Universität Konstanz

Isocyanate Chemistry

Ueber die Verbindungen der Cyanursäure und Cyansäure mit Aethyloxyd, Methyloxyd, Amyloxyd und die daraus entstehenden Producte; Acetyl- und Metacetylharnstoff, Methylamin, Aethylamin, Valeramin;
von *Adolph Wurtz* *).

Christa Gerlinger, Gaich Group Seminar, 19.07.2017

Isocyanate: History, physical- and chemical data

History

• first synthesis of an organic isocyanate reported in 1848 by Adolf Wurtz

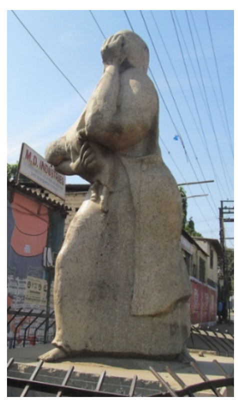
> Man erhält cyanursaures Aethyloxyd, wenn man alkalisch reagirendes cyanursaures Kali mit schwefelweinsaurem Kali im Oelbade destillirt. In dem Hals der Retorte und in der Vorlage condensirt sich das Product in der Form einer krystallinischen Masse, welche man durch wiederholtes Auflösen in Alkohol reinigt, woraus beim Erkalten sehr glänzende prismatische Krystalle sich ausscheiden.

A. von Wurtz, *Justus Liebigs Ann. Chem.* **1849**, *71*, 326–342

• commercially important synthesis by phosgenation of amines and amides discovered 1884 by W. Hentschel

• Since 1930 commercially polyurethane production discovered by O. Bayer at the I.G. Farben laboratories in Leverkusen

• Bhopal disaster 1984: Over half a million people exposed to MIC-Methly-Isocyanate. Over 5000 deaths, rest injured.



Physical Properties

• colourless liquids or low melting solids

• IR: 2300 to 2250 cm^{-1}

• ^{13}C: 115-135 ppm

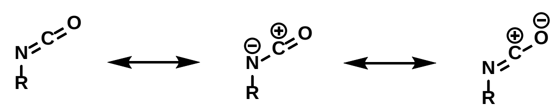
Chemical Properties

• versatile reactivity due to its electronic structure

• reaction with various nucleophiles; steric hindrance influences rate of reaction: primary > secondary > tertiary

• reaction with various electrophiles

• various addition, cycloaddition and insertion reactions along the N-C-bond

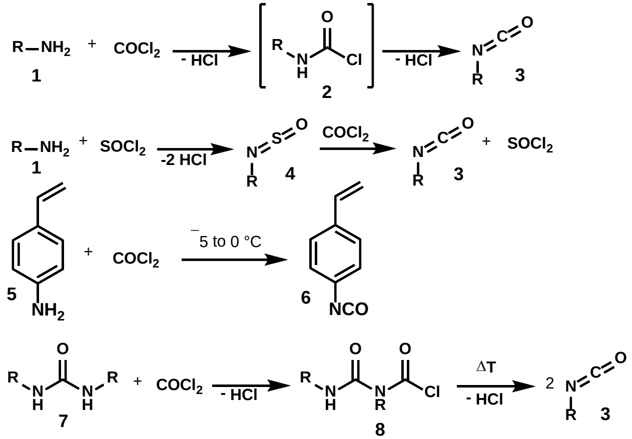


Syntheses of Isocyanates

1 Phosgenation reactions

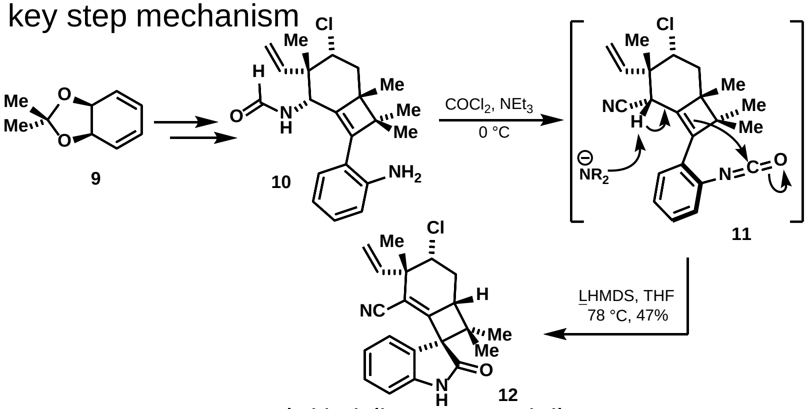
- Disadvantage: high toxicity
- Advantage: very clean reaction, merely no side products

- Reaction with amines



S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

Application in the Total Synthesis of Welwitindolinone A
- key step mechanism

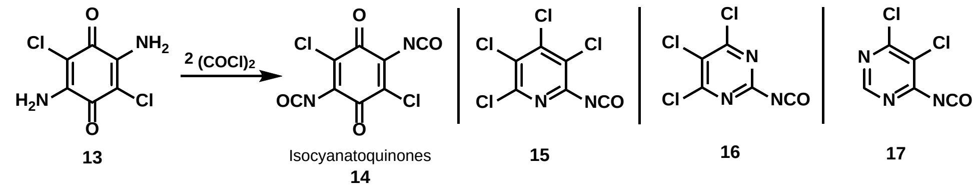


Welwitindolinone A-Isonitrile

S. E. Reisman, J. M. Ready, A. Hasuoka, C. J. Smith, J. L. Wood, *J. Am. Chem. Soc.* **2006**, *128*, 1448–1449.

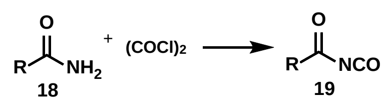
2 Reaction of amines and amides

- Reaction of oxalyl chloride with amines

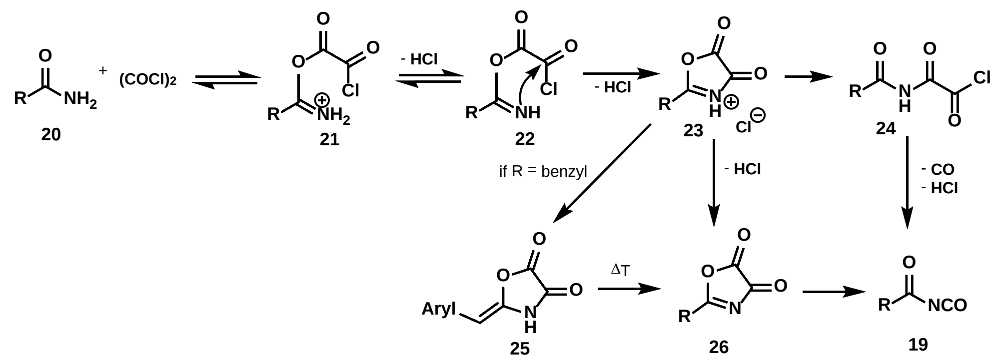


S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

- Reaction of amides with oxalyl chloride to deliver acyl isocyanates

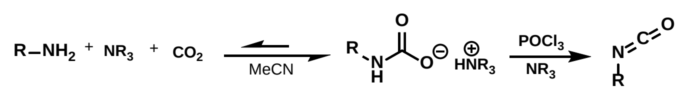


proposed mechanism



A. J. Speziale, L. R. Smith, *J. Org. Chem.* **1963**, *28*, 1805–1811

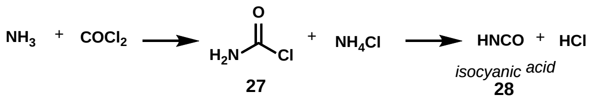
- Reaction of primary amines with amine bases and CO_2



T. E. Waldman, W. D. McGhee, *J. Chem. Soc. Chem. Commun.* **1994**, 957

Syntheses of Isocyanates

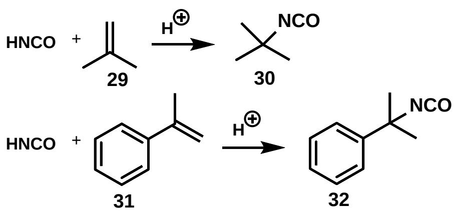
3 From isocyanic acid



H. S. Rothrock, **1964**, *111*, 3–5

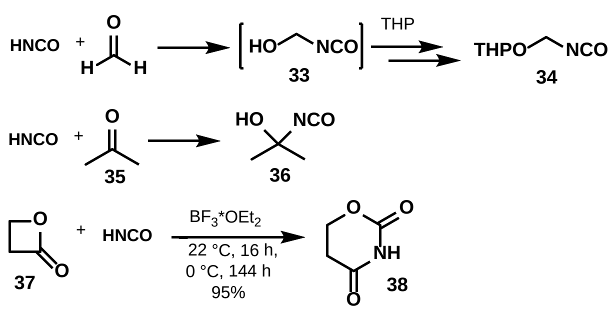
3a Reaction with Olefins

- exo-Methylene most reactive
- major drawback: harsh conditions, trimerization of isocyanic acid, polymerization of olefins
- ionizable H-N bond makes HNCO behave like pseudo hydrogen halide



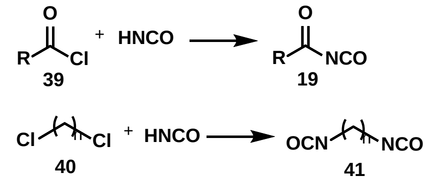
H. S. Rothrock, **1964**, *111*, 3–5

3b Reaction with Carbonyls



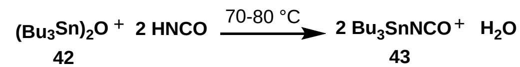
H. S. Rothrock, **1964**, *111*, 3–5

3c Reaction with Acid Chlorides and Alkyl Chlorides



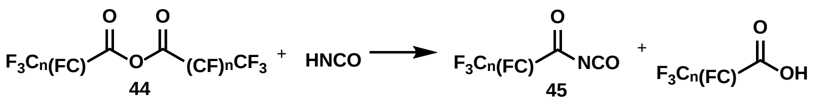
S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

3d Reaction with Organometal Oxides



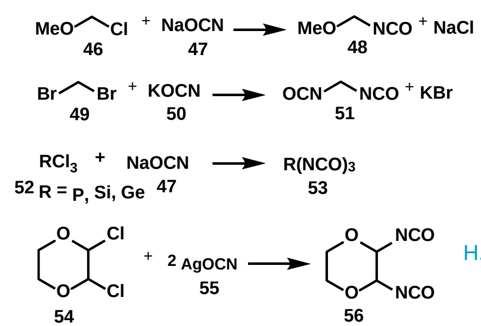
S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

3e Reaction with Acid Anhydrides



S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

3f Reaction of Alkylhalides with Alkali Cyanates

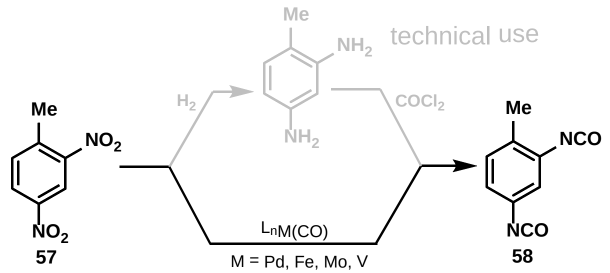


H. S. Rothrock, **1964**, *111*, 3–5

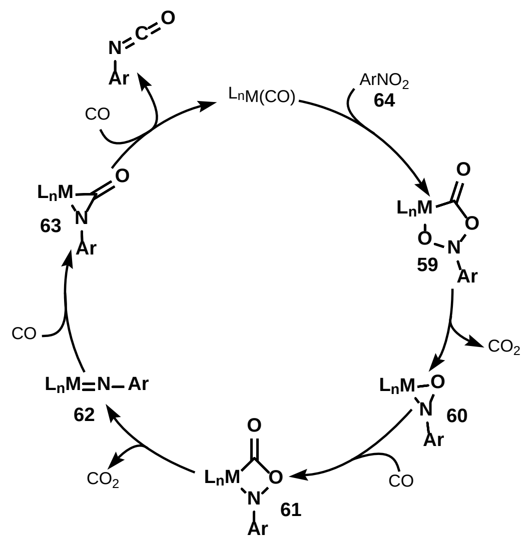
S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

Syntheses of Isocyanates

4 Reduction of Nitrocompounds with "CO"

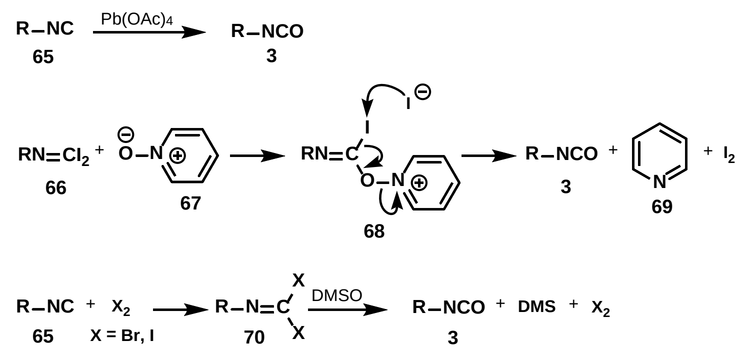


Proposed mechanism:

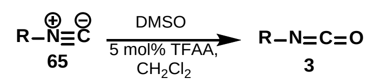


A. M. Tafesh, J. Weiguny, *Chem. Rev.* **1996**, *96*, 2035–2052

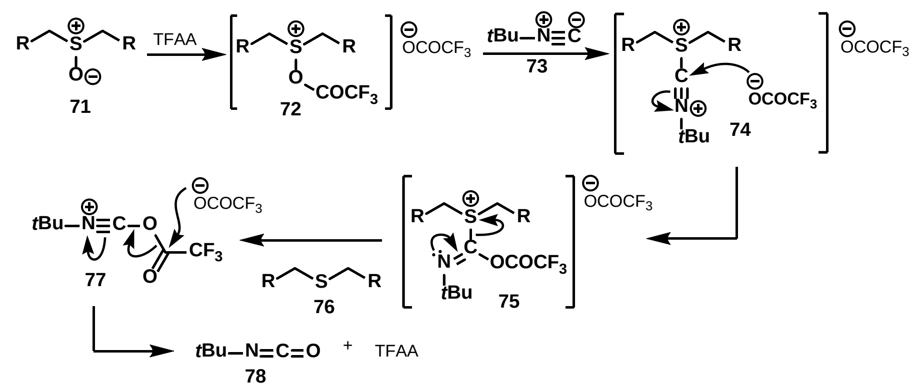
5 Oxidation of Isonitriles



S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496



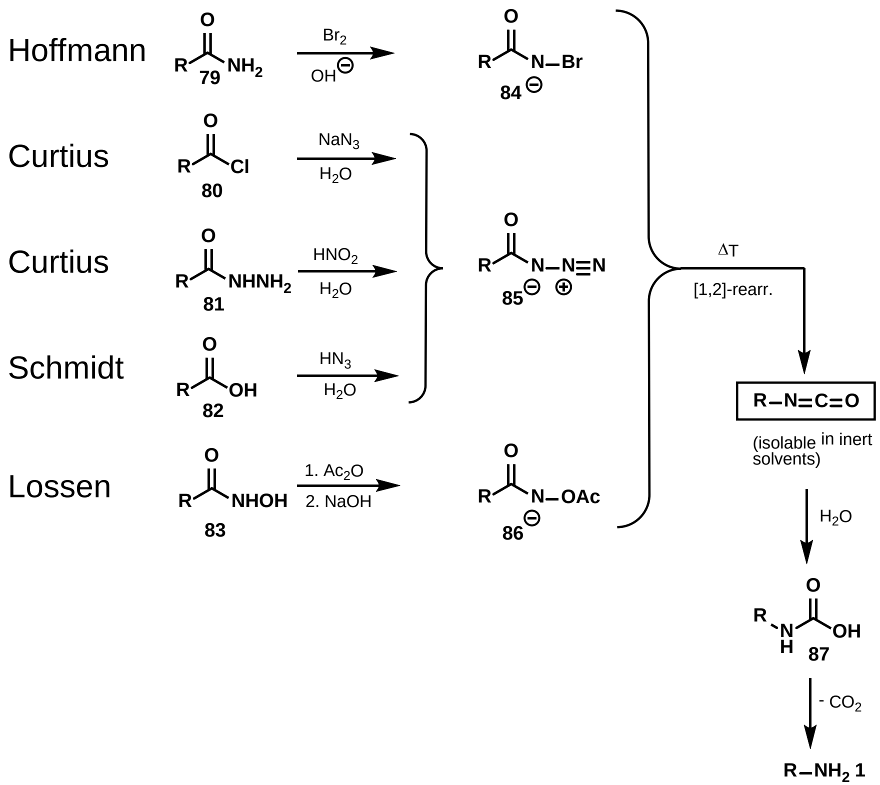
Proposed mechanism for the Oxidation of Isonitriles by Sulfoxides with TFAA:



H. V. Le, B. Ganem, *Org. Lett.* **2011**, *13*, 2584–2585

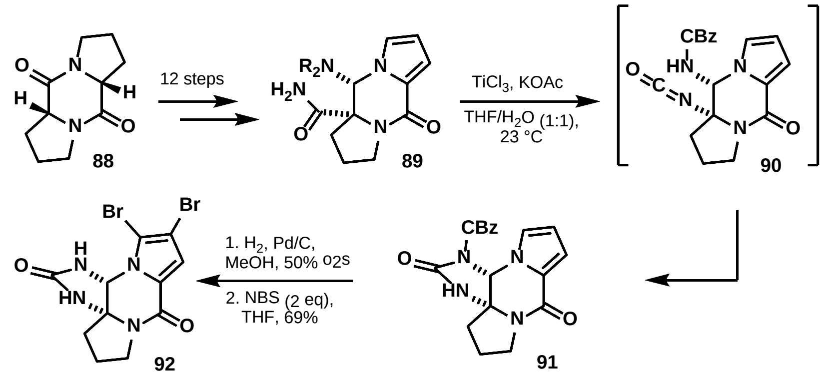
Syntheses of Isocyanates

7 Rearrangement Reactions



Slocombe *Chem. Rev.*, **1948**, *43* (2), pp 203–218

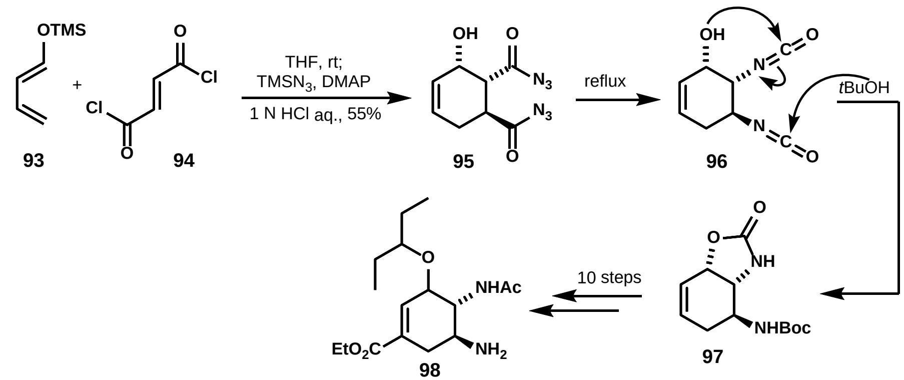
Application of the Hofmann rearrangement in the Total Synthesis of (+)-Dibromophakellstatin - key step mechanism



(+)-Dibromophakellstatin

D. Romo *J. Am. Chem. Soc.*, **2003**, *125* (21), pp 6344–6345

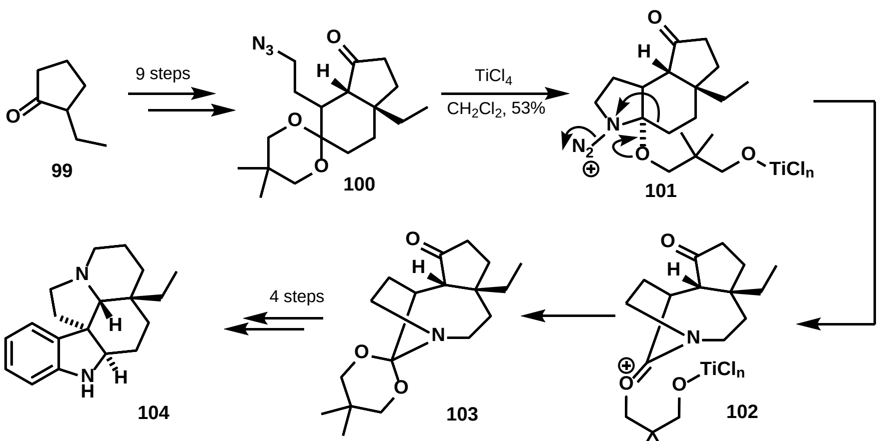
Application of the Curtius rearrangement in the Total Synthesis of Tamiflu - key step mechanism



Tamiflu

K. Yamatsugu, S. Kamijo, Y. Suto, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2007**, *48*, 1403–1406

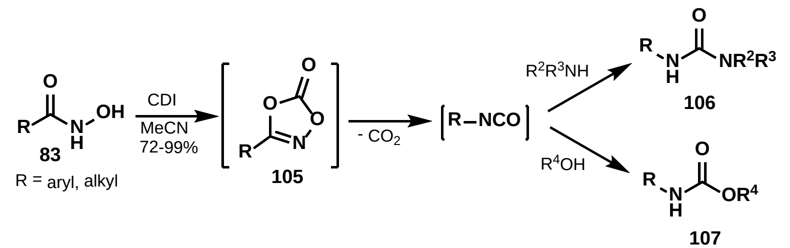
Application of the Schmidt rearrangement in the Total Synthesis of (+)-Aspidospermidine - key step mechanism



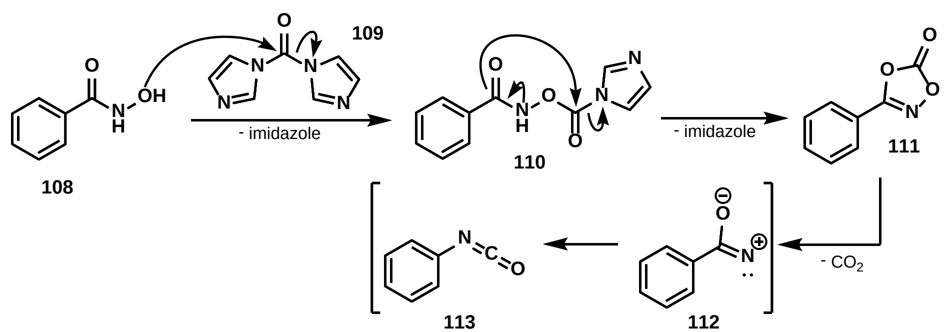
(+)-Aspidospermidine

R. Iyengar, K. Schildknegt, J. Aubé, *Org. Lett.* **2000**, *2*, 1625–7

Carbonyldiimidazole-mediated Lossen-rearrangement



proposed mechanism:

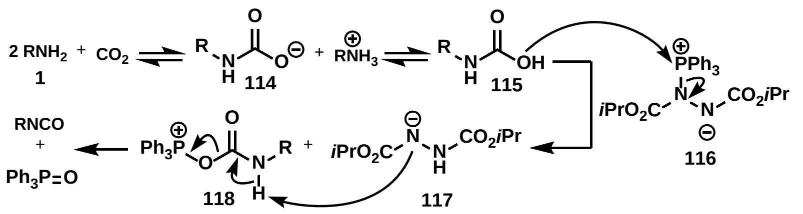


P. Dubé, N. F. Fine Nathel, M. Vetelino, M. Couturier, C. L. Aboussafy, S. Pichette, M. L. Jorgensen, M. Hardink, *Org. Lett.* **2009**, *11*, 5622–5625

Syntheses of Isocyanates

8 More phosgene-free preparation methods

8a Isocyanate formation using Mitsunobu Chemistry



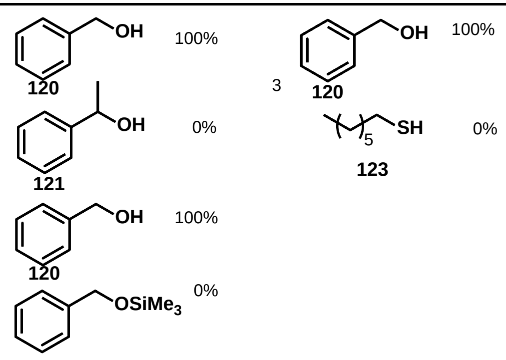
D. Saylik, M. J. Horvath, P. S. Elmes, W. R. Jackson, C. G. Lovel, K. Moody, *J. Org. Chem.* **1999**, *64*, 3940–3946

8b Alkyl isocyanates from Alcohol, Thiol, TMS-Ethers

R–X (**119**) —[PPh$_3$, DDQ, Bu$_4$NOCN; 54-98%]→ R–NCO

X = OH, SH, OSiMe$_3$

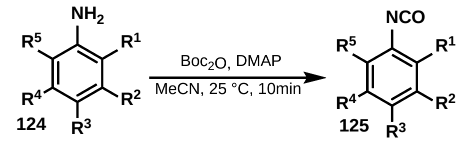
R = prim., second., tert.- alkyl



Entry	Substrate	Conversion	Entry	Substrate	Conversion
1	**120**	100%	3	**120**	100%
	121	0%		**123**	0%
2	**120**	100%			
	122	0%			

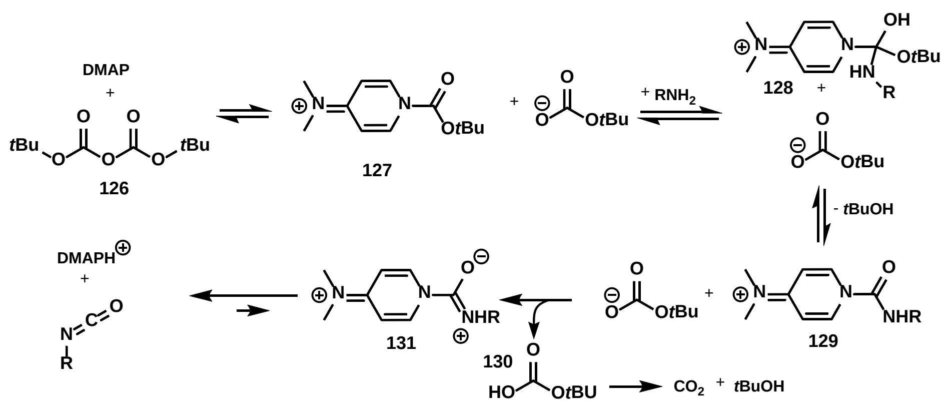
B. Akhlaghinia, S. Samiei, *Turkish J. Chem.* **2007**, *31*, 35–43

8c Mild phosgene free synthesis of isocyanates



R^1	R^2	R^3	R^4	R^5	Yield [%]
Me	H	Me	H	Me	96
Me	H	H	H	Me	94
*i*Pr	H	H	H	*i*Pr	99
OMe	H	OMe	H	OMe	97
Me	H	H	H	H	44
OMe	H	H	H	H	86
OMe	H	Me	H	H	88
OMe	H	OMe	H	H	76
Me	H	OMe	H	H	58
Me	Me	OMe	H	H	89
Ch	Ch	OMe	H	H	42
H	H	OMe	H	H	41

Proposed Mechanism:

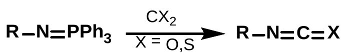


H. J. Knolker, T. Braxmeier, G. Schlechtingen, *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2497–2500

Syntheses of Isocyanates

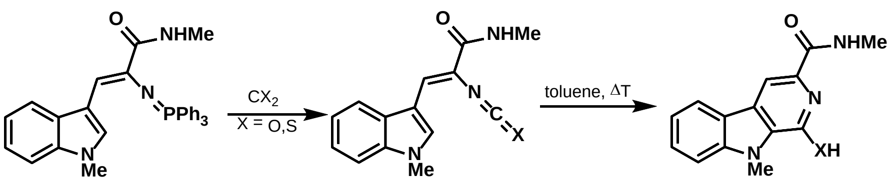
9 The Staudinger-Aza-Wittig Reaction

Main advantage: replacement of toxic phosgene by CO_2 (nontoxic, abundant, economical)



9a Aza-Wittig/intramolecular electrocyclic ring closure

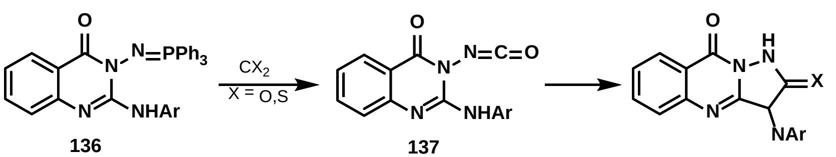
Synthesis of ß-carbolines



132 133

134 X = O (80%)
135 X = S (90%)

Synthesis of 1,2,4-triazolo[5,1-*b*]quinazolin-9(3*H*)-ones



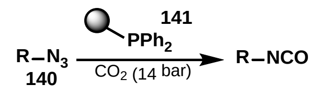
136 137

138 X = O (43%)
139 X = S (83-87%)

F. Palacios, C. Alonso, D. Aparicio, G. Rubiales, J. M. de los Santos, *Tetrahedron* **2007**, *63*, 523–575

9b Microwave assisted Staudinger-Aza-Wittig-Reaction

• polymer-bound diphenylphosphine (advantage: easily removable by filtration)

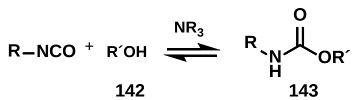


R = Alkyl, Aryl, Arylether

D. Carnaroglio, K. Martina, G. Palmisano, A. Penoni, C. Domini, G. Cravotto, *Beilstein J. Org. Chem.* **2013**, *9*, 2378–2386

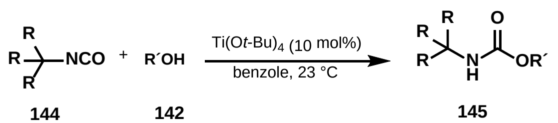
Reactions of Isocyanates

1a Reaction with Alcohols – Carbamate Formation

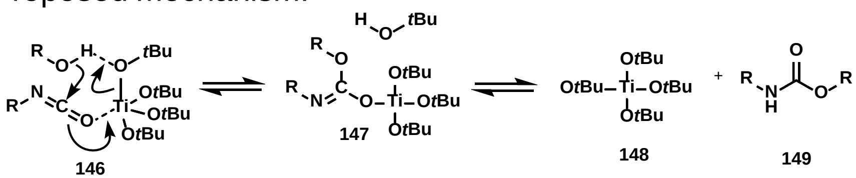


S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

Ti-catalyzed reaction of highly hindered Isocyanates with Alcohols:

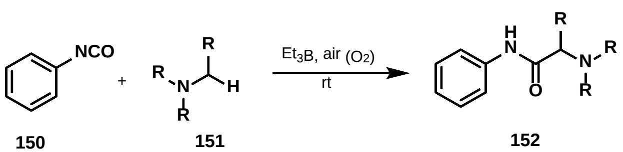


Proposed mechanism:



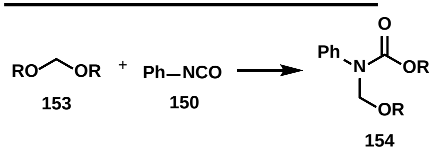
C. Spino, M. A. Joly, C. Godbout, M. Arbour, *J. Org. Chem.* **2005**, *70*, 6118–6121

1b Reaction with tertiary Amines – Carbamoylation



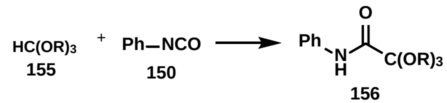
Tanaka *Org. Lett.*, **2007**, *9* (24), pp 5115–5118

1c Reaction with Acetals



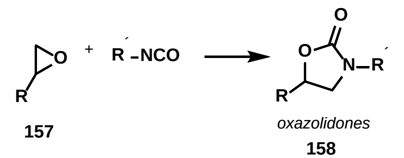
S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

1d Reaction with ortho-Esters



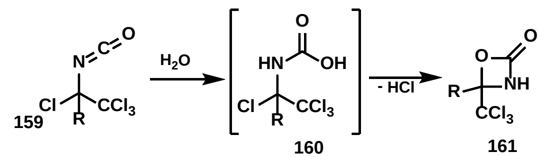
S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

1e Reaction with Epoxides



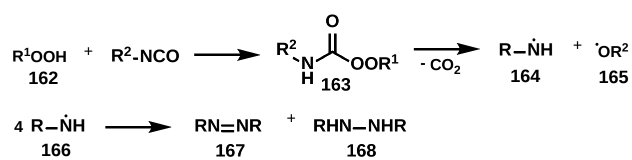
A. Baba, M. Fujiwara, H. Matsuda, *Tetrahedron Lett.* **1986**, *27*, 77–80

Synthesis of oxazetidinones:



S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

1f Reaction with Peroxy-compounds

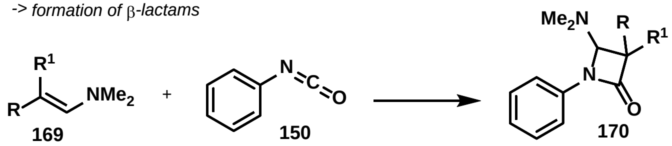


S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

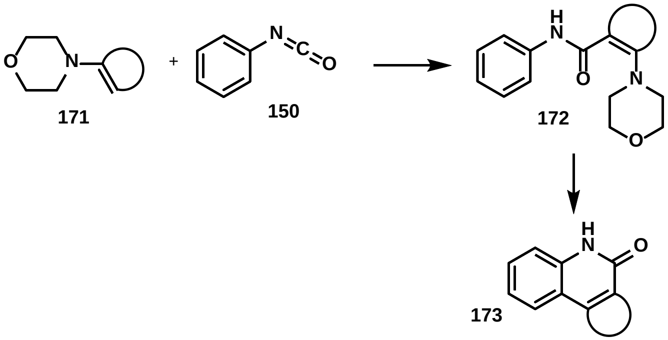
Reactions of Isocyanates

2a Reaction with Enamines

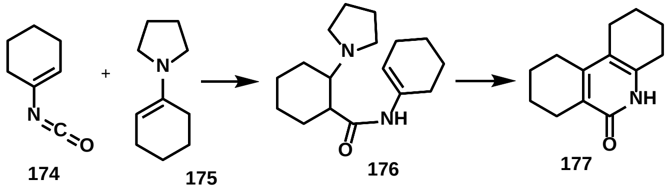
-> *formation of β-lactams*



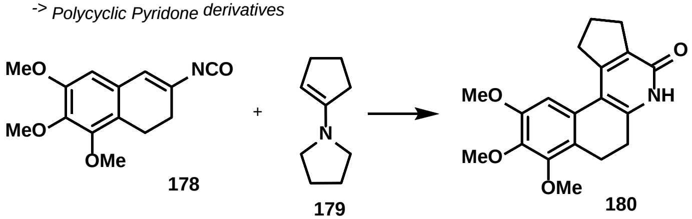
-> *Quinoline derivatives*



-> *Pyridone derivatives*

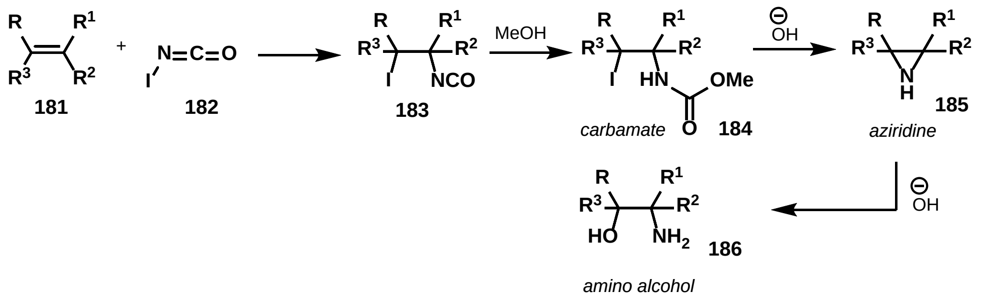


-> *Polycyclic Pyridone derivatives*



Rigby *J. Org. Chem.*, **1989**, *54* (1), pp 224–228

2b Reaction of Iodo Isocyanates with double bonds

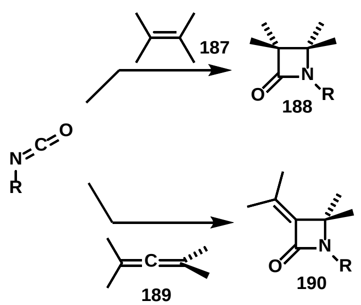


S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

3 Cycloaddition Reactions – Formation of Heterocyclic Ring Systems

3a [2+2]-Cycloaddition reaction

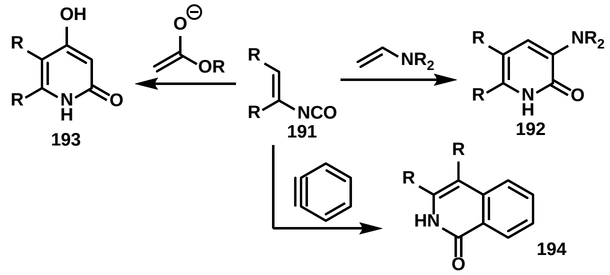
Synthesis of ß-Lactams (Azetidinones)



F. P. Cossío, G. Roa, B. Lecea, J. M. Ugalde, *J. Am. Chem. Soc.* **1995**, *117*, 12306–12313

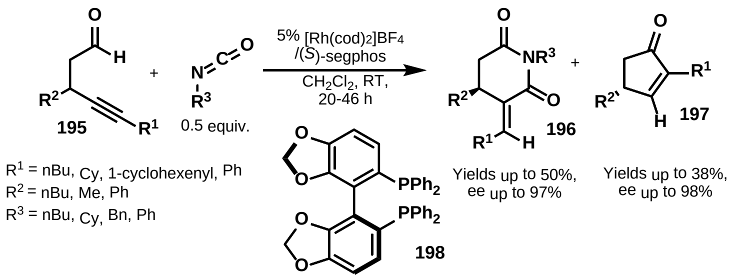
Reactions of Isocyanates

3b Formal [4+2]-Cycloaddition

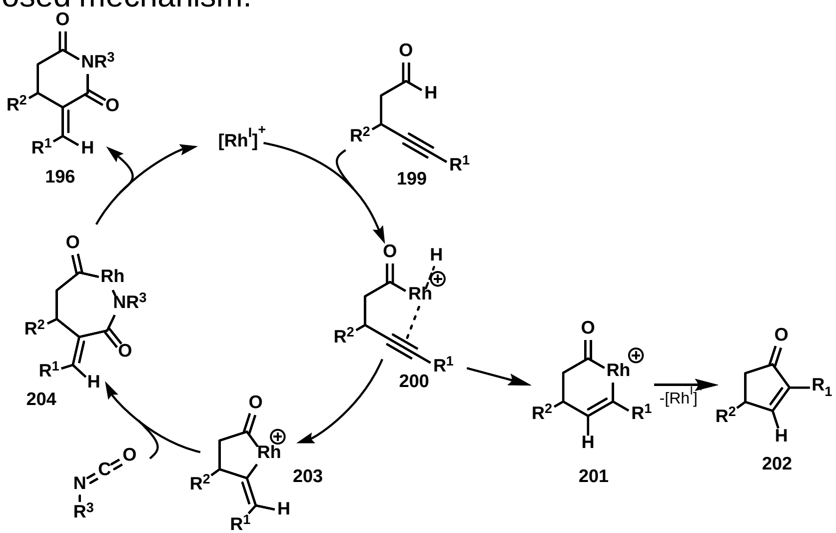


J. H. Rigby, M. Qabar, G. Ahmed, R. C. Hughes, *Tetrahedron* **1993**, *49*, 10219–10228

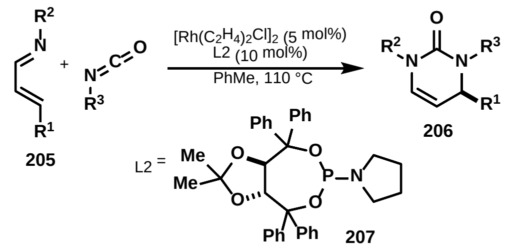
Synthesis of 4-alkylideneglutarimides:

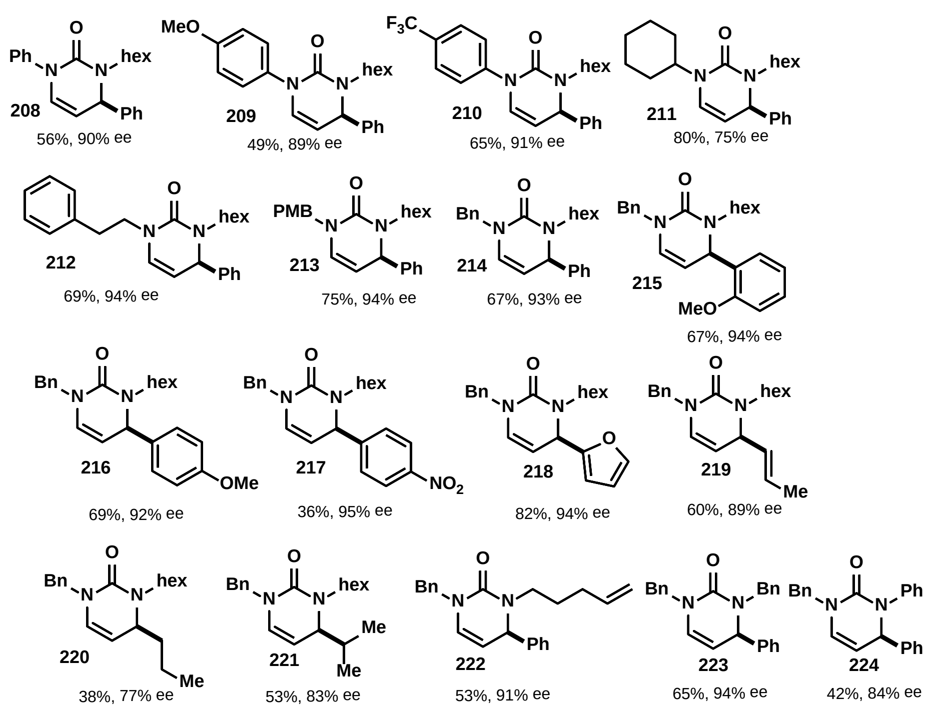


Proposed mechanism:



Enantioselective Synthesis of Pyrimidinones:





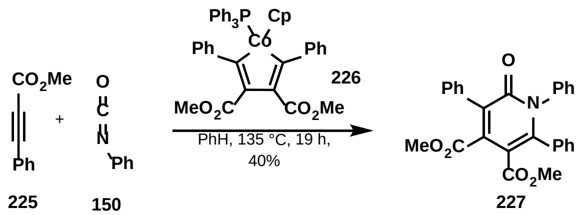
K. M. Oberg, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 4785–4787

 K. Tanaka, Y. Hagiwara, M. Hirano, J. H. Rigby, D. D. Holsworth, K. James, K. M. Oberg, T. Rovis, *J. Am. Chem. Soc.* **2006**, *133*, 4019–4020

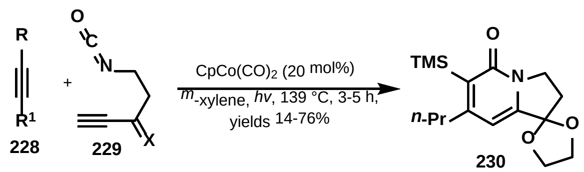
Reactions of Isocyanates

3c [2+2+2]-Cycloaddition

Cobalt-catalyzed:

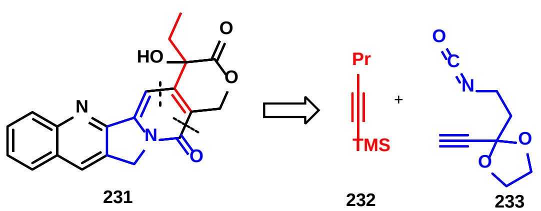


Yamazaki, Tet. Lett. 1977, 18, 1333-1336.



R = TMS, nPr, tBu, Me, ketal, CH_2OR
R^1 = TMS, Et, CO_2Et
X = H_2, ketal

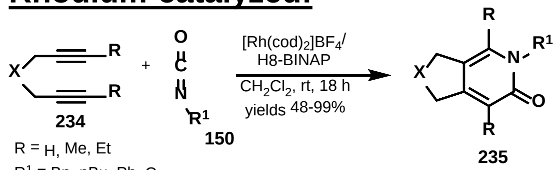
Application in the Total Synthesis of Camptothecin:



camptothecin

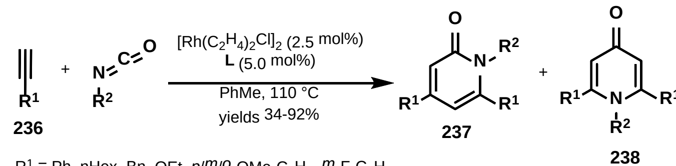
R. A. Earl K. P. Vollhardt, **1983**, 6991–6993

Rhodium-catalyzed:



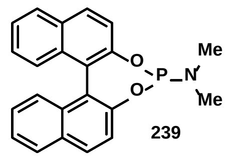
R = H, Me, Et
R^1 = Bn, nBu, Ph, Cy
X = $C(CO_2Me)_2$, NTs, alkyl

K. Tanaka, A. Wada, K. Noguchi, *Agriculture* **2005**, 2117–2119



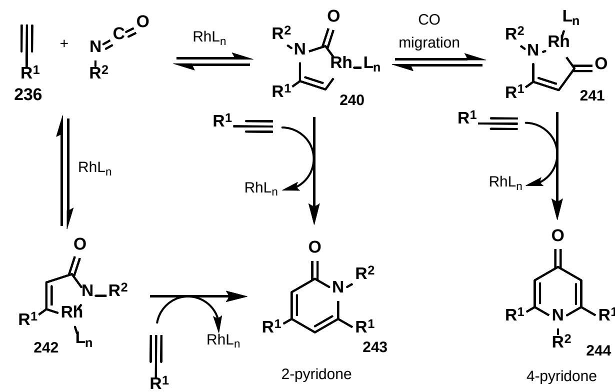
R^1 = Ph, nHex, Bn, OEt, p/m/o-OMe-C_6H_4, m-F-C_6H_4
R^2 = Bn, PMB, Ph, nHex, Cy, p-F-C_6H_4, p-OMe-C_6H_4

L =



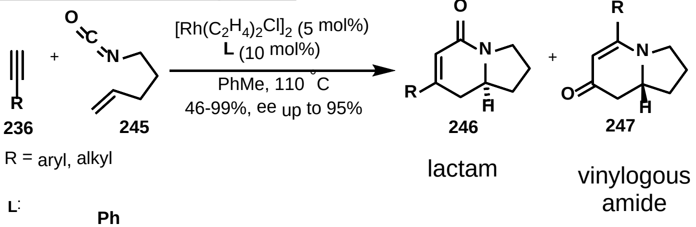
K. M. Oberg, E. E. Lee, T. Rovis, *Tetrahedron* **2009**, *65*, 5056–5061

Proposed Mechanism:



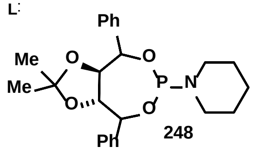
Reactions of Isocyanates

Rhodium-catalyzed:

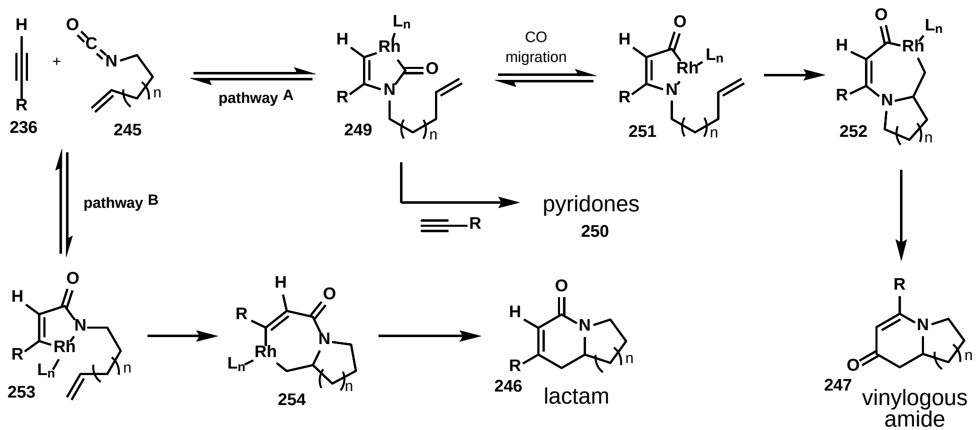


R = aryl, alkyl

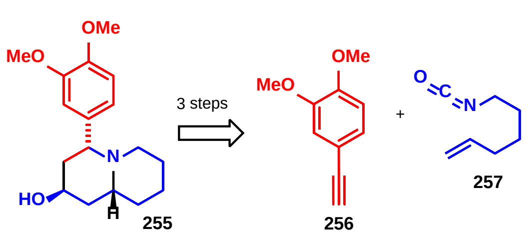
L:



Proposed Mechanism:



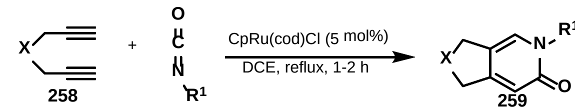
Application in the Total Synthesis of (+)-Lasubine II:



(+)-lasubine II

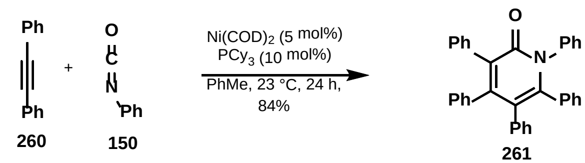
R. T. Yu, T. Rovis, *J. Am. Chem. Soc.* **2006**, 12370–12371

Ruthenium-catalyzed:

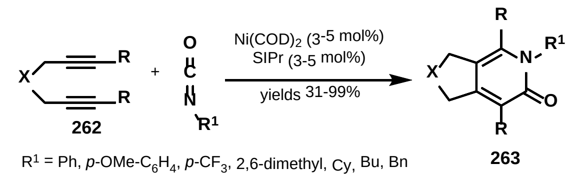


Yamamoto Y, Itho K, *Org.. Lett.* **2001**, *3*, 2117.

Nickel-catalyzed:

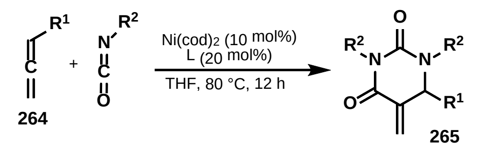


H. Hoberg, B. W. Oster, *Synthesis (Stuttg).* **1982**, *1982*, 324–325



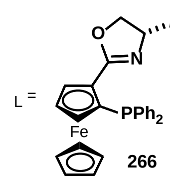
R^1 = Ph, *p*-OMe-C_6H_4, *p*-CF_3, 2,6-dimethyl, Cy, Bu, Bn
R = H, Me, Et, *i*Pr
X = $C(CO_2Me)_2$, C_2H_4, NTs, O

H. A. Duong, M. J. Cross, J. Louie, *J. Am. Chem. Soc.* **2004**, *126*, 11438–11439



R^1 = hex, CH_2Cy, $(CH)_2Cy$, Cy, $(CH_2)_4OBn$, $(CH_2)_4OTBS$, $(CH_2)_2CH{=}CMe_2$, Oct
R^2 = Tol, 4-Me_2N-C_6H_4, 4-OMe-C_6H_4, Ph, 4-Cl-C_6H_4, 4-CO_2Me-C_6H_4’
4-MeCO-C_6H_4, 4-CF_3-C_6H_4, 3-Me-C_6H_4, 2-Naphthyl, Bn

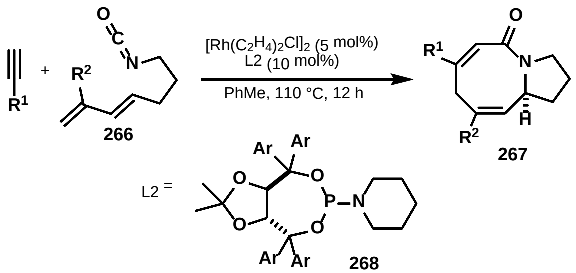
L =

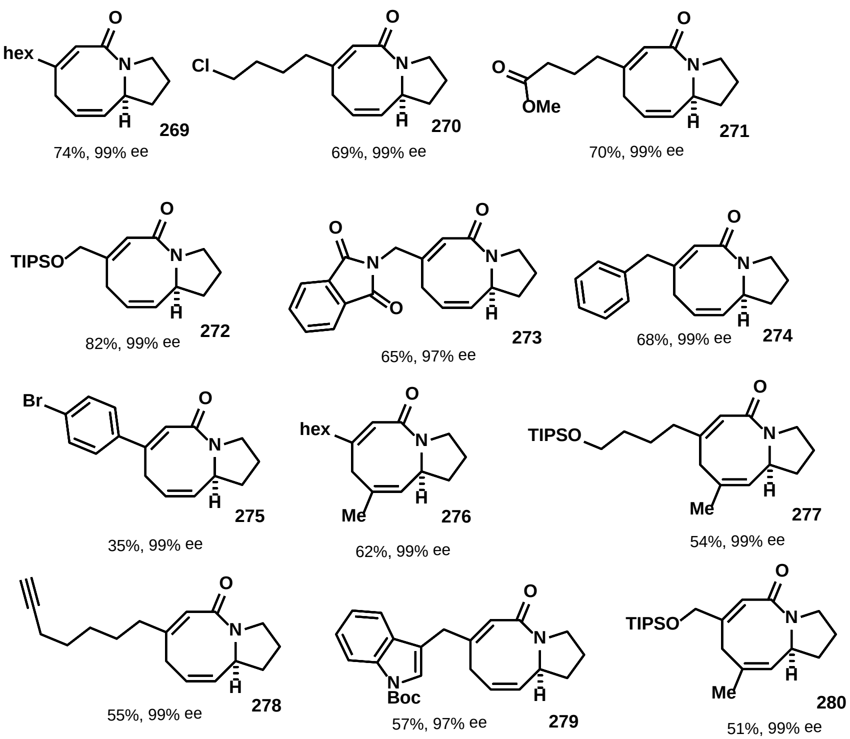


T. Miura, M. Morimoto, M. Murakami, *J. Am. Chem. Soc.* **2010**, *132*, 15836–15838

Reactions of Isocyanates

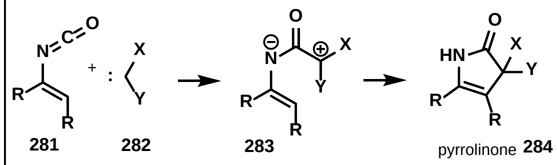
3e [4+2+2]-Cycloaddition – Synthesis of Bicyclic Azocine Rings





R. T. Yu, R. K. Friedman, T. Rovis, *Angew. Chem. Int. Ed. Engl.* **2009**, 13250–13251

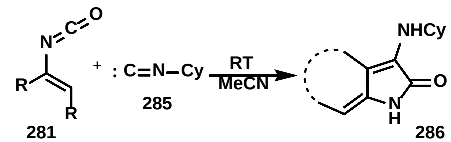
3g [4+1]-Cycloaddition of Isocyanates with various carbenes

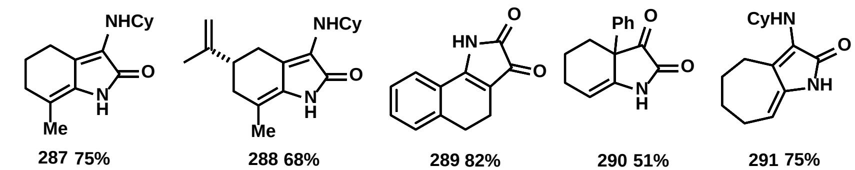


- rapid entry to functionalized pyrrolidinone rings
- well-suited for installation of quaternary stereocenters

J. H. Rigby, M. Qabar, G. Ahmed, R. C. Hughes, *Tetrahedron* **1993**, *49*, 10219–10228

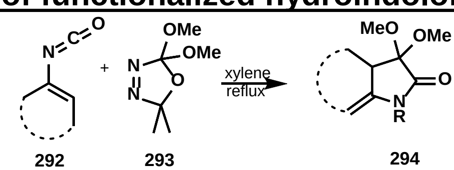
Synthesis of functionalized Pyrrolinone derivatives:



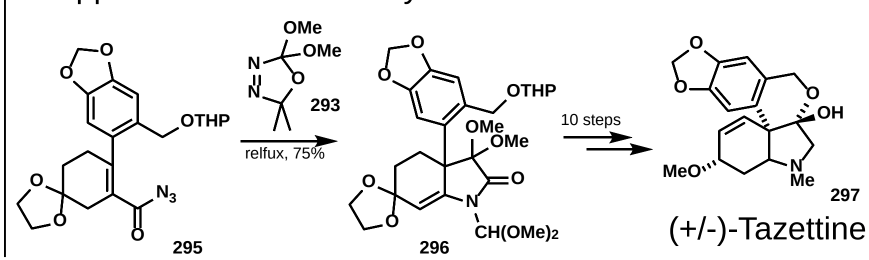


J. H. Rigby, M. Qabar, G. Ahmed, R. C. Hughes, *Tetrahedron* **1993**, *49*, 10219–10228

Synthesis of functionalized hydroindolones:



Application in the Total Synthesis of Tazettine:

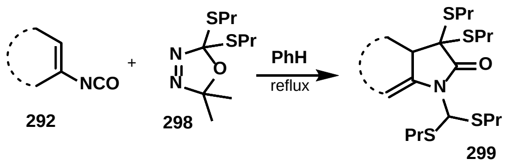


(+/-)-Tazettine:

Rigby *J. Am. Chem. Soc.*, **1996**, *118* (50), pp 12848–12849

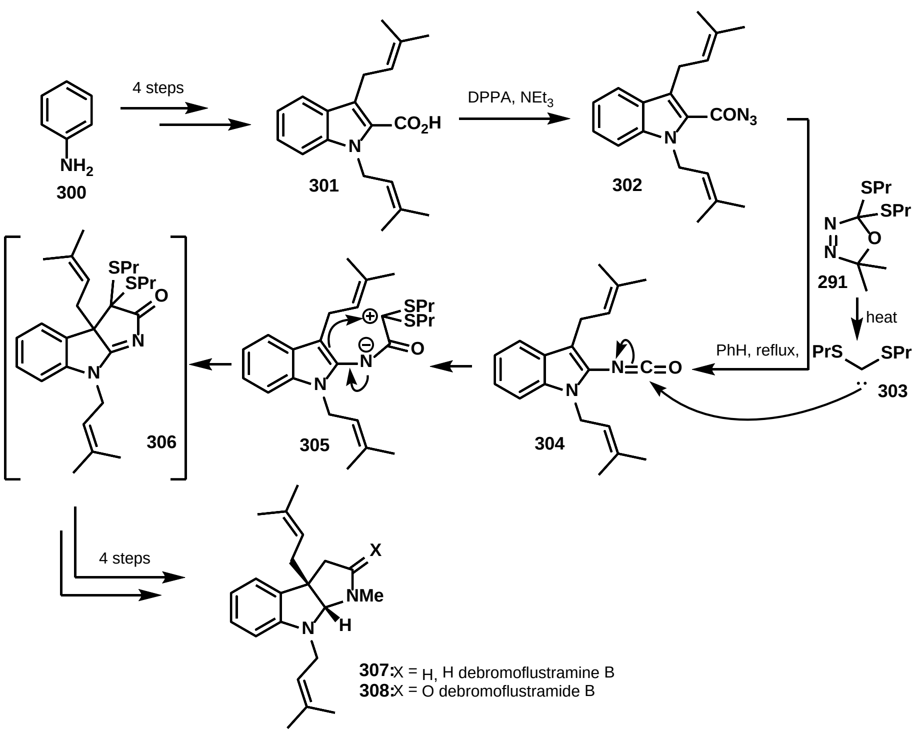
Reactions of Isocyanates

[4+1]-Cycloaddition with bis(alkylthio)carbenes



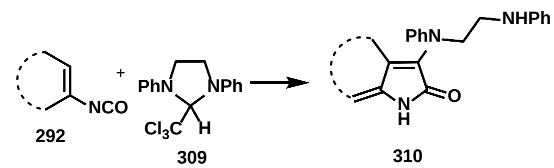
J. H. Rigby, S. Laurent, *J. Org. Chem.* **1999**, *64*, 1766–1767

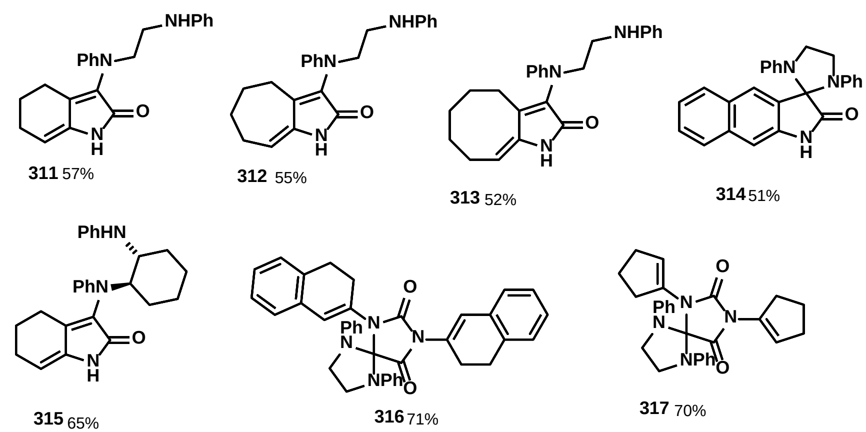
Application in the Total Synthesis of debromoflustramide/-amine:



S. De, J. H. Rigby, *Tetrahedron Lett.* **2013**, *54*, 4760–4762

[4+1]-Cycloaddition with cyclic carbenes



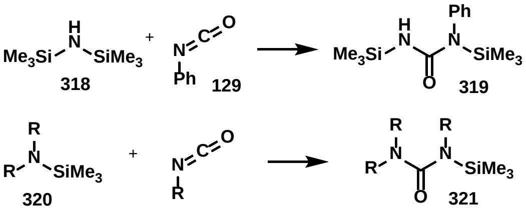


J. H. Rigby, Z. Wang, *Org. Lett.* **2002**, 22–24

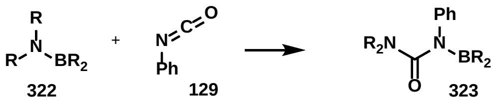
Reactions of Isocyanates

4 Insertion Reactions

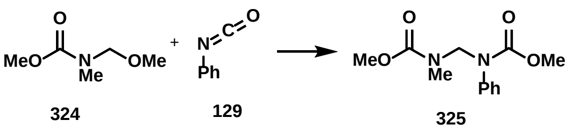
4a Insertion in Si-N bond



4b Insertion in B-N bond

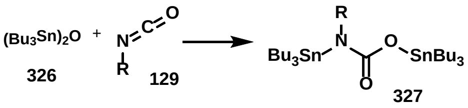


4c Insertion in labile Methoxy Derivatives



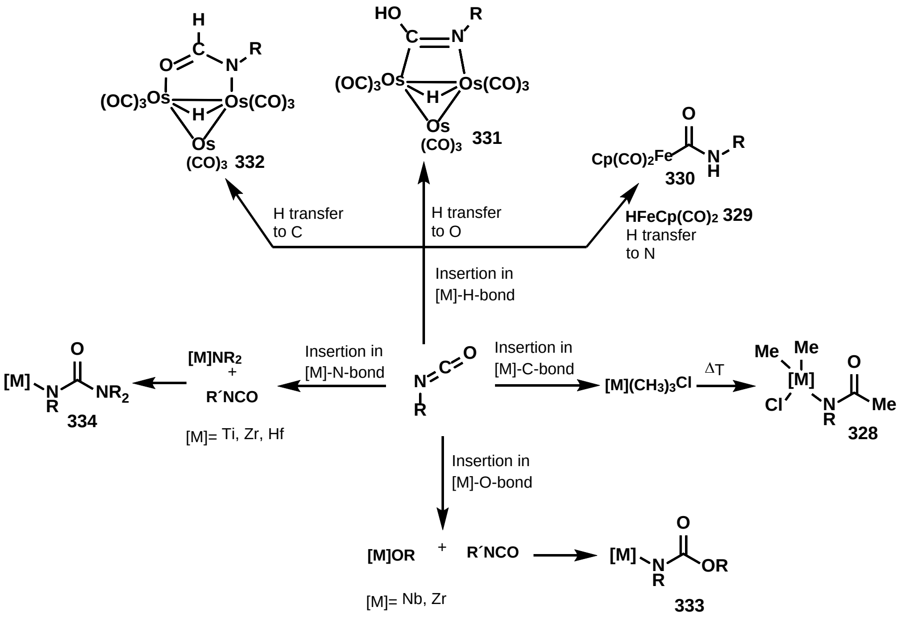
S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

4d Insertion in Organotin Oxides



S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

4e Insertion in Metal-C/H/N/O bond

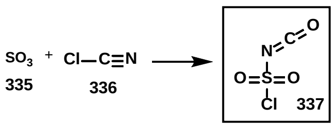


P. Braunstein, D. Nobel, *Chem. Rev.* **1989**, *89*, 1927–1945

C. Chang, J. Chen, B. Srinivas, M. Y. Chiang, G. Lee, S. Peng, G. J. C. Soc, D. Trans, J. A. A. Chem, I. E. Engl, et al., *Organometallics* **1997**, *7333*, 4980–4984

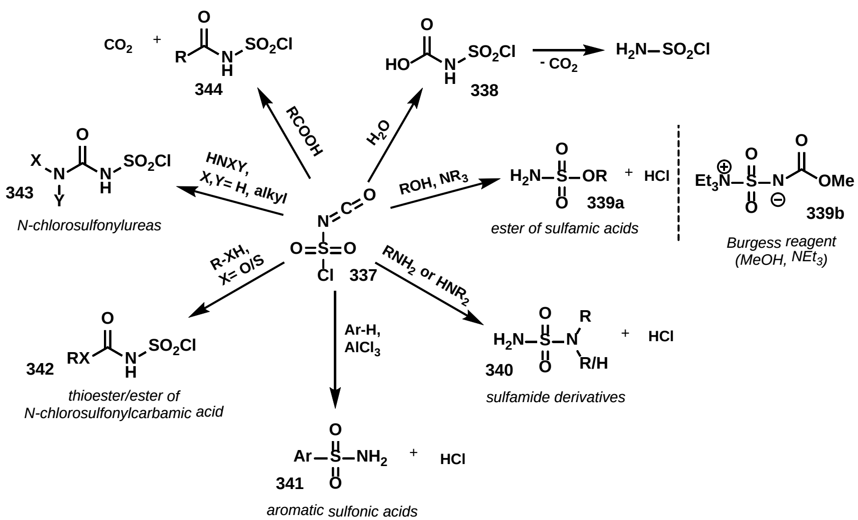
Reactions of Isocyanates

5 Chlorosulfonyl Isocyanate

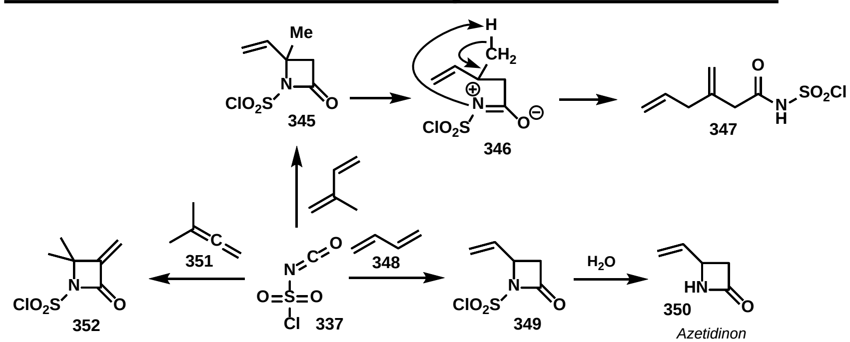


- colorless liquid
- mp -44 to -43 °C, bp 107-108 °C
- thermally stable up to 300 °C
- most reactive isocyanate species

5a Reaction with H-X

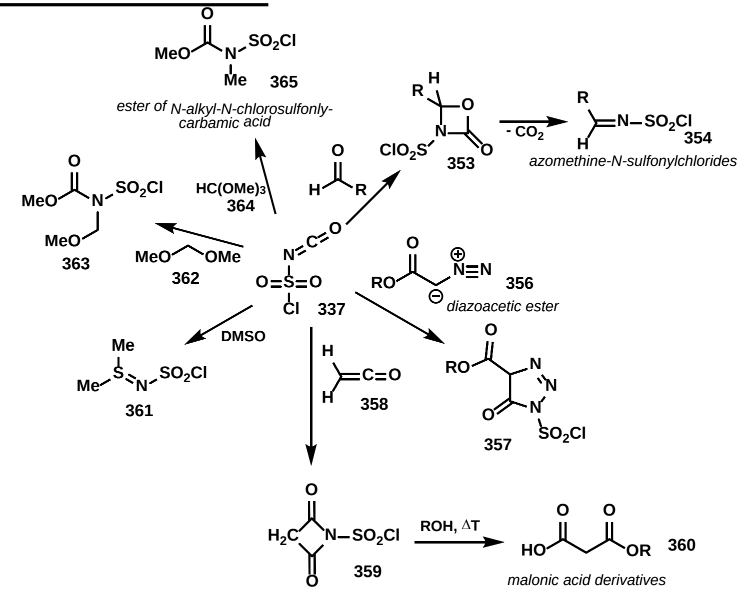


5b Reaction with Olefines – Synthesis of ß-lactams



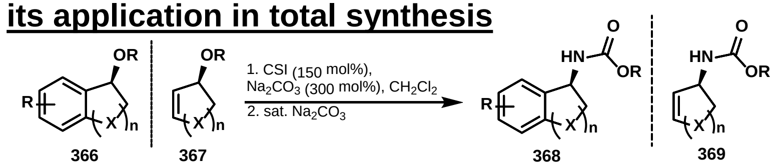
S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

5c Various Reactions

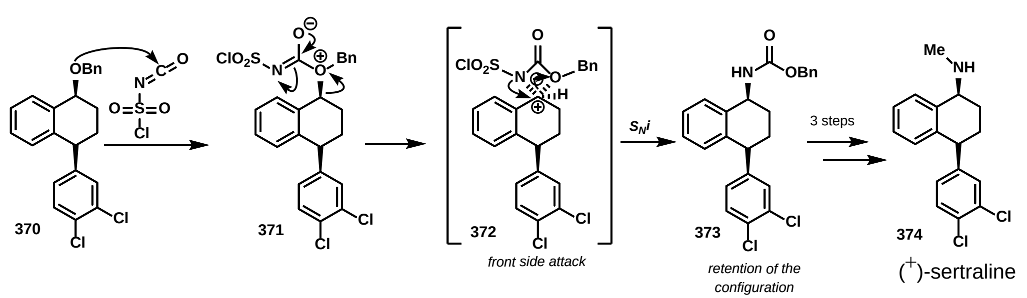


S. Ozaki *Chem. Rev.*, **1972**, *72* (5), pp 457–496

5d Stereoselective amination of chiral benzylic ethers and its application in total synthesis



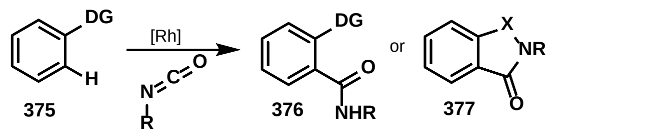
Yields up to 89%,
ee up to 99%

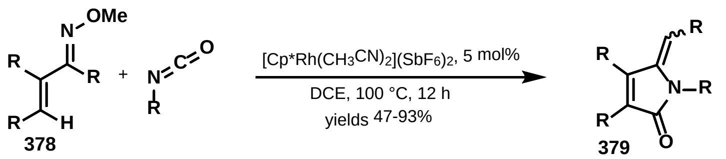


S. H. Lee, I. S. Kim, Q. R. Li, G. R. Dong, L. S. Jeong, Y. H. Jung, *J. Org. Chem.* **2011**, *76*, 10011–10019

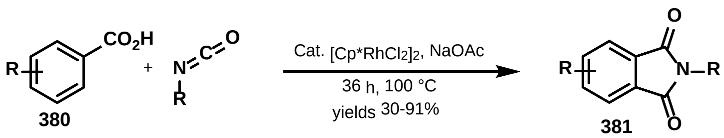
Reactions of Isocyanates

6 Catalytic C-H Amidation Reactions

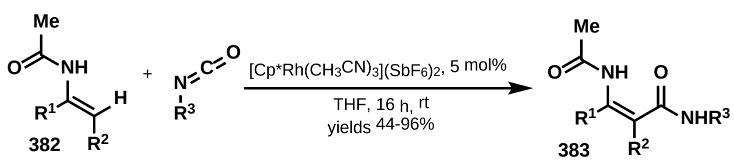




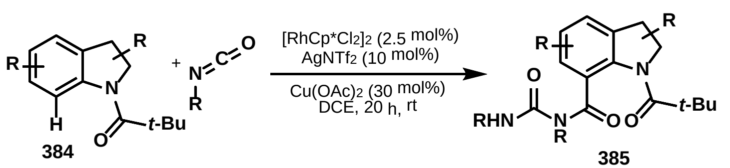
W. Hou, B. Zhou, Y. Yang, H. Feng, Y. Li, *Org. Lett.* **2013**, *2*, 1–42



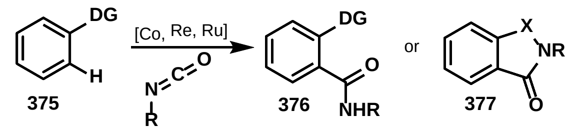
X. Y. Shi, A. Renzetti, S. Kundu, C. J. Li, *Adv. Synth. Catal.* **2014**, *356*, 723–728

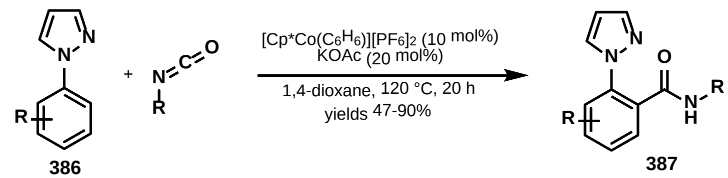


J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *113*, 11430-11433.

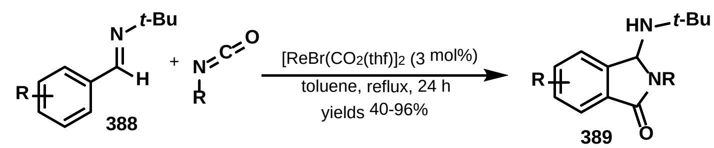


I. S. Kim, O. P. Zee, Y. H. Jung, *Adv. Synth. Catal.* **2017**, *359*, 1-9.

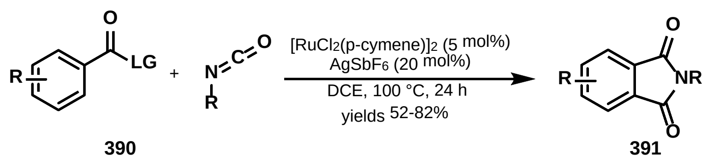




J. R. Hummel, J. A. Ellman, *Org. Lett.* **2015**, *17*, 2400–2403



Y. Kuninobu, Y. Tokunaga, A. Kawata, K. Takai, *J. Am. Chem. Soc.* **2006**, 202–209



S. Desarkar, L. Ackermann, *Chem. - A Eur. J.* **2014**, *20*, 13932–13936

Isocyanate Chemistry

Take Home Message

Synthesis of Isocyanates

• despite the high toxicity of phosgene, very clean reaction with merely no side products

• synthesis from isocyanic acid with a large amount of functional groups.

• a lot of mild, phosgene free methods available with various functional groups

Reactions of Isocyanates

• Isocyanate reacts with a huge amount of different functionalities

• Cycloaddition and C-H-Amidation reactions as very powerful reactions for the synthesis of heterocyclic systems

• Chlorosulfonyl isocyanate a very powerful and versatile applicable reagent!