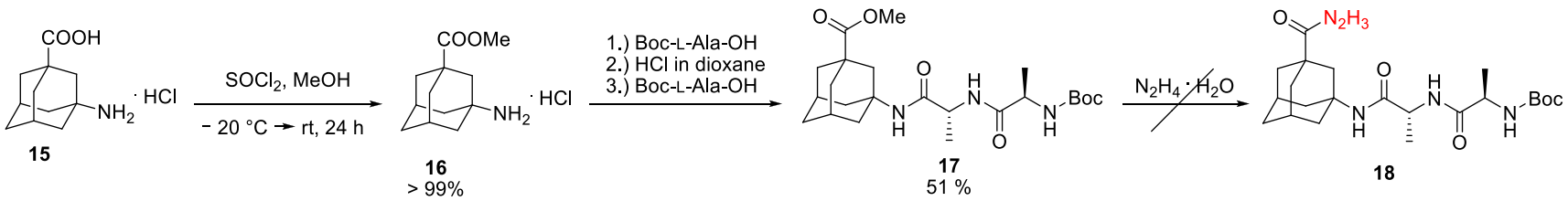






Functionalizing Sn/S-Clusters

Functionalization with Peptides

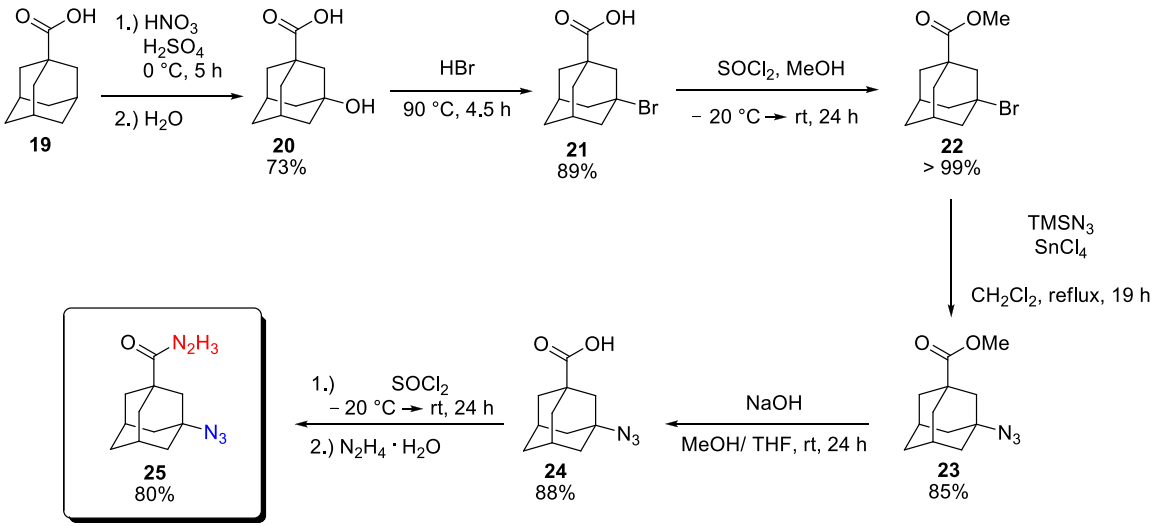


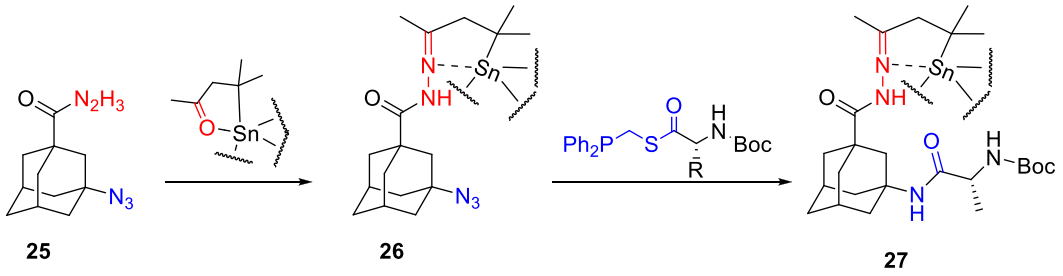
Solvent	Temperature	Reaction time	$(NH_2)_2$ [eq]
MeOH	rt	24 h	2
MeOH	60 ° C	24 h	2
DMF	80 ° C	24 h	2
EtOH	reflux	24 h	ex

Barth B.E.K., Tkachenko B.A., Eußner J.P., Schreiner P.R., Dehnen S., *Organometallics*, **2014**, *33*, 1678.

Functionalizing Sn/S-Clusters

Synthesis of the Chemoselective Building Block (Postfunctionalization)

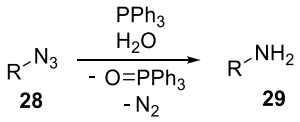




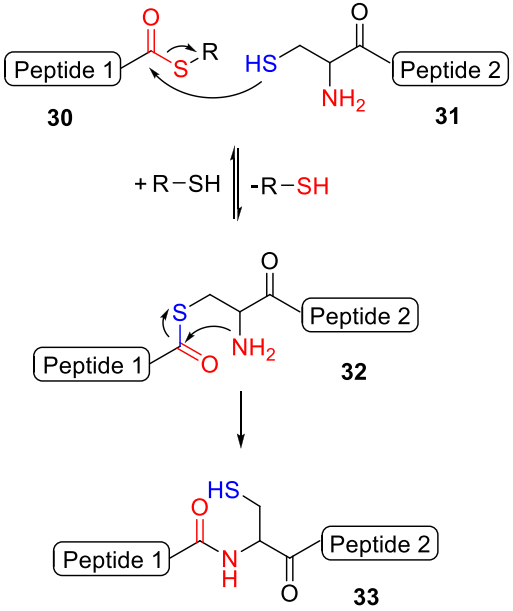
Functionalizing Sn/S-Clusters

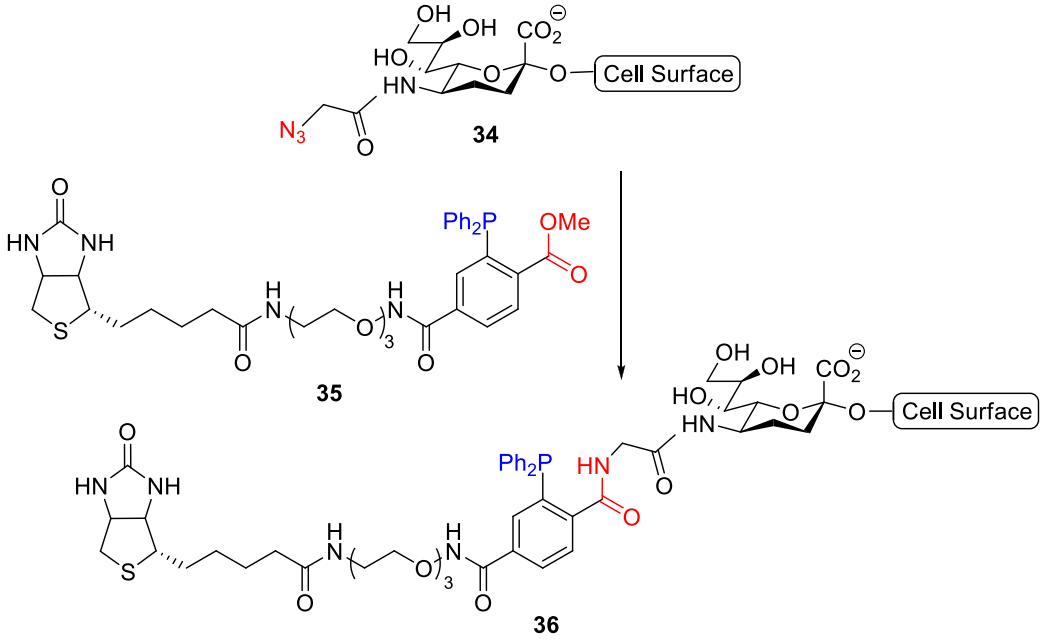
Staudinger Ligation (2000) – Conjugation of Biomolecules

Staudinger Reduction



Native Chemical Ligation

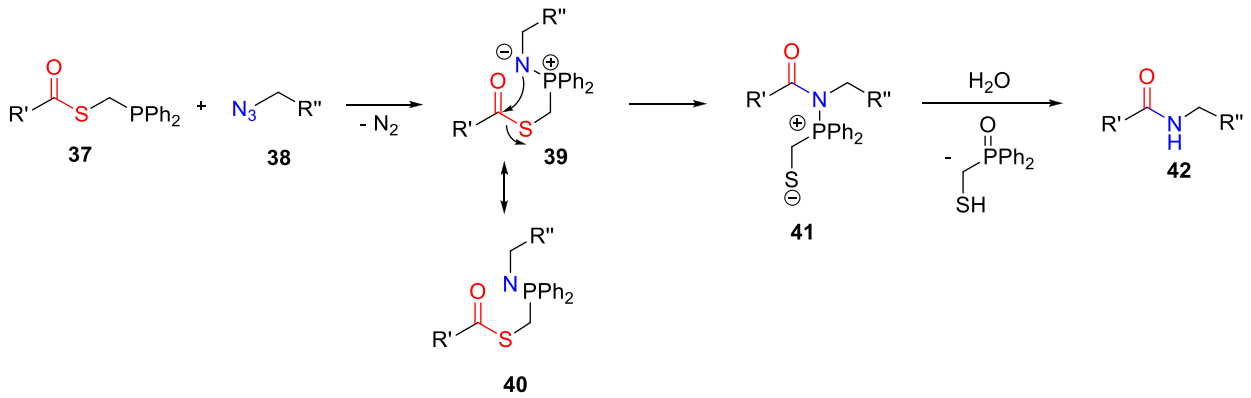


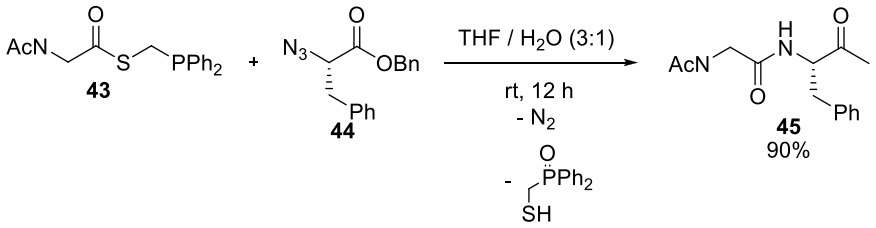


Saxon E., Bertozzi C.R., *Science*, **2000**, *287*, 2007. Dawson P.E., Muir T.W., Stephen I. C-L.,Kent B.H., *Science*, **1994**, *266*, 776.
Staudinger H., Meyer J., *Helv. Chim. Acta.,* **1919**, *2,* 635.

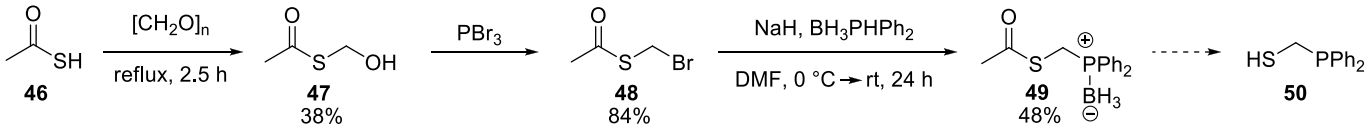
Functionalizing Sn/S-Clusters

Traceless Staudinger Ligation (2000)



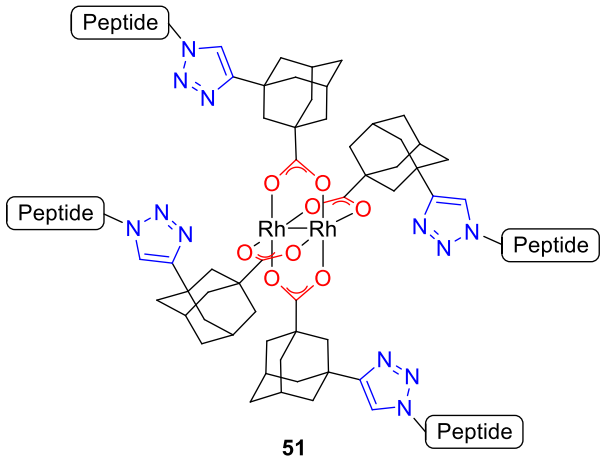


- Stereoretentive
- Steric hindrance plays no roll
- High yields (huge driving force)
- Tolerates a broad range of fg



Nilsson B.L., Kiessling L.L., Raines R.T., *Org. Lett.,* **2000**, *2*, 1939. Saxon E., Armstrong J.I., Bertozzi C.R., *Org. Lett.,* **2000**, *2*, 2141.
Saxon E., Luchansky S.J., Hang H.C., Yu C., Lee S.C., Bertozzi C.R., *J. Am. Chem. Soc.*, **2002**, *124*, 14893.
Soellner M.B., Nilsson B.L., Raines R.T., *J. Org. Chem.*, **2002**, *67*, 4993.
Köhn M., Breinbauer R., *Angew. Chem. Int. Ed.*, **2004**, *35*.

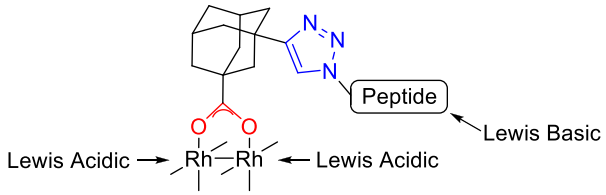
Functionalizing Rh-Complexes



51

Artificial Enzyme

Multicatalysis: Lewis Acid + Lewis Base



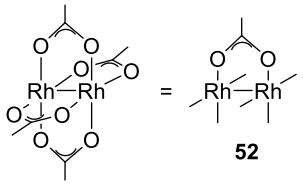
Cancer Drug?

- Water and air stable
- Column chromatography is possible

http://en.wikipedia.org/wiki/Rhodium%28II%29_acetate#mediaviewer/File:Rhodium%28II%29_acetate.jpg (03.09.2014)

Functionalizing Rh-Complexes

State of Art

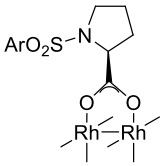


52

52

1. Synthesis of Ligands
2. Ligand Exchange

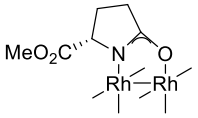
Rhodium(II) Carboxylates



53 Ar=*p*-$(C_{12}H_{25})C_6H_4$

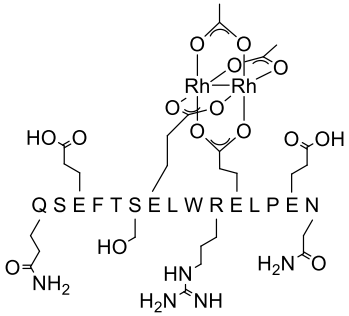
$Rh_2(DOSP)_4$

Rhodium(II) Carboxamidates



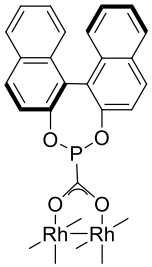
54

Rhodium(II) Metallopeptides



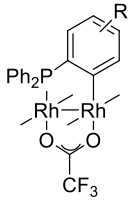
57

Rhodium(II) Phosphates



56

Rhodium(II) Ortho-Metalated Arylphosphines

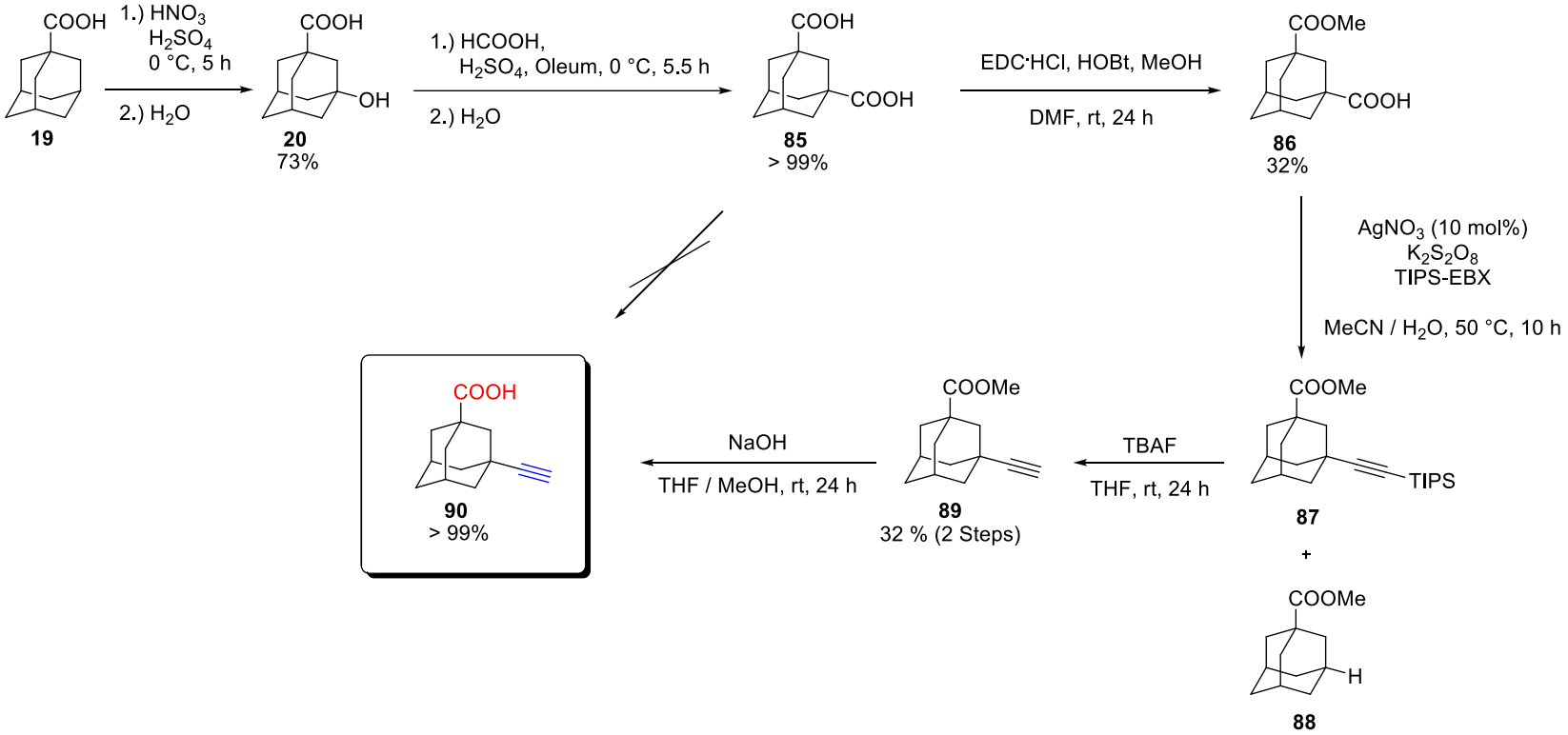


55

Pirrung M.C., Zhang J., *Tetrahedron Lett.*, **1992**, *33*, 5987. Ball Z.T., *Accounts Chem. Res.,* **2013**, *46*, 560.
Doyle M.P., Winchester W.R., Hoorn J.A.A., Lynch V., Simonsen S.H., Ghosh R., *J. Am. Chem. Soc.*, **1993**, *115*, 9958.
Davies H.M.L., Bruzinski P.R., Lake D.H., Kong N., Fall M.J., *J. Am. Chem. Soc.*, **1996**, *118*, 6897.
Estevan F., Herbst K., Lahuerta P., Barberis M., Pérez-Prieto J., *Organometallics*, **2001**, *20*, 950.

Functionalizing Rh-Complexes

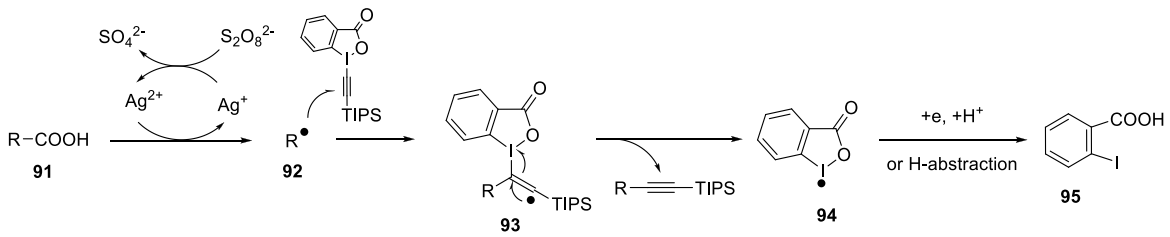
Synthesis of the Chemoselective Building Block

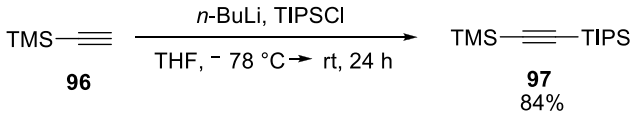


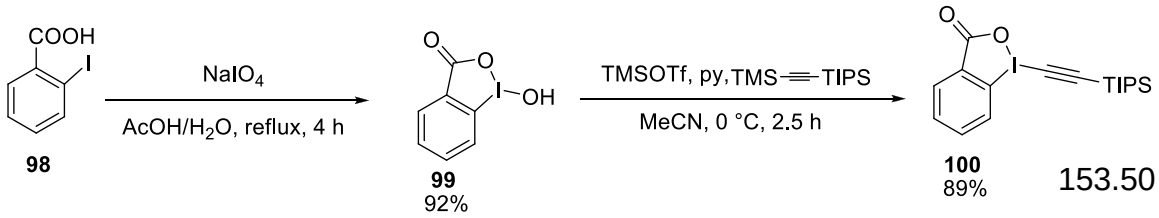
Liu X., Wang Z., Cheng X., Li C., *J. Am. Chem. Soc.*, **2012**, *134*, 14330.

Functionalizing Rh-Complexes

Keystep: Silver Catalyzed Decarboxylative Alkynylation

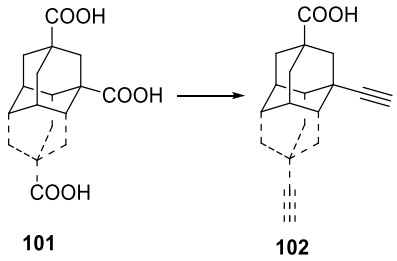






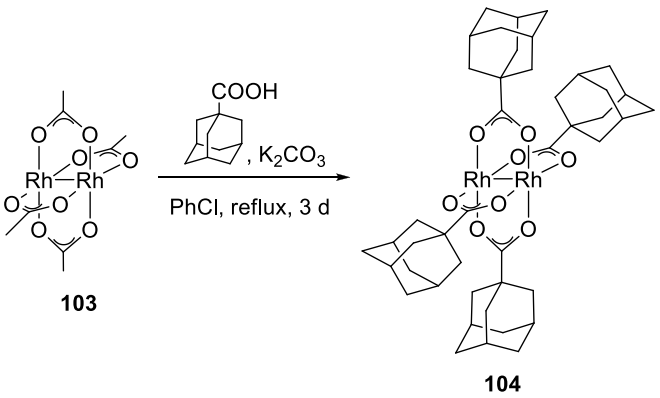
153.50 €/g

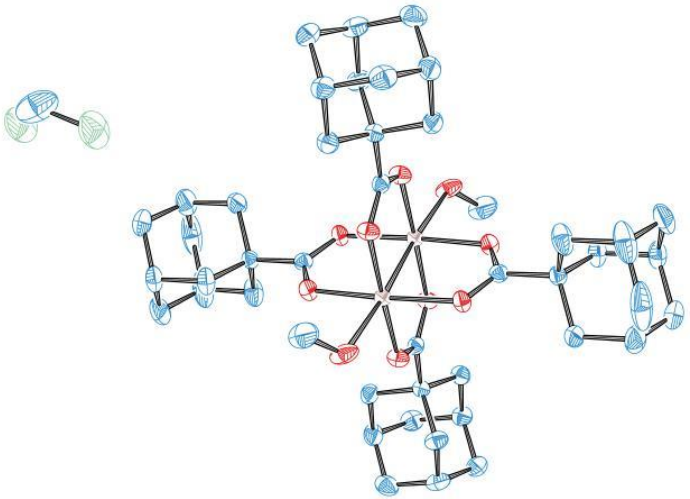
Desymmetrisation of Diamandoid acids?

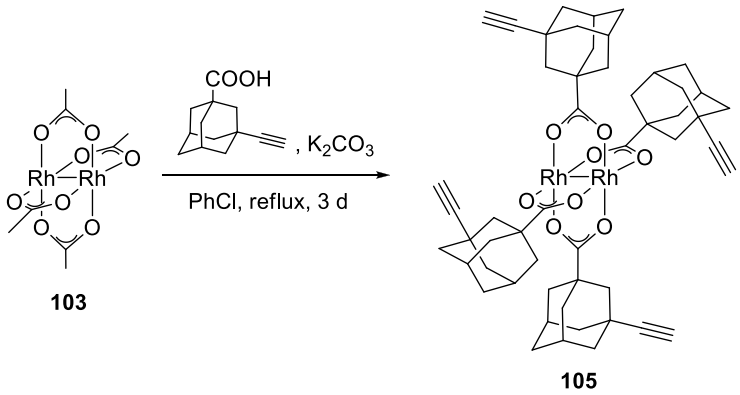


Liu X., Wang Z., Cheng X., Li C., *J. Am. Chem. Soc.*, **2012**, *134*, 14330.

Functionalizing Rh-Complexes



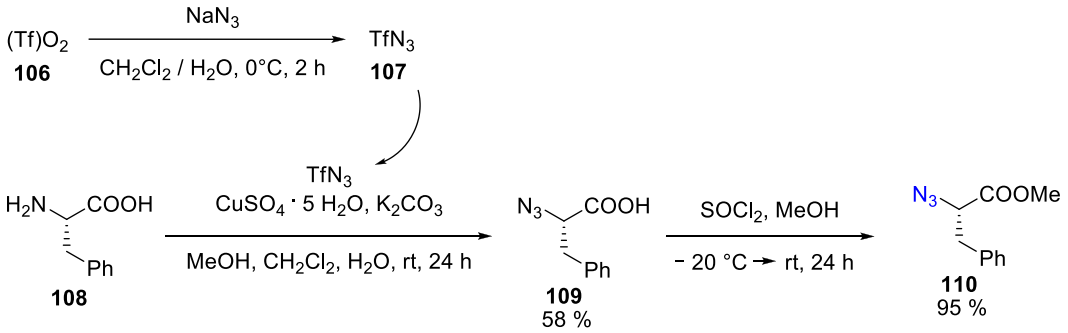




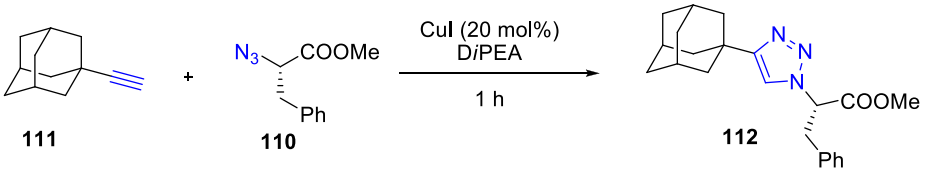
Vanier S.F., Larouche G., Wurz R.P., Charette A.B., *Org. Lett.*, **2010**, *12*, 672.

Functionalizing Rh-Complexes

Synthesis of Azido-Aminoacid



Preoptimization of the CuAAC

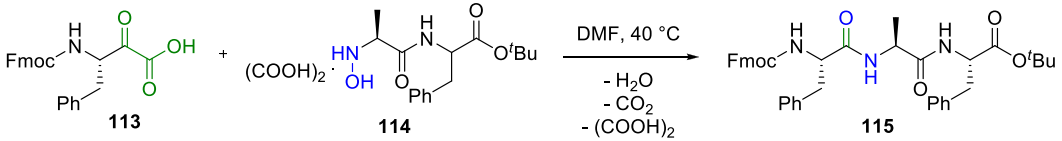


Conditions	Conversion [%]
$CHCl_3$, 50 ° C, 200 W	0
DMF, 50 ° C, 200 W	100
DMF, 50 ° C	100
DMF, rt	100

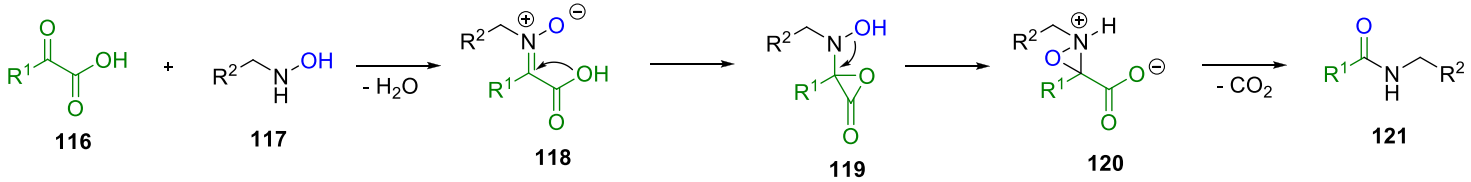
Alper P.B., Hung S-C, Wong C-H., *Tetrahedron Lett.*, **1996**, *37*, 6029.
Lundquist J.T., Pelletier J.C., *Org. Lett.,* **2001**, *3, 781.*

Ketoacid-Hydroxylamine-Ligation

KAHA-Ligation (2006)

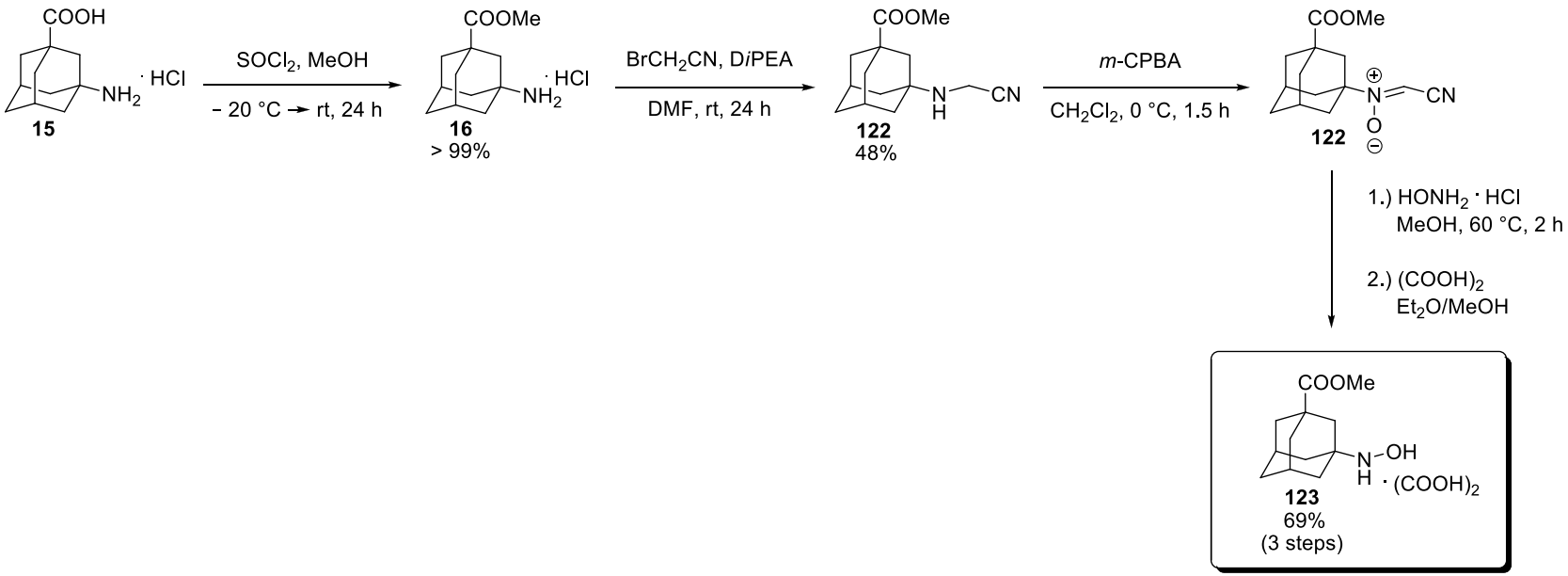


- Stereoretentive
- Tolerates a broad range of functional groups



Pusterla I., Bode J.W., *Angew. Chem. Int. Ed.*, **2012**, *51*, 513.

Ketoacid-Hydroxylamine-Ligation



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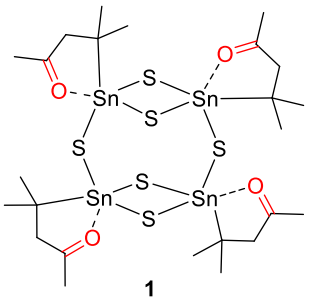
Outlook



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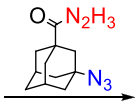

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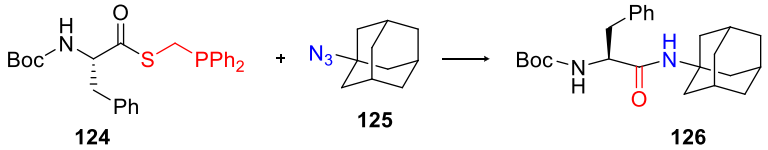

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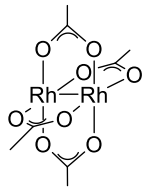

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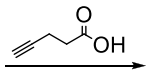

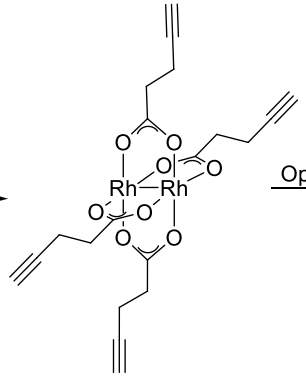

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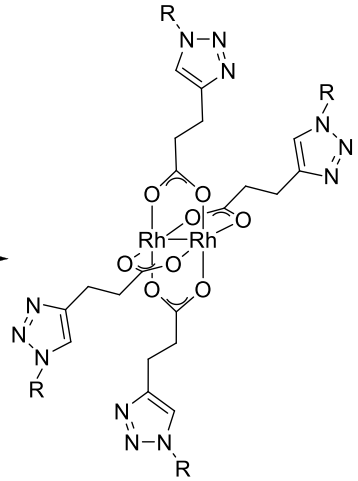
Optimizing CuAAC



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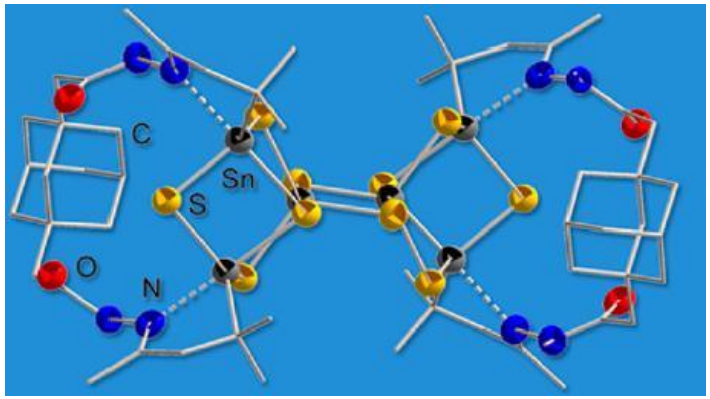
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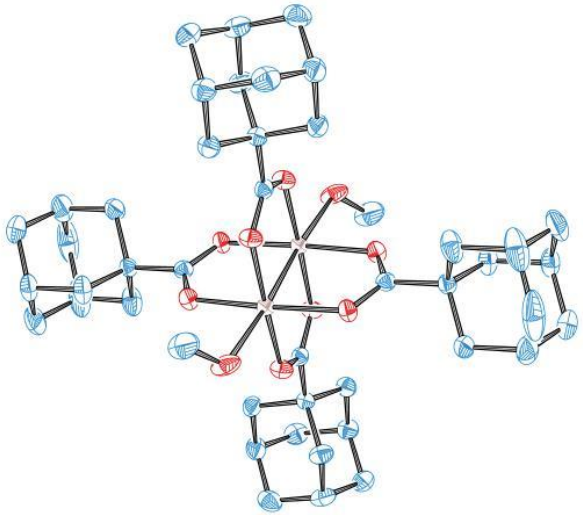

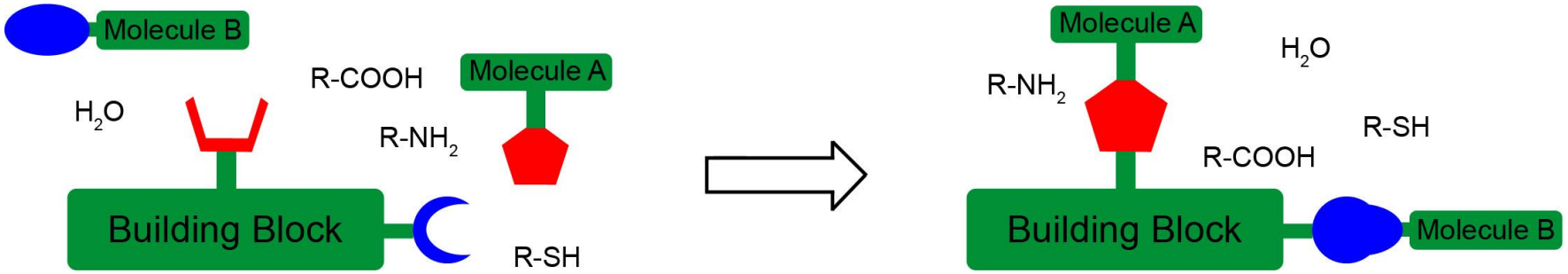
Molecule B
R-COOH
Molecule A
H2O
R-NH2
Building Block
R-SH
Molecule A
H2O
R-NH2
R-SH
R-COOH
Building Block
Molecule B