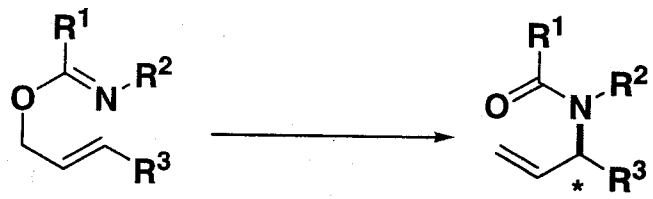
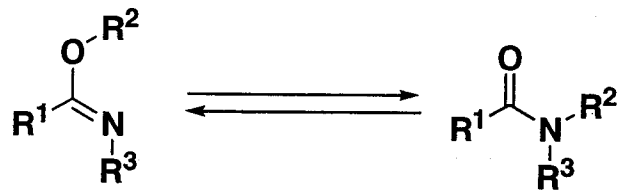
Rearrangement of Allylic Imidates:
Development of Asymmetric Catalysts and Applications in Synthesis



Denmark Group Meeting
11/25/03
Shinji Fujimori

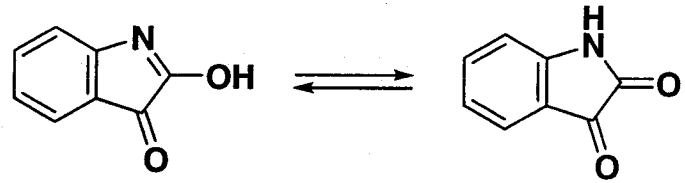
Imidic Acids and Imidates



imidic acid (R^2 = H)
imidate ($R^2 \neq$ H)

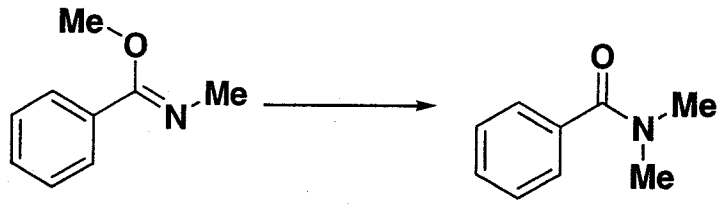
amide

Baeyer (1882)

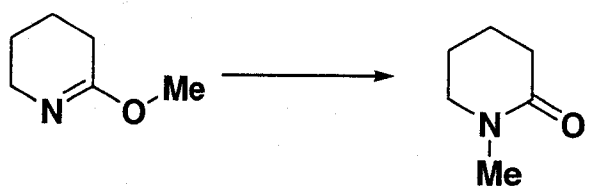


isatin

Beak (1978)



Δ H = -17.8 Kcal/mol



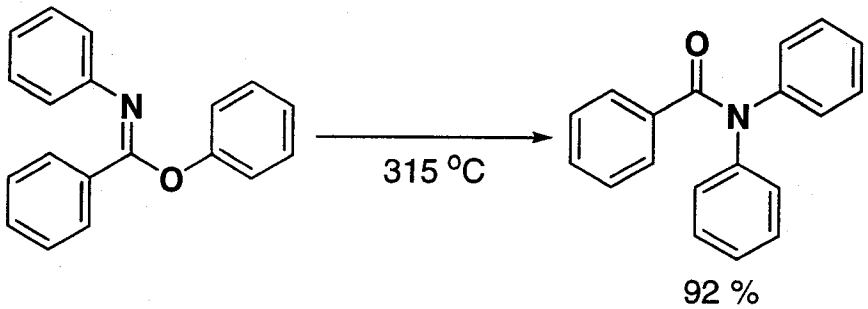
Δ H = -17.4 Kcal/mol

Conversion of imidate to amide is thermodynamically favorable transformation

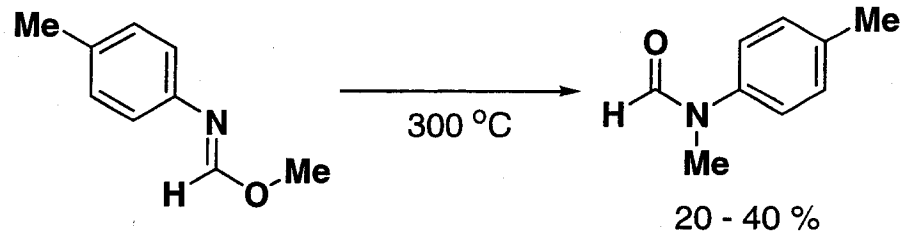
Baeyer, A.; Oekonomides, S. *Chem. Ber.* **1882**, *15*, 2093.
Beak, P.; Lee, J.; Ziegler, J. M. *J. Org. Chem.* **1978**, *43*, 1536.

Rearrangements of Imidates to Amides

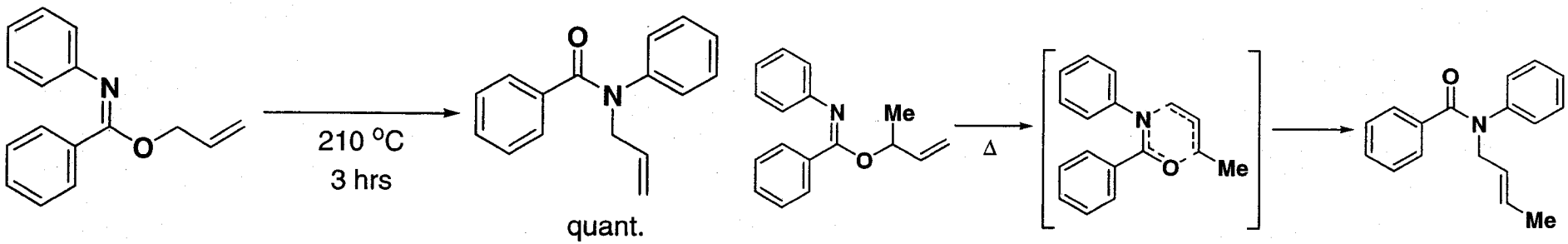
Aryl imidates: Chapman Rearrangement



Alkyl imidates:



Allyl imidates: Mumm and Moller (1937)

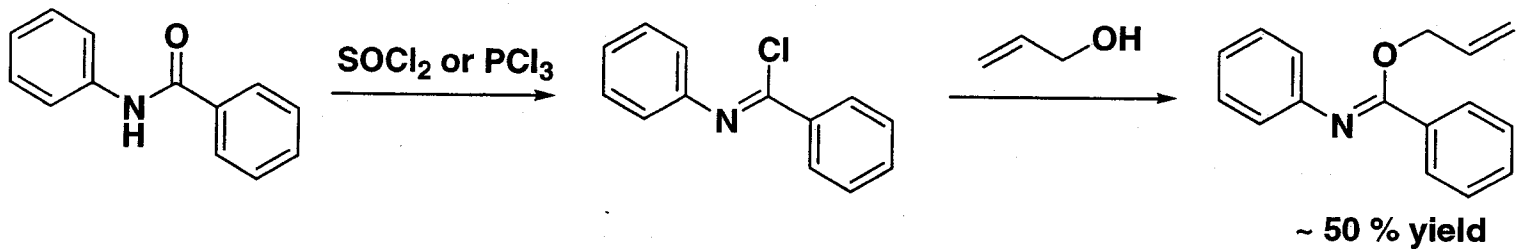


Allylic imidates undergo [3,3]-sigmatropic rearrangement

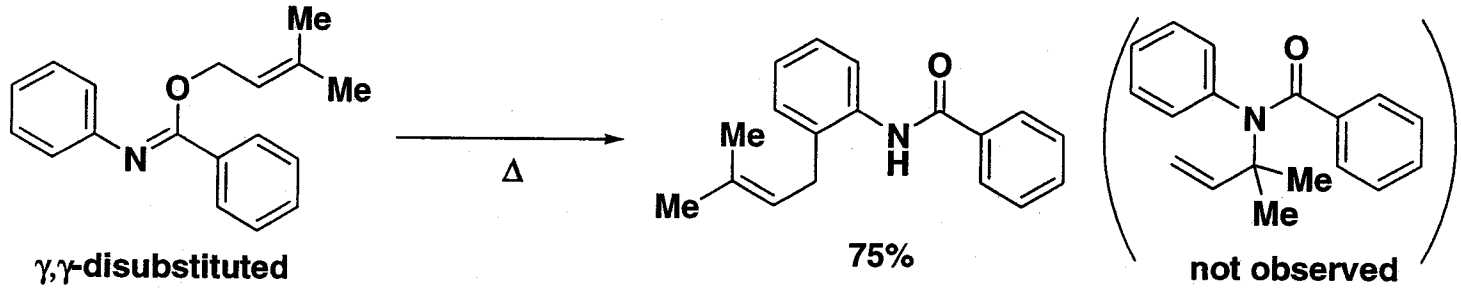
McCarty, C. G.; Garner, L. A. "The Chemistry of Amidines and Imidates"; Patai, S. ed.; Wiley: New York, 1975; Chapter 4.

Thermal Rearrangement of Allylic Imidates - Limitations

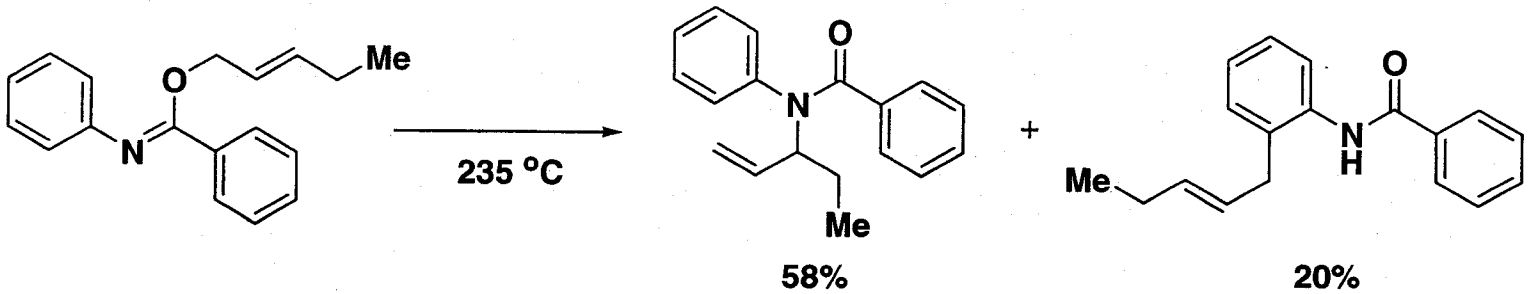
- Low yield preparation of allylic imidates:



- Steric limitations:



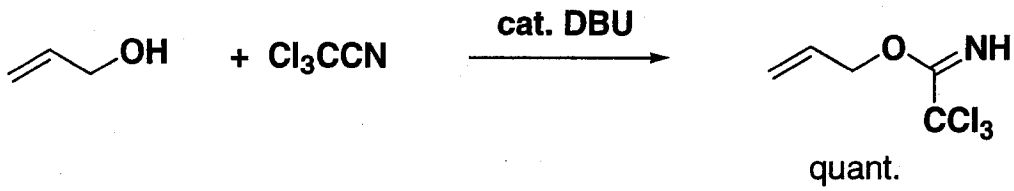
- Harsh reaction conditions:



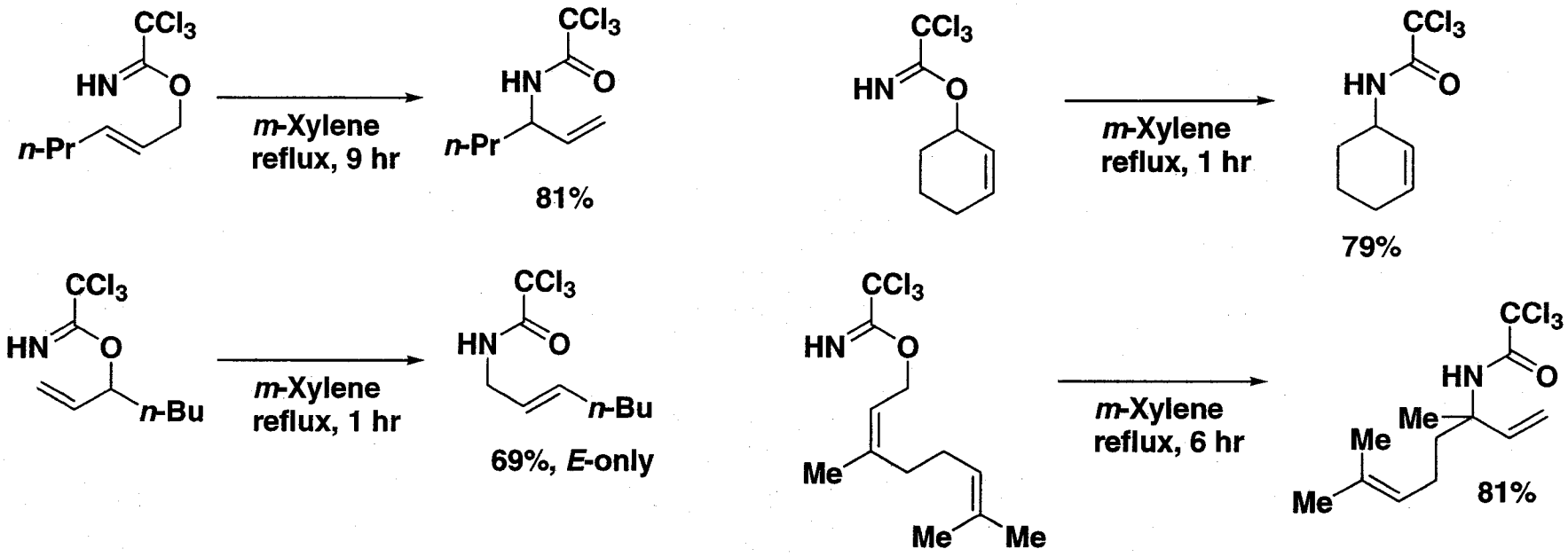
Lauer, W. M.; Lockwood, R. G. *J. Am. Chem. Soc.* **1954**, *76*, 3974.
Lauer, W. M.; Benton, C. S. *J. Org. Chem.* **1959**, *24*, 804.

Thermal Rearrangement of Allylic Trichloroacetimidates

- Preparation of trichloroacetimidate



- Rearrangement occur under milder conditions:

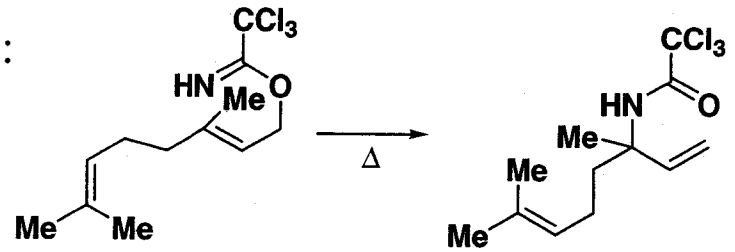


Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.
Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.

Mechanism for Thermal Rearrangement of Allylic Imidates

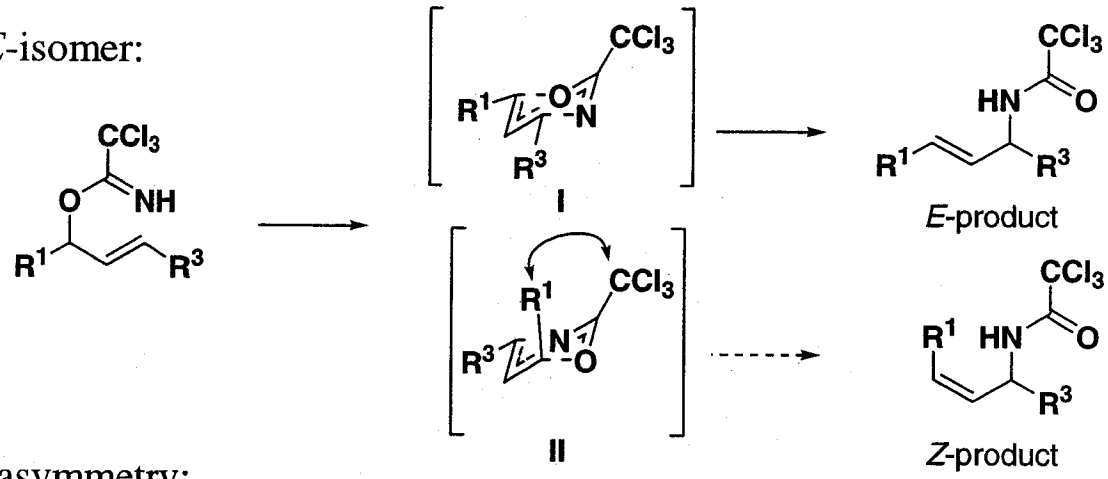
Evidence for concerted rearrangement mechanism

- Regiospecificity
- Kinetic parameters:

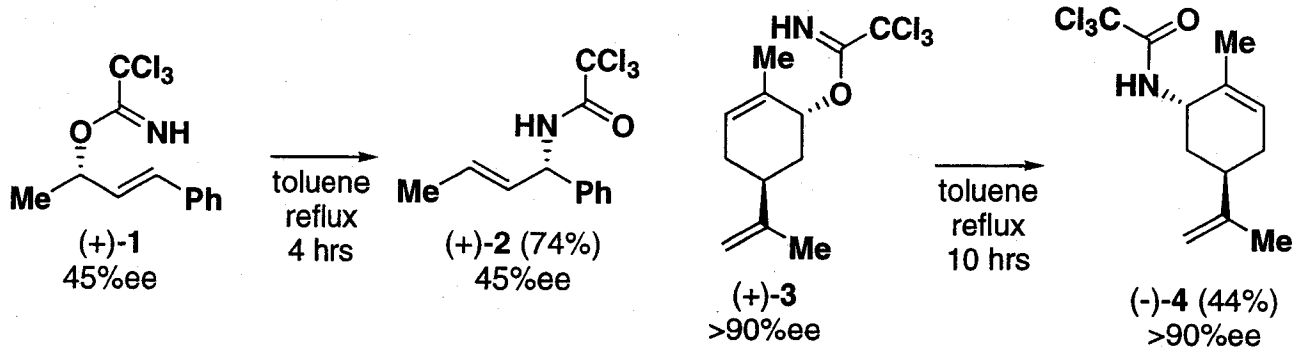


$\Delta H^{\ddagger}$ = 24 kcal/mol
$\Delta S^{\ddagger}$ = -19 eu

- Selective formation of *E*-isomer:



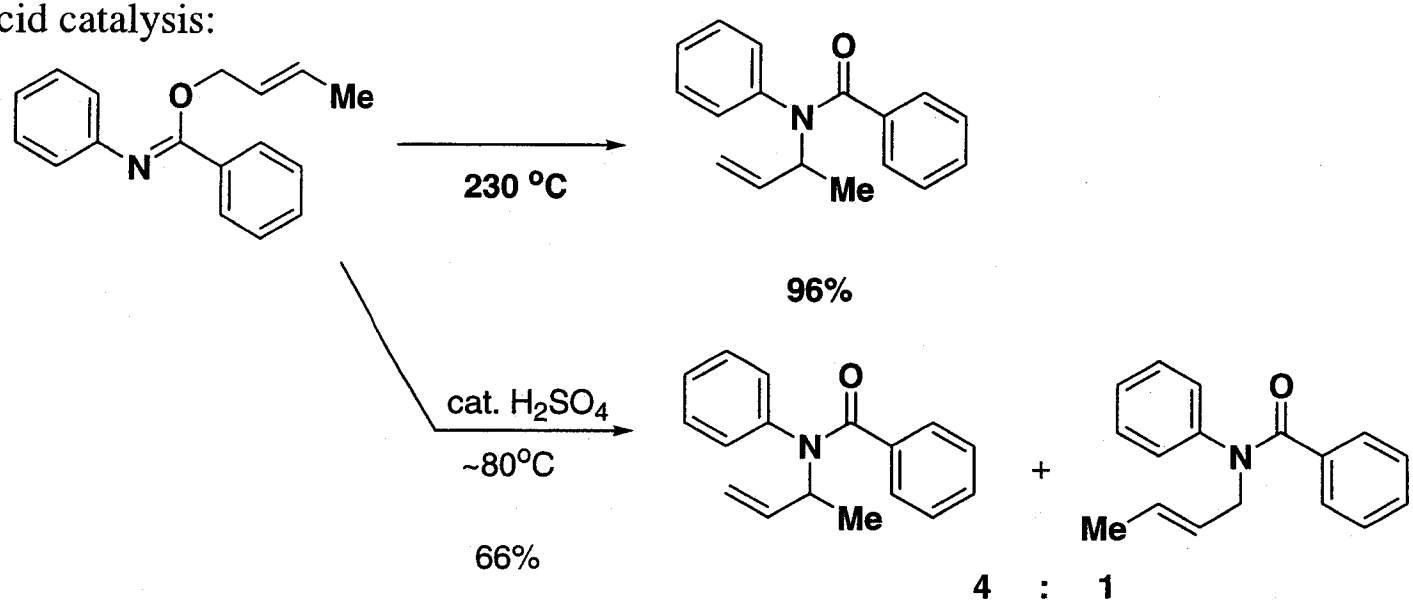
- Quantitative transfer of asymmetry:



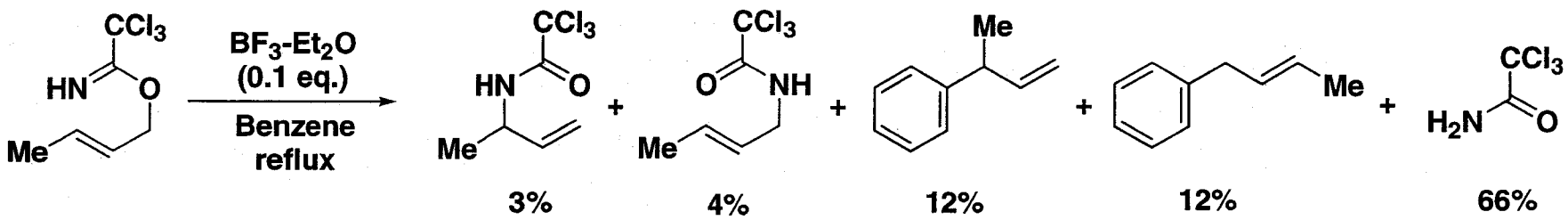
Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.
Yamamoto, Y.; Shimoda, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247.

Catalyzed Rearrangement of Allylic Imidates

- Bronsted acid catalysis:



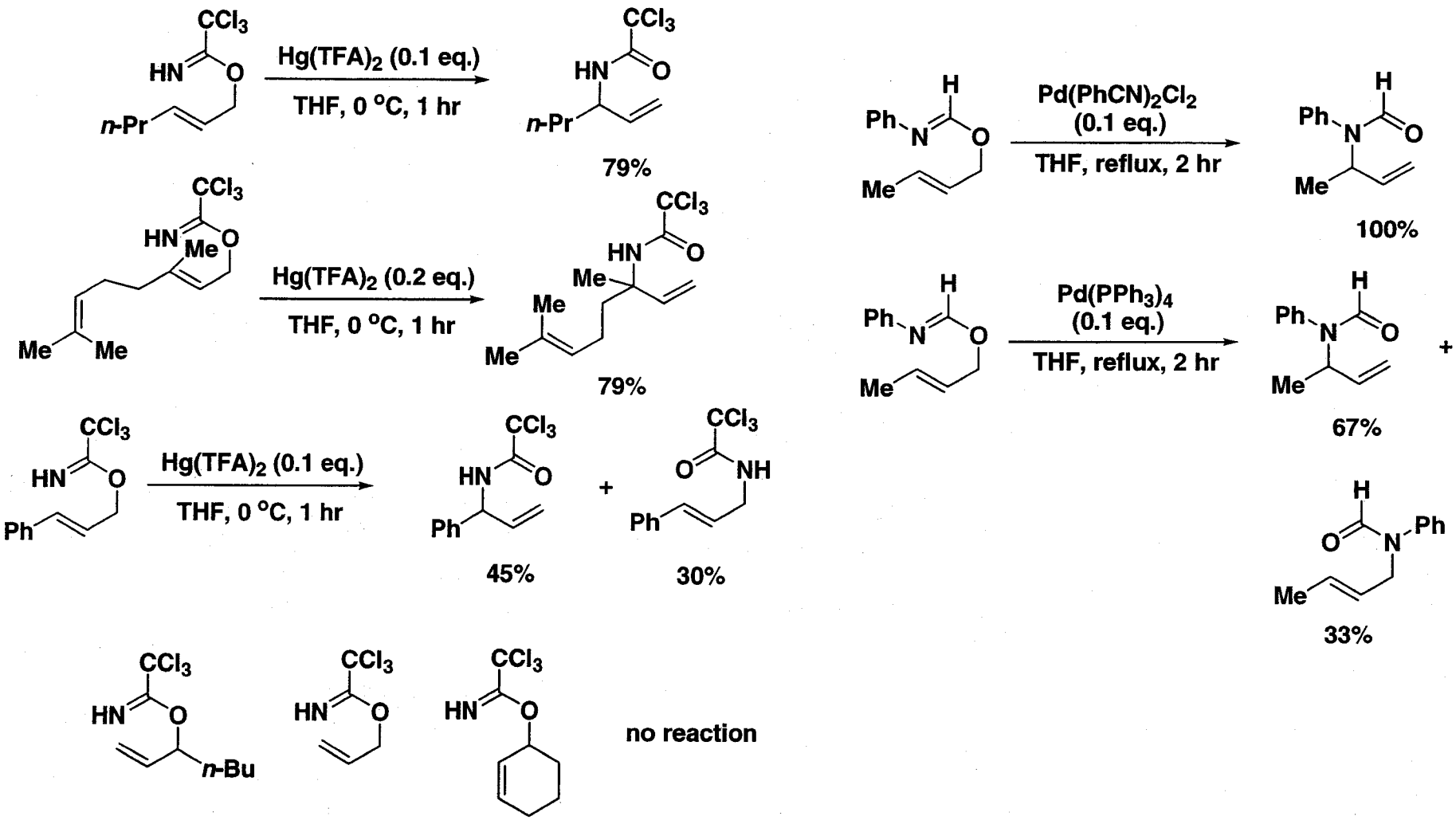
- Hard Lewis acid catalysis:



Roberts, R. M.; Hussein, F. A. *J. Am. Chem. Soc.* **1960**, *82*, 1950.
Cramer, F.; Hennrich, N. *Chem. Ber.* **1961**, *94*, 976.

Catalyzed Rearrangement of Allylic Imidates

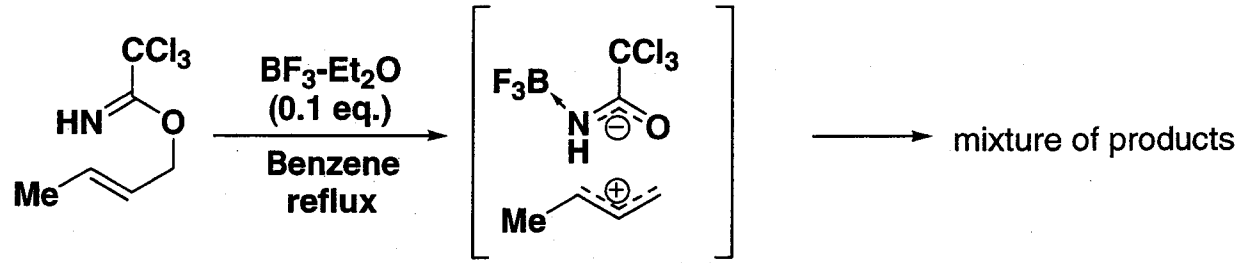
- Transition metal catalysis: soft metals (Hg(II) and Pd(II))

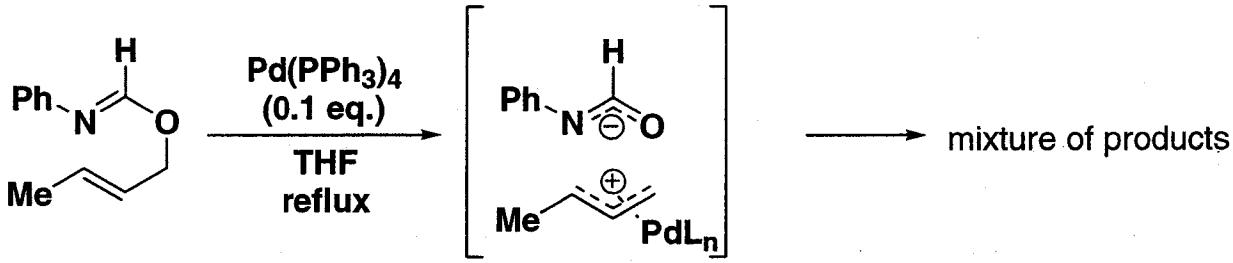


Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.
Ikariya, T.; Ishikawa, Y.; Hirai, K.; Yoshikawa, S. *Chem. Lett.* **1982**, 1815.

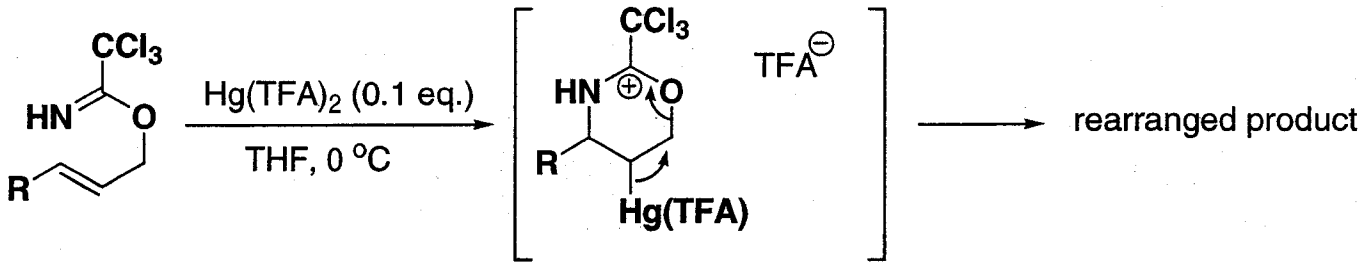
Mechanism for Catalyzed Rearrangements

- S_Ni mechanism:



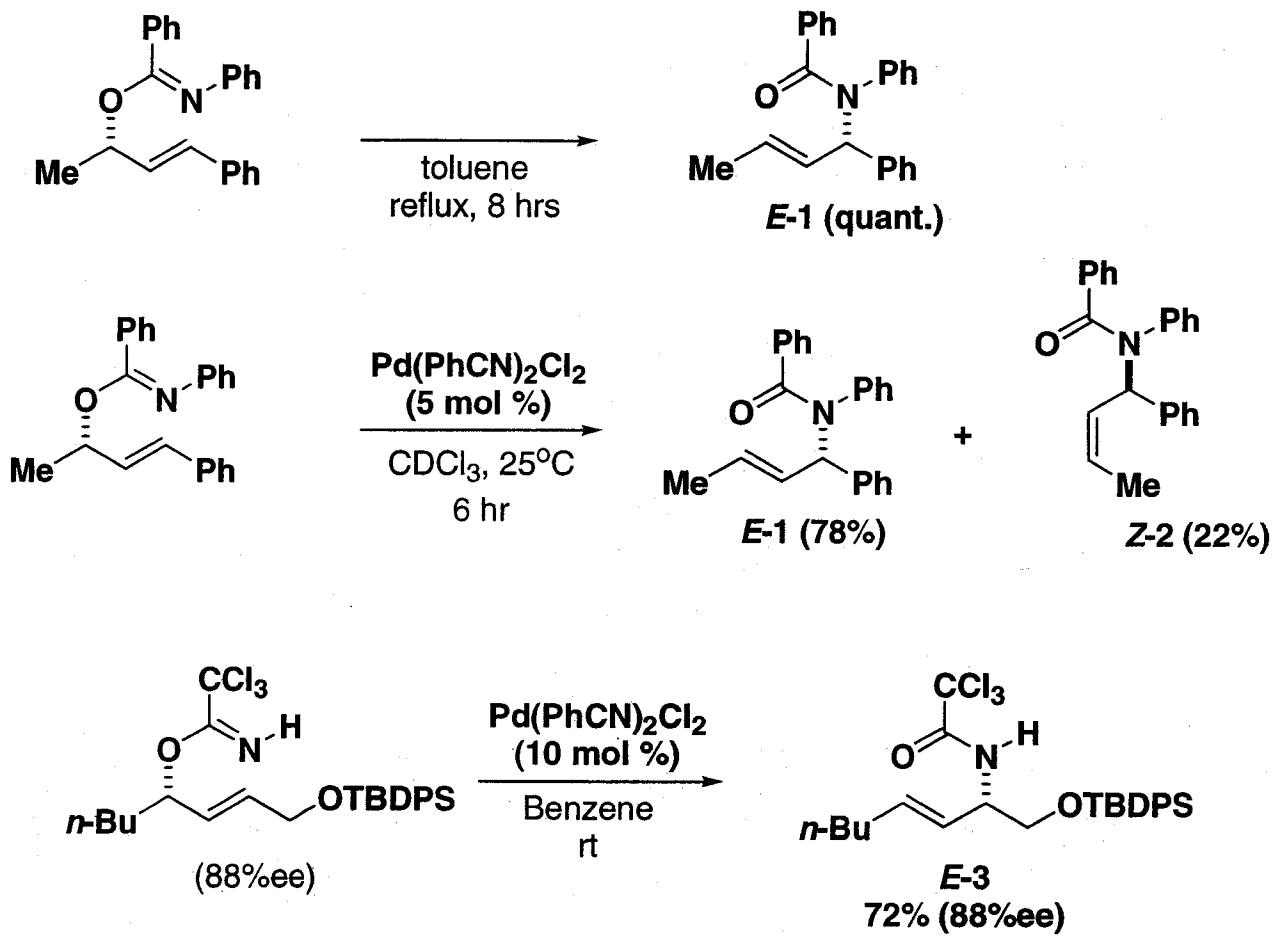


- Cyclization-induced rearrangement:



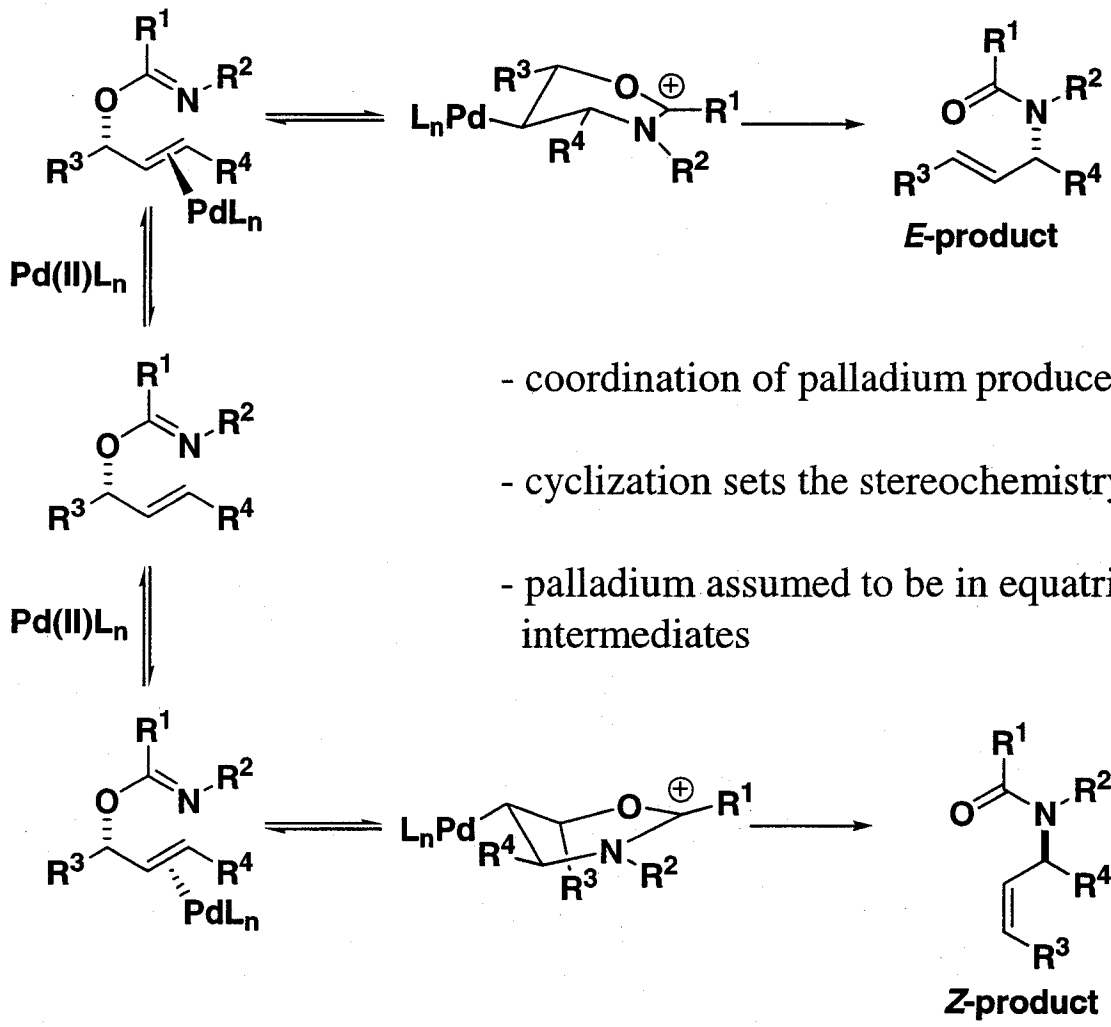
Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.
Yamamoto, Y.; Shimoda, H.; Oda, J.; Inouye, Y. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3247.

Catalyzed Rearrangement of Chiral Imidates



Schenk, T. G. Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058.
Mehmadoust, M.; Petit, Y.; Larchevique, M. *Tetrahedron Lett.* **1992**, *33*, 4313.

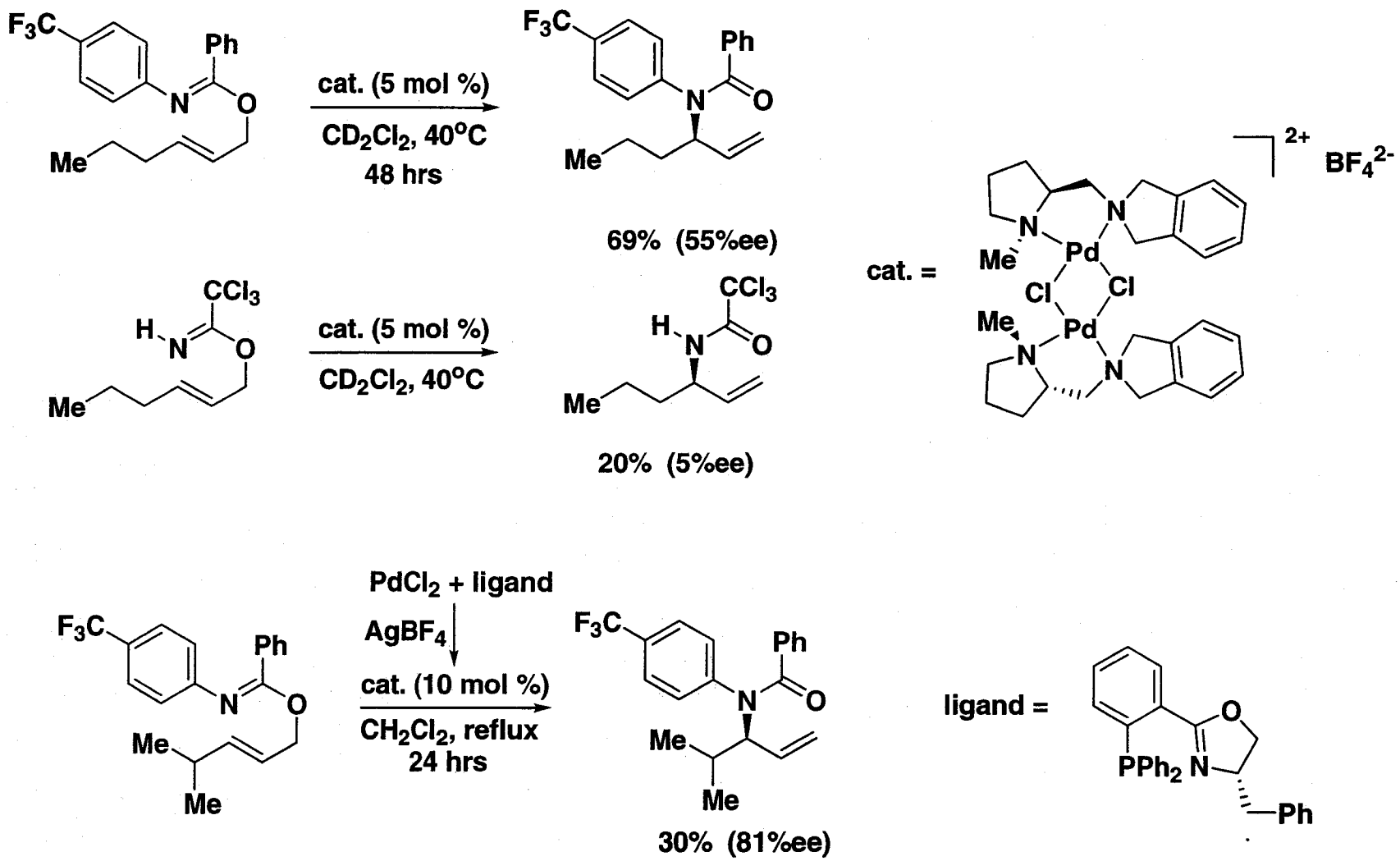
More Detailed Mechanism for Pd(II)-Catalyzed Rearrangement



- coordination of palladium produces two diastereomeric complexes
- cyclization sets the stereochemistry of the product
- palladium assumed to be in equatrial position in the charged intermediates

Schenk, T. G. Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058.
Mehmadoust, M.; Petit, Y.; Larchevique, M. *Tetrahedron Lett.* **1992**, *33*, 4313.

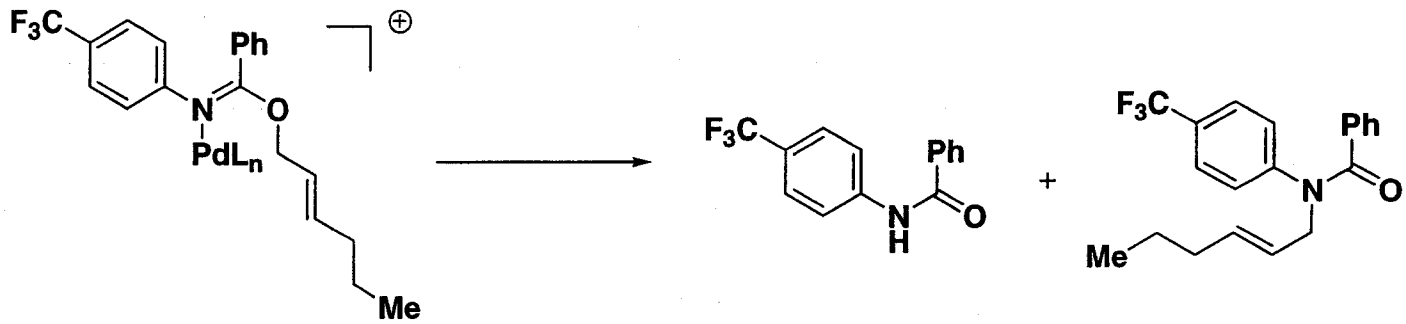
Quest for the Best Ligand – Cationic Palladium Catalysts



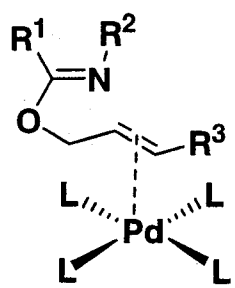
Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449.
Uozumi, Y.; Kato, K.; Hayashi, T.. *Tetrahedron Asymm.* **1998**, *9*, 1065.

Catalyst Design: Two Considerations

- Cationic palladium complex:
  - not a good catalyst compared to $PdCl_2(MeCN)_2$ (neutral catalyst)
  - Cationic complex responsible for competing side processes



- Better ligand:
  - should project steric bulk below and above the place of planar palladium complex



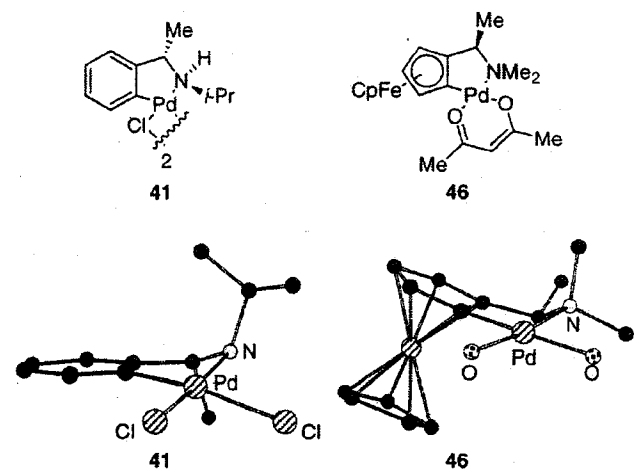
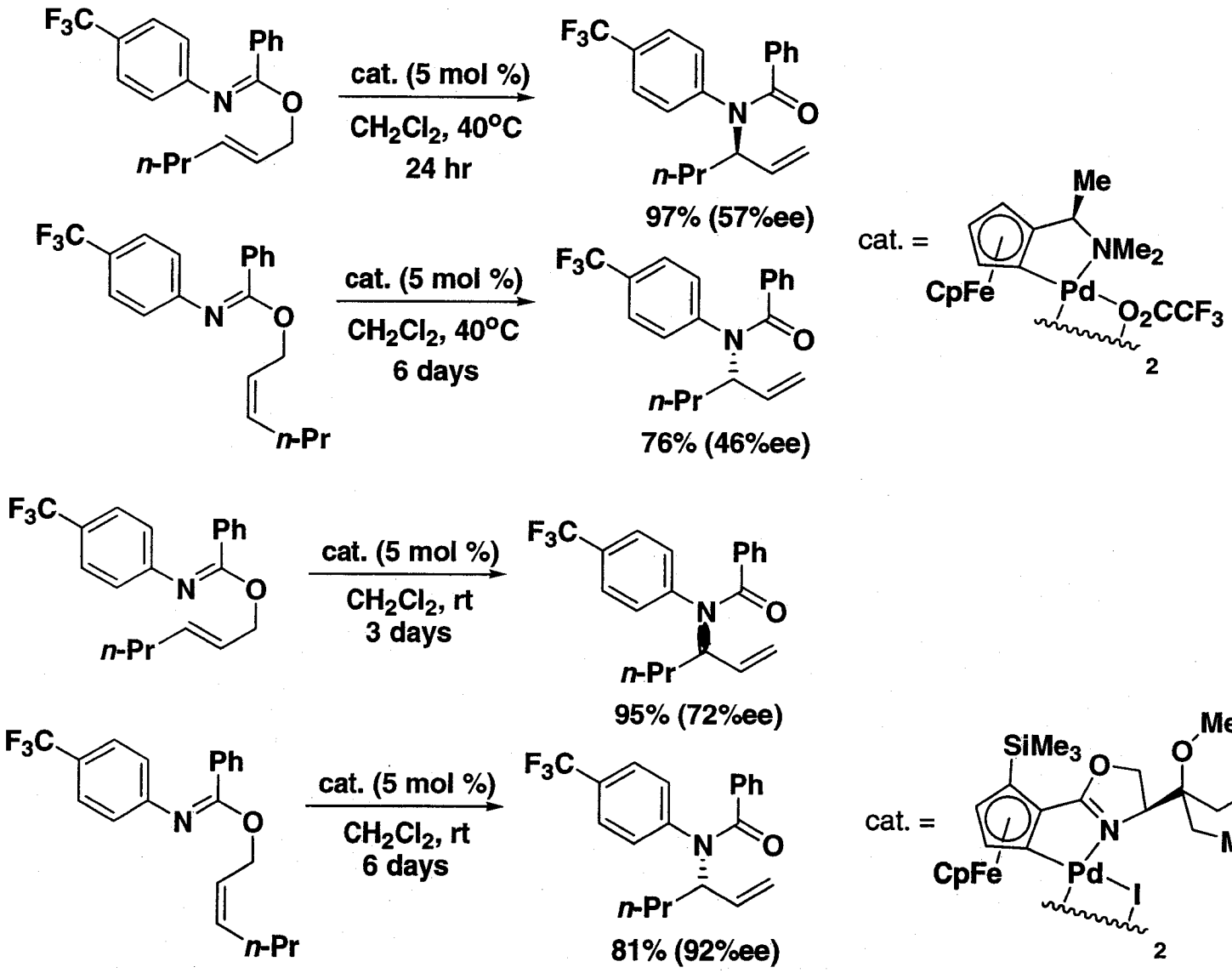


Fig. 1. Chemdraw and crystal structures of cyclopalladated complexes [12.28]. Hydrogens and parts of the structures are omitted for clarity.

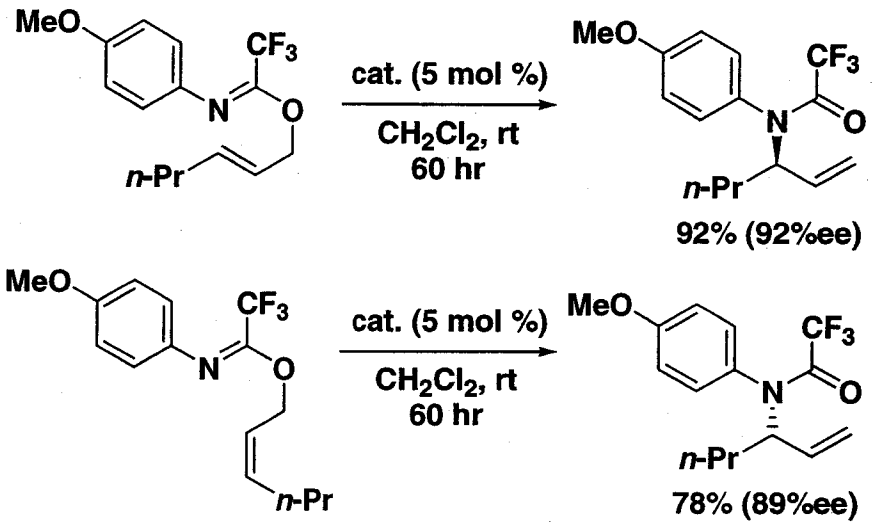
Hollis, T. E.; Overman, L. E. *J. Organometallic Chem.* **1999**, *576*, 290.

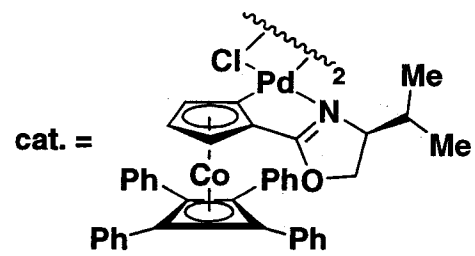
Quest for the Best Ligand – Neutral Palladium Catalysts



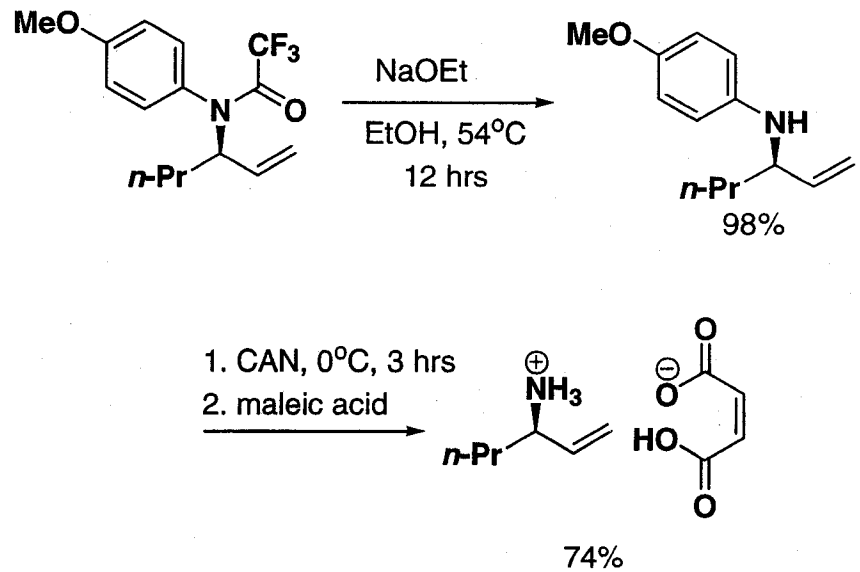
Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837.
Donde, Y.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933.

Rearrangement of *N*-*p*-Methoxyphenyl Imidate



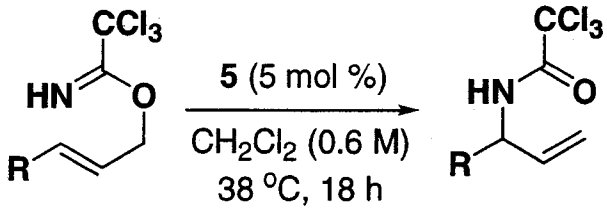


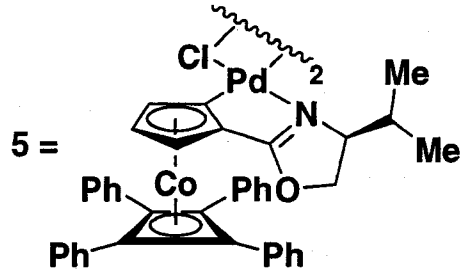
entry	R	*E*/*Z*	yield (%)	%ee/ config.
1	Me	*E*	85	82 / *S*
2	Me	*Z*	87	86 / *R*
3	CH_2CH_2Ph	*E*	86	93 / *S*
4	CH_2CH_2Ph	*Z*	99*	96 / *R*
5	*i*-Bu	*E*	88	94 / *S*
6	*i*-Bu	*Z*	58	90 / *R*



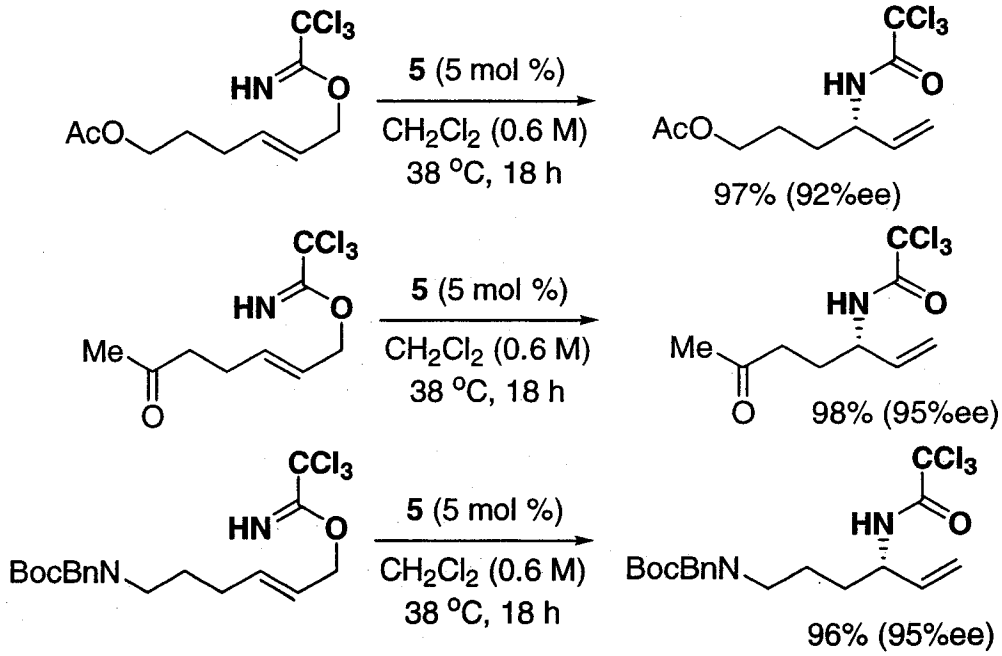
Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org Lett.* **2003**, *5*, 1809.

Catalytic Asymmetric Rearrangement using COP-Cl





entry	R	*E/Z*	yield (%)	%ee/ config.
1	*i*-Pr	*E*	99	95 / *S*
2	*i*-Pr	*Z*	17	71 / *R*
3	*i*-Bu	*E*	95	96 / *S*
4	*i*-Bu	*Z*	8	73 / *R*
5	Cyclohexyl	*E*	82	96 / *S*
6	Ph	*E*	13	nd
7	*t*-Bu	*E*	7	nd



Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412.

1,3-Interchange of Functionality

X, Y = C : Cope rearrangement, no functionality change

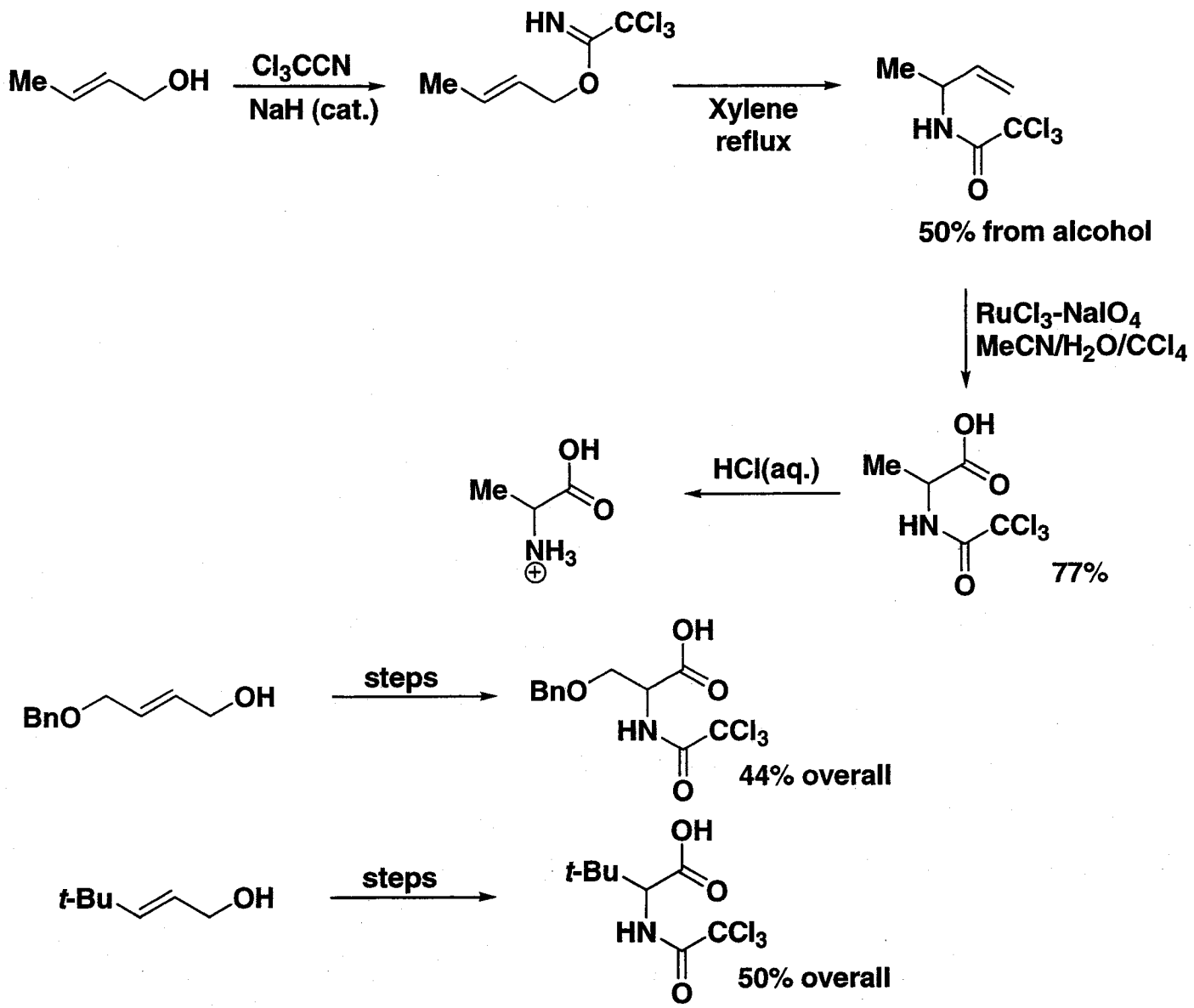
X = O, Y = C : Claisen rearrangement, functionality change from ether (C-O) to alkane (C-C)

X = O, Y = N: Rearrangement of Allylic Imidate, functionality change from alcohol (C-O) to amine (C-N)
When Z = CCl_3 : (so called) Overman rearrangement

Can rearrangements of allylic imidates be useful for allyl amine synthesis?

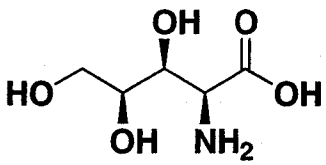
Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.
Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.

Amino Acid synthesis

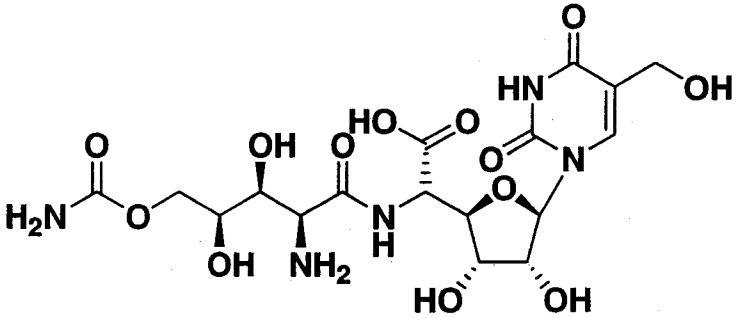


Takano, S.; Akiyama, M.; Ogasawara, K. *J. Chem. Soc. Chem. Commun.* **1984**, 770.

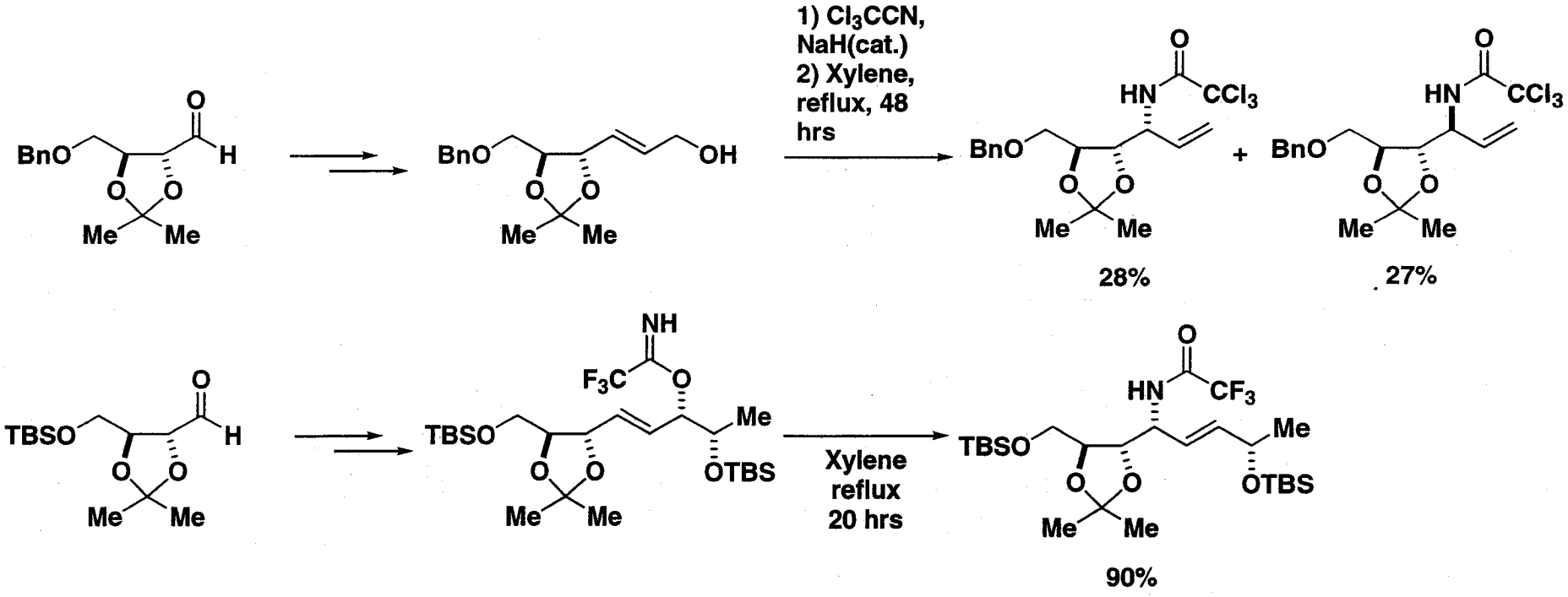
Synthesis of Polyoxamic Acid



(+)-polyixamic acid

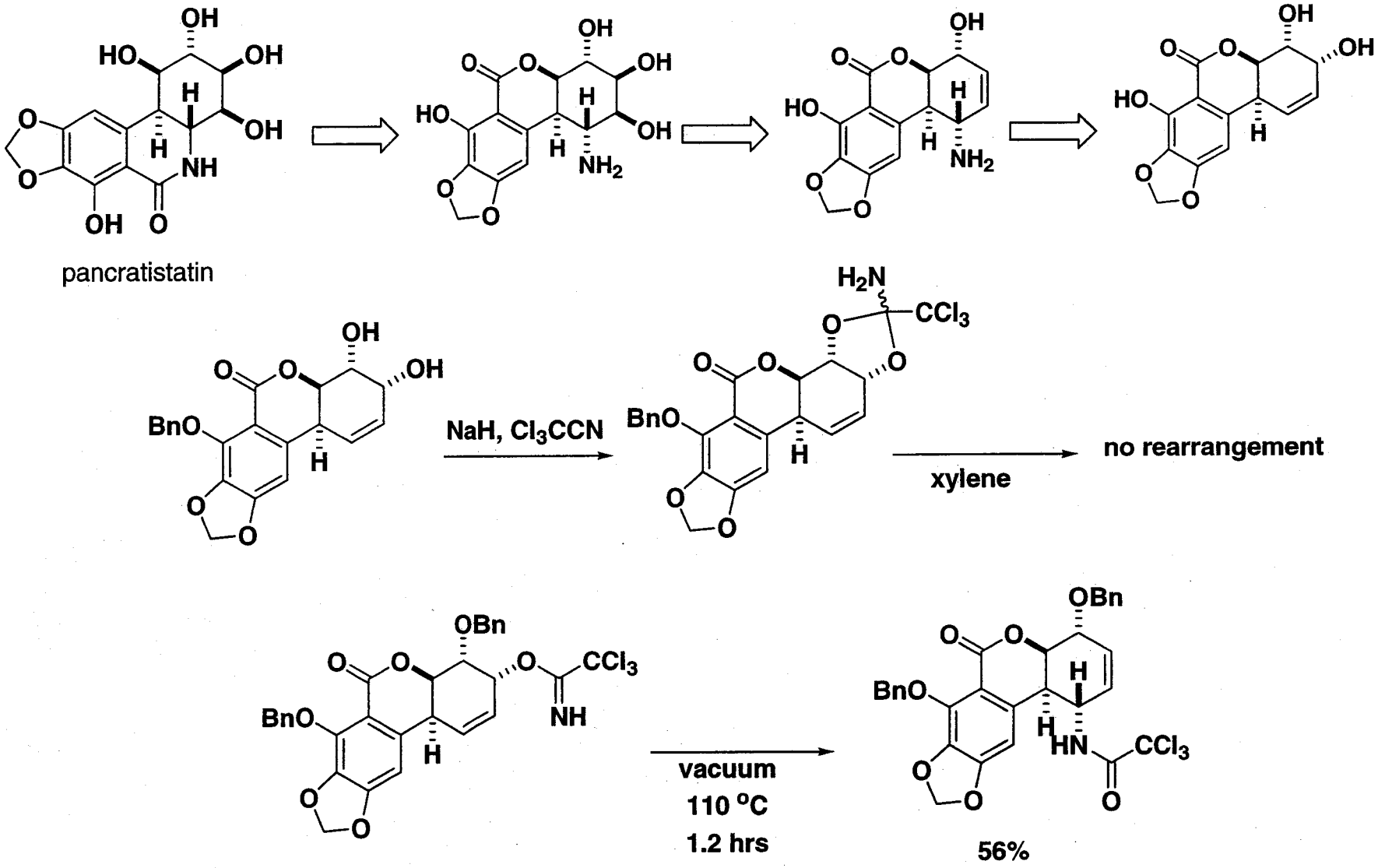


polyoxin B



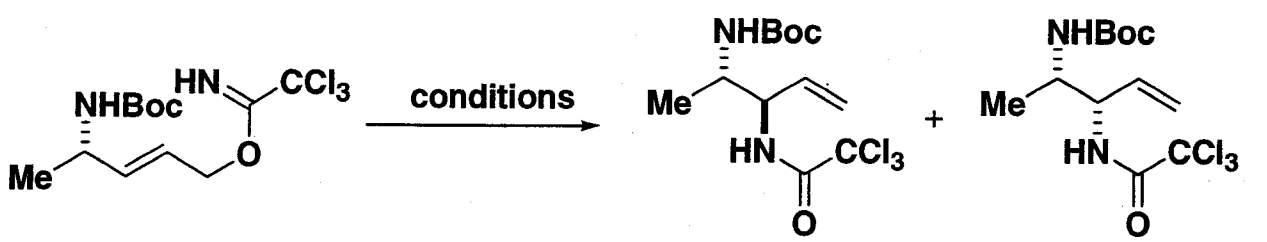
Saksena, A. K.; Lovey, R. G.; Girijavallabhan, V. M.; Ganguly, A. K.; McPhail, A. T. *J. Org. Chem.* **1986**, *51*, 5024.
Savage, I.; Thomas, E. J. *J. Chem. Soc. Chem. Commun.* **1989**, 717.

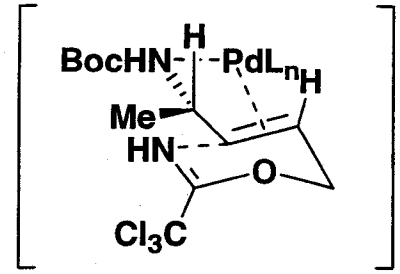
Synthesis of Pancratistatin



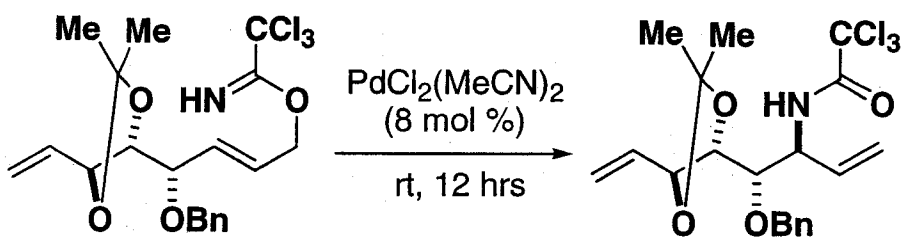
Danishefsky, S.; Lee, J. Y. *J. Am. Chem. Soc.* **1989**, *111*, 4829.

Catalyzed Rearrangements





conditions	yield	anti/syn
xylene, 140°C, 24 hrs	85%	62/38
$Pd(MeCN)_2Cl_2$ (6-8mol%), rt, 3hrs	48%	>99/1

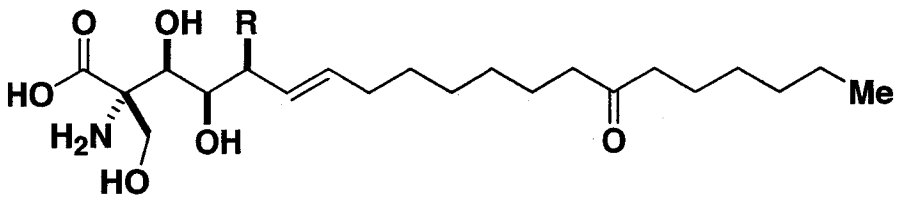


73%

- Under catalyzed conditions, elimination of imidate moiety becomes competitive
- Excellent substrate control by neighboring heteroatom can be achieved

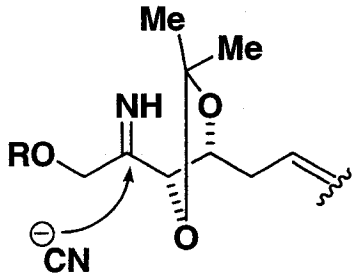
Gonda, J.; Helland, J.-C.; Ernst, B.;Bellus, D. *Synthesis*, **1993**, 729.
Van Boom, J. H. *et. al. Tetrahedron Lett.* **1999**, *40*, 5063.

Synthesis of Myriocin and Sphingofungin E



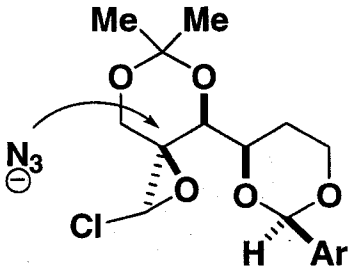
R = H: Myriocin
R = OH: Sphingofungin E

Strecker synthesis



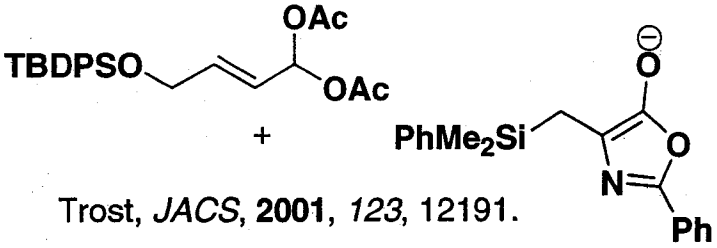
Just and Payette, *TL*, **1980**, *21*, 3219.

Epoxide opening



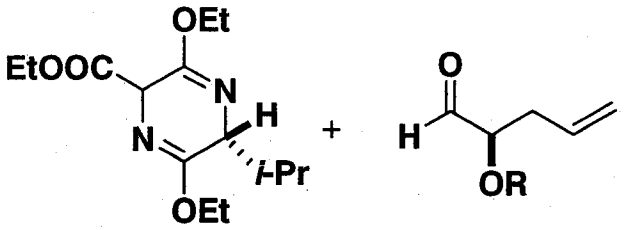
Yoshikawa, *Tetrahedron*, **1995**, *51*, 6209.

Pd-catalyzed asymmetric alkylation



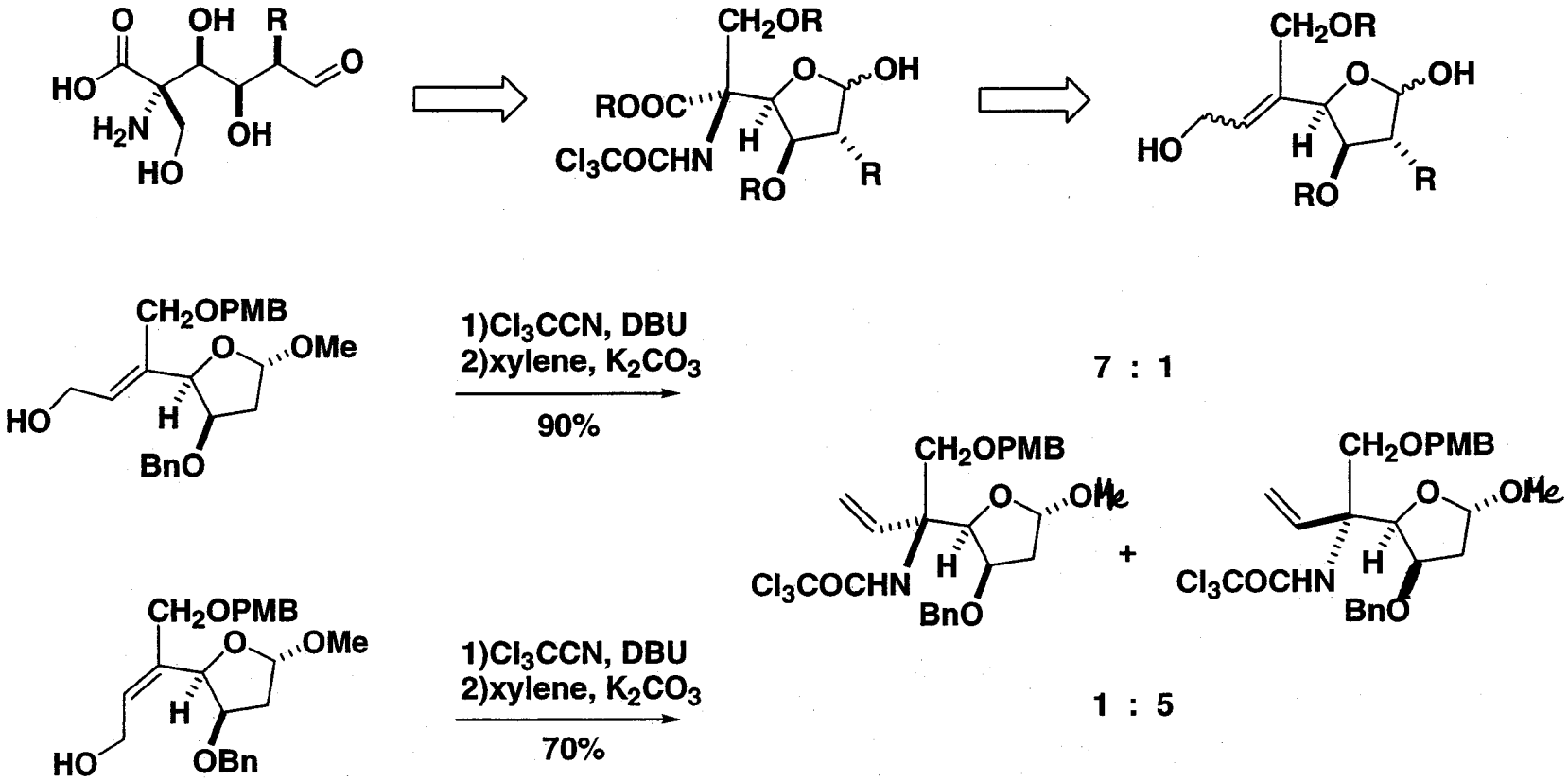
Trost, *JACS*, **2001**, *123*, 12191.

Aldol



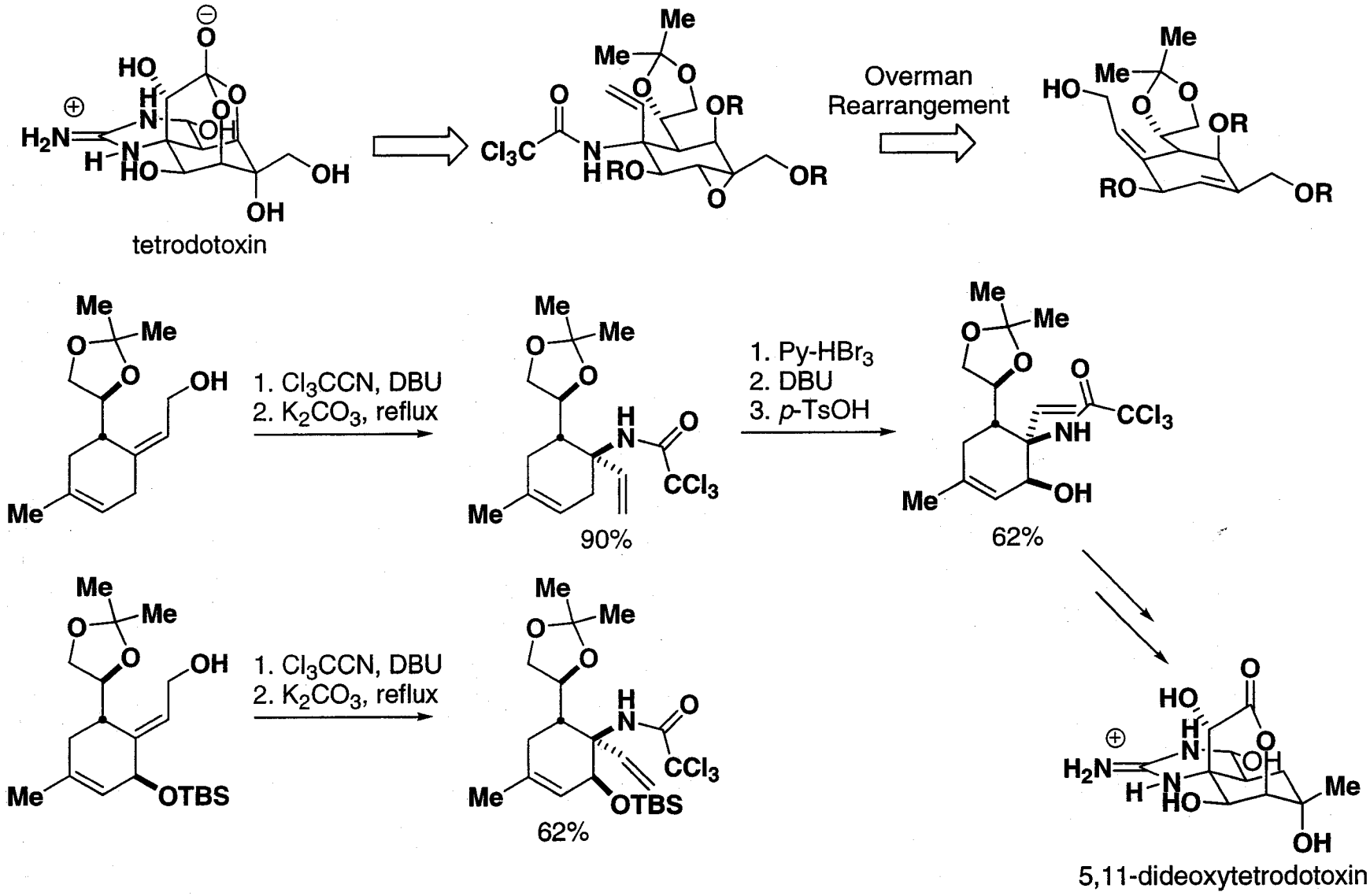
Nagao, *TL*, **1995**, *36*, 2097.

Synthesis of Myriocin and Sphingofungin E



Chida, N. *et. al. Bull Chem. Soc. Jpn.* **2002**, *75*, 1927.

Synthesis of Tetrodotoxin-type Compounds



Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J.Org. Chem.* **1998**, *63*, 188.
Nishikawa, T.; Asai, M.; Ohyabu, N.; Yamamoto, N.; Isobe, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3081.

Conclusion

- Imidate chemistry has a long history
- Allylic imidates can be prepared readily from allylic alcohols
- Rearrangement of trichloroacetimidates is a practical method for preparing allylic amines
    - Predictable stereochemistry for thermal rearrangement
    - Good enantioselectivities using chiral ligand for palladium under catalyzed conditions