# Isocyanide Chemistry

Tanja Gaich

## Introduction

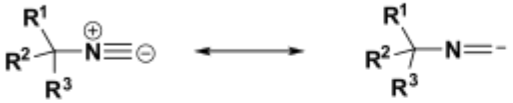
Isonitriles known since 1850s. Their exact structure was solved later with modern abinitio calculations.
Characteristic hideous smell or pungent stench
Term "isonitrile" not accepted by IUPAC

Physical data:

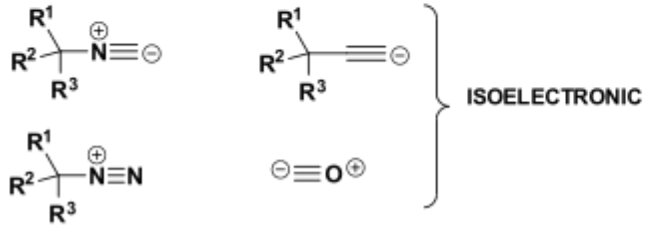
IR: 2150-2110 cm-1 weak-medium intensity
13C-NMR: 156-170 ppm
Their carbon atom is formally divalent.

-> Very unusual electronic structure:

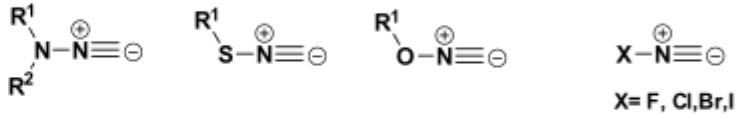
- Reacts as carbene,
- with nucleophiles,
- with electrophiles,
- in radical reactions
- and is isoelectronic with CO therefore a broad organometallic chemistry



a) I. Ugi (Ed.): *Isocyanide Chemistry*, Academic Press, New York 1971; b) J. A. Green, P. T. Hoffmann in [1a], p. 1; c) H. M. Walborsky, M. P. Periasamy in S. Patai, Z. Rappoport (Eds.): *The Chemistry of Triple Bond-ed Functional Groups, Part 2, Supplement*, Wiley-Interscience, New York 1983, p. 835.




Furthermore and not covered here:




## Literature Reviews

α-Anion chemistry of isocyanides

Hoppe, D. ACIE, 1974, 789
Suginome, M.; Ito, Y. Product class 7: isocyanides and related compounds. Science of Synthesis 2004, 19 445-530.

Multicomponent reactions

Domling, A.; Ugi, I.. Multicomponent reactions with isocyanides. ACIE 2000, 3168-3210.
Domling, A.; Chem. Rev. 2006, 17-89.
Ugi, I.; Lohberger, S.; Karl, R. The Passarini and Ugi reactions in Comp. Org. Synth. (eds Trost, B; Fleming I ), 2, 1083-1109, Pergamon press, Oxford 1991.
Dyker, G; Amino acid derivatives by multicomponent reactions Organic Synthesis Highlights, IV 2000, 53-57.

Organometallic chemistry of isocyanides

Perst, H. Product class 17: ketenimines. Science of Synthesis (2006), 23 781-898.
Aumann, R.; ACIE, 1988, 1456-1467.

Radical reactions of isocyanides

Minozzi, M.; Nanni, D.; Spagnolo, P. Imidoyl radicals in organic synthesis. Current Organic Chemistry (2007), 11(15), 1366-1384.
Ryu, I.; Sonoda, N.; Curran, D. P. Chem. Rev. 1996, 96, 177-194.
Campo, J.; Garcia-Valverde, M.; Marcaccini, S.; Rojo, M. J.; Torroba, T. Synthesis of indole derivatives via isocyanides. Organic & Biomolecular Chemistry (2006), 4(5), 757-765.

TosMic reagent

Tandon, V. K.; Rai, S. Sulfur reports, 2003, Vol 24, No3, 307-385.

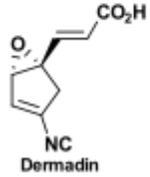
Natural products

Edenborough, M. S.; Herbert, R. B. Naturally occurring isocyanides, NPR, 1988,229-245.
Chang, C. W. J. Naturally occurring isocyano/isothiocyanato and related compounds in Progress in the chemistry of natural products (eds. Falk, W. H. H.; Moore, E. R.; Kirby G. W. ), 80, 1-186, SpringerVerlag Wien/New York, 2000.

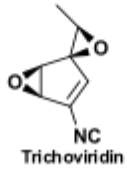
## Isocyanide containing natural products

- Xanthocillin first reported NP 1956 Hagedorn and Toenjes.
- From a biogenetical point of view isothiocyanates, formamides, isocyanates, and thiocyanates belong there too.
- Historical : First found in marine sources then terrestrial. Xanthocillin and cyclopentyl type.
- To day isolated from: bacteria, fungi, cyanobacteria, marine sponges and their predators.
- Isolation of isocyanide containing NPs difficult due to reactivity (trace acid, nucleophiles etc.)

**Cyclopentyl isocyanides**



Dermadin



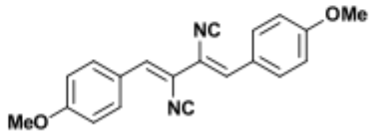
Trichoviridin

Dermadin and trichoviridin soil sample (fungus)

active against staphylococcus aureus

Tamura, a.; Kotani, H.; *J.of Antibotics*, 1975, 161.
1968,671.

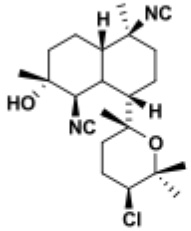
**Xanthocillines**



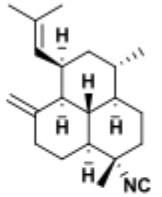

xanthocillines soil sample (fungus)
antiviral antibiotics

Suzuki, S. et al..; *J.of Antibotics*,

**Diterpenes**



Kalihinol E

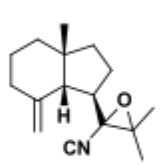


Amphilectanes

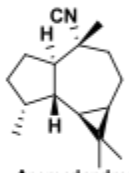
Diterpenes with trans or cis decalin core
Devided in Tetrahydrofuran and -pyran types
Isolation: marine sponge
active against Bacillus subtilis, Staphylococcus aureus, and Candida albicans.

Scheuer, P. J.; Patra, A.; Baker, J. A.; Chang, C. W. J.; *J. Amer. Chem. Soc. 1987, 6119.*

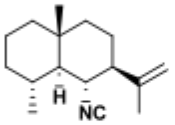
**Sesquiterpenes**



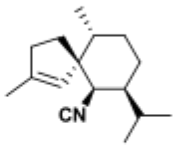
Axanes



Aromadendrane



Eudesmane

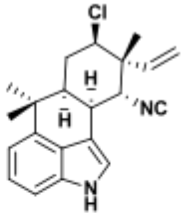


spiroxane

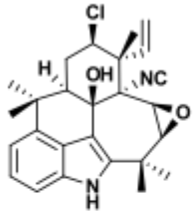
Skeletal types that contain isocyanides
(Eudesmanes, Axanes, Aromadendrane, Epimaaliane, Cadinane, Spiroaxane, Bisabolane, Pupukeanane, Guaiane.)
Only contain one NC-functionality in contrast to diterpenes.
Isolation : marine organisms (mollusks, sponges)

Adinolfi, M.; De Napoli, L.; Di Blasio, B.; Iengo, A.; Pedone, C.; Santacroce, C. *Tet. Lett.* 1977, (32), 2815.
Ciminiello, P.; Fattorusso, E.; Magno, S.; Mayol, L. *Can. J. of Chem.* 1987, 65, 518.
Minale, L.; Riccio, R.; Sodano, G. Tetrahedron 1974, 30, 1341.

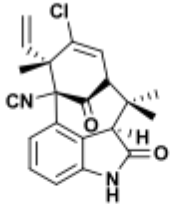
**Indolalkaloids**



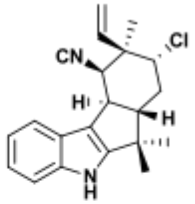
Hapalindole A



Ambiguine E



Welwitindolinones



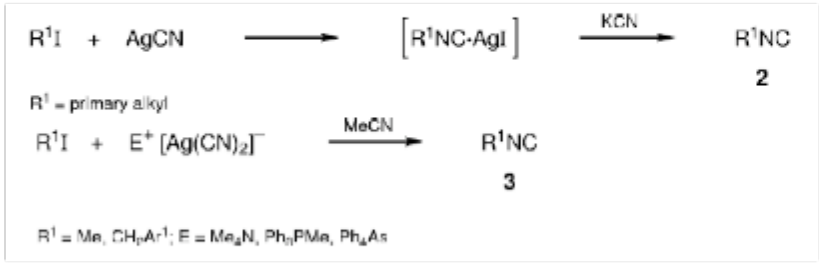
Fischer indole L

Isolated by cyanobacteria fischerella species
prenylated indolalkaloids

Moore, R. E.; Cheuk, C.; Yang, Xu Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; J. Org. Chem. 1987, 1036.
Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, Richard E.; Patterson, G. M. L. J. Org. Chem. 1992, 857.
Stratmann, K.; Moore, R. E.; Bonjouklian, R.; Deeter, J. B.; Patterson, G. M. L.; Shaffer, S.; Smith, C. D.; Smitka, T. A. J. Am.Chem. Soc. 1994, 9935.
Park, A.; Moore, R. E.; Patterson, G. M. L.. Tet. Lett. 1992, 3257.

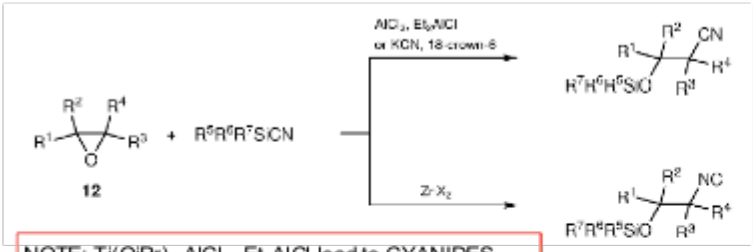
# Syntheses of Isocyanides

## 1. Reaction of alkyliodides with silver salts



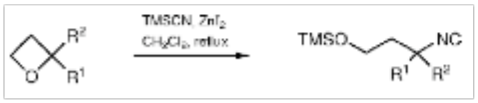

Green, J. A., II; Hoffmann, R. T., *In Isonitrile Chemistry*, Ugi, I., Ed., Academic: New York, (1971), p 1.
Gautier, A., *Justus Liebigs Ann. Chem.*, (1867) **142**, 289.
Hoffmann, A. W., *Justus Liebigs Ann. Chem.*, (1867) **144**, 114.
Lieke, W., *Justus Liebigs Ann. Chem.*, (1859) **112**, 316.
Meyer, L., *J. Pharm. Chem.*, (1869) **67**, 147.
Songstad, J.; Stangeland, E. J.; Austad, T., *Acta. Chem. Scand.*, (1970) **24**, 305.
Engemyr, L. B.; Martinson, A.; Songstad, J., *Acta. Chem. Scand., Ser. A*, (1974) **28**, 255.

## 2. From epoxides and oxetanes



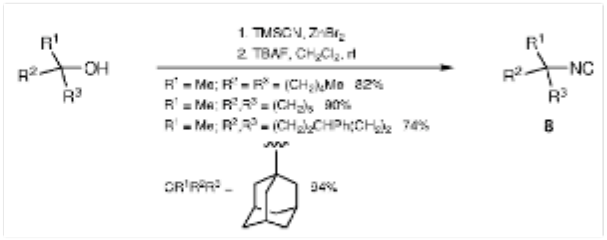

NOTE: $Ti(OiPr)_4AlCl_3$, $Et_2AlCl$ lead to CYANIDES
$ZnI_2$, $ZnCl_2$ lead to ISOCYANIDES

Gassman, P. G.; Haberman, L. M., *J. Org. Chem.*, (1986) **51**, 5010.
Gassman, P. G.; Guggenheim, T. L., *J. Am. Chem. Soc.*, (1982) **104**, 5849.
Gassman, P. G.; Gruetzmacher, R. S., *Tetrahedron Lett.*, (1984) **25**, 3259.



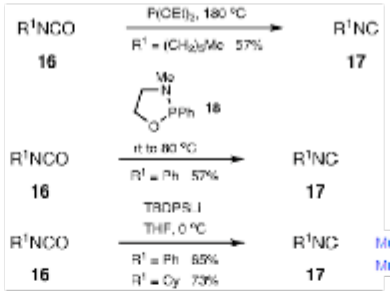

Gassman, P. G.; Haberman, L. M., *Tetrahedron Lett.*, (1985) **26**, 4971.
Carr, S. A.; Weber, W. P., *Synth. Commun.*, (1985) **15**, 775.

## 3. Reaction of tertiary alcohols with TMS-cyanide




Sasaki, T.; Nakanishi, A.; Ohno, M., *J. Org. Chem.*, (1981) **46**, 5445.
Kitano, Y.; Chiba, K.; Tada, M., *Tetrahedron Lett.*, (1999) **39**, 1911.

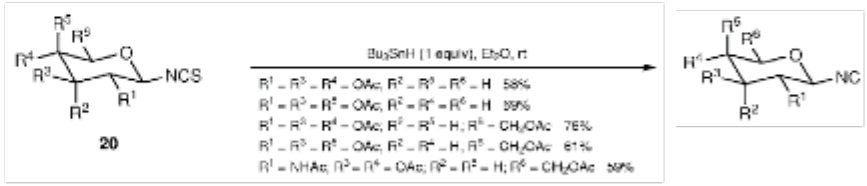
## 4. From deoxygenation of isocyanates




NOTE: Comparison of several phosphites revealed that triethyl-, and tributyl phosphites are effective, but trimethyl and triphenyl are not. Conventional phosphites DON'T work with aromatic isocyanates therefore **18**

Mukaiyama, T., Nambu, H., Okamoto, M., *J. Org. Chem.*, (1962) **27**, 3651.
Mukaiyama, T.; Yokota, Y., *Bull. Chem. Soc. Jpn.*, (1965) **38**, 858.

## 5. From desulfuration of isocyanates

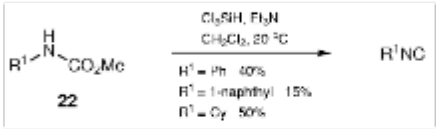



Alternative conditions: $P(OEt)_3$ rt

**same principle different name - which ?**

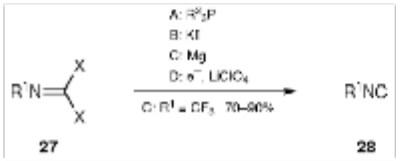
Witczak, Z. J., *Tetrahedron Lett.*, (1986) **27**, 155.
Lorenz, D. H.; Becker, E. I., *J. Org. Chem.*, (1963) **28**, 1707.

## 6. From Carbamates by deoxygenation with trichloro silane/triethylamine



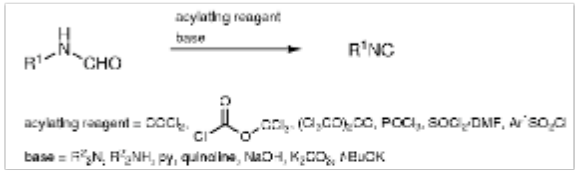

Baldwin, J. E.; Bottaro, J. C.; Riordan, P. D.; Derome, A. E., *J. Chem. Soc., Chem. Commun.*, (1982), 942.

## 7. By dehalogenation of isocyanide dihalides



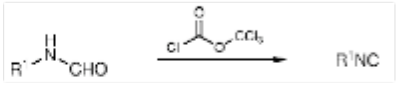

Hoftschmidt, H., *Angew. Chem.*, (1952) **74**, 861
Lentz, D., *J. Fluorine Chem.*, (1984) **24**, 523.
Collado, A.; Zapata, A.; Fonor, M., *Tetrahedron Lett.*, (1990) **33**, 4779.

## 8. By dehydration of Formamides




Ugi, I.; Meyr, R., *Chem. Ber.*, (1960) **93**, 239.

## 8a. By dehydration with phosgene or diphosgene

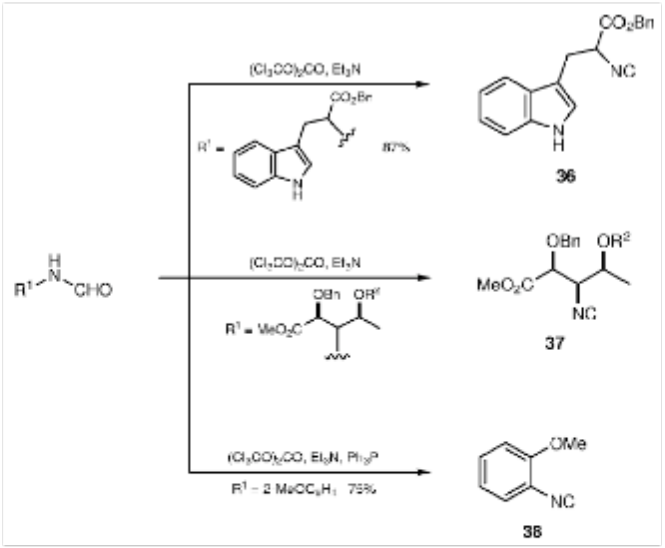



**a.** $NEt_3$ **and DCM used at -30°C**
**b.** $NBu_3$ **as base solvent 1,2-dichlorobenzene**
**c. 1,2-dichlorobenzene as solvent**
**d. base: 4-methylmorpholine**

| $R^1$ | Yield (%) | | Ref |
|---|---|---|---|
| | Trichloromethyl Chloroformate[A] | Phosgene | |
| Me | 47[b] | 37 | [43] |
| t-Bu | 97[c] | 82 | [43] |
| Cy | 90 | 88 | [43] |
| Bn | 95 | 92 | [43] |
| 4-$MeOC_6H_4$ | 95 | 64 | [43] |
| $CH_2CO_2Me$ | 82 | 47 | [43] |
| CHBnCONHCHBnCO$_2$Me | 75[d] | 51 | [43] |

Ugi, I.; Fetzer, U.; Eholzer, U.; Knupfer, H.; Offermann, K., *Angew. Chem.*, (1965) **77**, 492; *Angew. Chem. Int. Ed. Engl.*, (1965)
Skoma, G.; Ugi, I., *Angew. Chem.*, (1977) **89**, 268; *Angew. Chem. Int. Ed. Engl.*, (1977) **16**, 269.

## 8b. By dehydration with triphosgene



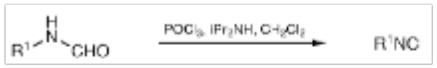

Eckert, H.; Forster, B., *Angew. Chem.*, (1987) **99**, 922; *Angew. Chem. Int. Ed. Engl.*, (1987) **26**, 894.
Motawia, M. S.; Pedersen, E. B.; Nielsen, C. M., *Arch. Pharm. (Weinheim, Ger.)*, (1990) **323**, 971.

Bourne, G. T.; Horwell, D. C.; Pritchard, M. C., *Tetrahedron*, (1991) **47**, 4763.
Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Garcia, J. M., *J. Org. Chem.*, (1993), **58**, 1646.
Wells, A., *Synth. Commun.*, (1994), **24**, 1745.

## 8c. By dehydration with vilsmeier reagent or thionylyl chloride

| $R^1$ | Yield (%) | Ref |
|---|---|---|
| Tr | 95 | [52] |
| $CMe_2CH_2$-*t*-Bu | 93 | [52] |
| (*R*)-(+)-CMeEtPh | 92 | [52] |
| $CMePh_2$ | 90 | [52] |
| (*R*)-(−)-2,2-diphenyl-1-methylcyclopropyl | 88 | [52] |
| Cy | 87 | [52] |
| (*E*)-CPh=CHPh | 84 | [52] |
| $(CH_2)_5Me$ | 82 | [52] |
| 4-$MeOC_6H_4$ | 82 | [52] |
| 2,6-$Me_2C_6H_3$ | 74 | [52] |
| 1-naphthyl | 72 | [52] |
| Bn | 63 | [52] |
| Ph | 60 | [52] |
| *t*-Bu | 55 | [52] |

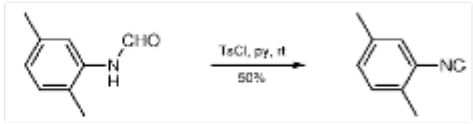
Walborsky, H. M.; Niznik, G. E., *J. Org. Chem.*, (1972) **37**, 187.
Niznik, G. E.; Morrison, W. H., III; Walborsky, H. M., *Org. Synth., Coll. Vol. VI*, (1988), 751.




| $R^1$ | Yield (%) | Ref |
|---|---|---|
| $CH_2CO_2Me$ | 75 | [56] |
| $CH_2CO_2Et$ | 84 | [56] |
| $CH(iPr)CO_2Me$ | 70 | [56] |
| 2-Tol | 59 | [56] |
| | 53–73 | [56] |
| Cy | 67–72 | [57] |
| 2,4,6-$iPr_3C_6H_2$ | 60 | [56] |
| 4-$O_2NC_6H_4$ | 77 | [56] |
| 4-TBDMSO$C_6H_4$ | 56 | [56] |

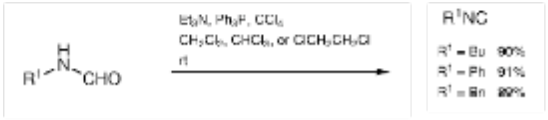
Ugi, I.; Meyr, R., *Chem. Ber.*, (1960) **93**, 239.
Ugi, I., Meyr, R., *Angew. Chem.*, (1958) **70**, 702.
Obrecht, R.; Herrmann, R.; Ugi, I., *Synthesis*, (1985), 400.
Ugi, I.; Meyr, R., *Org. Synth., Coll. Vol. V*, (1973), 1060.
Ugi, I.; Meyr, R.; Lipinski, M., *Org. Synth., Coll. Vol. V*, (1973), 300.
Hoogenboom, B. E.; Oldenziel, O. H.; van Leusen, A. M., *Org. Synth., Coll. Vol. VI*, (1988), 987.

## 8d. By dehydration with vilsmeier reagent or phosphoryl chloride

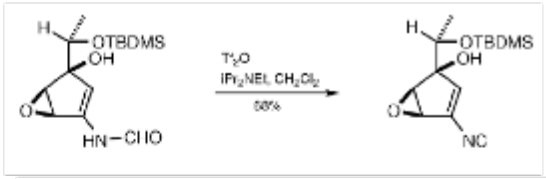



Hortler, W. R.; Corey, E. J., *J. Org. Chem.*, (1966) **23**, 1221.
Casanova, J., Jr.; Schuster, R. E.; Werner, N. D., *J. Chem. Soc.*, (1963), 4280.

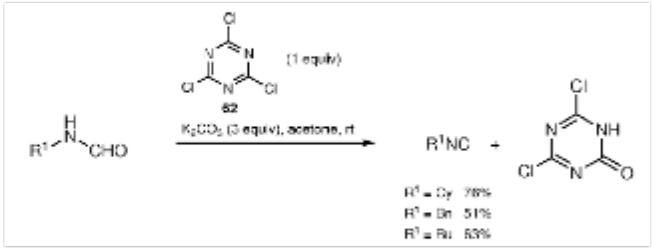
## 8e. With other reagents




Appel, R., Kleinstruck, R., Ziehn, K. D., *Angew. Chem.*, (1971) **83**, 143; *Angew. Chem.*, (1971) **10**, 132.



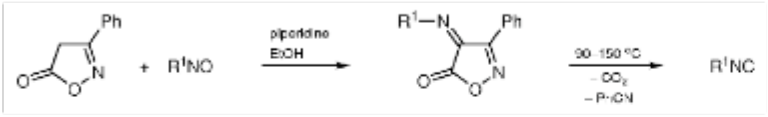

Baldwin, J. E.; Adlous, D. J.; Chan, C.; Harwood, L. M.; O'Neil, I. A.; Peach, J. M., *Synlett*, (1989), 9.




Wittmann, R., *Angew. Chem.*, (1961) **73**, 210.

**Mechanism ?**

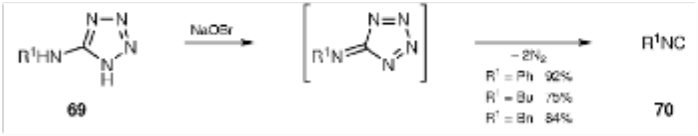
**Mechanism ?**



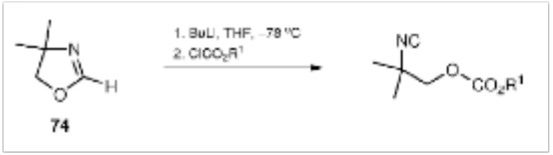

$R^1$ mostly aromatic heterocycles

Weinlup, C.; Stutz, U.; Wollweber, H.-J., *Angew. Chem.*, (1978) **90**, 731; *Angew. Chem. Int. Ed. Engl.*, (1978) **17**, 588

**Mechanism ?**



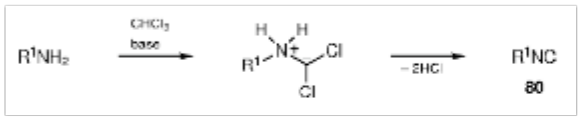

Höfle, G.; Lange, B., *Angew. Chem.*, (1976) **88**, 80; *Angew. Chem. Int. Ed. Engl.*, (1976) **15**, 113
Höfle, G.; Lange, B., *Org. Synth., Coll. Vol. VII*, (1990), 27.




**Mechanism ?**

Gerhart, F.; Schöllkopf, U., *Tetrahedron Lett.*, (1968), 6231
Meyers, A. I.; Adickes, H. W., *Tetrahedron Lett.*, (1969), 5161

**8f. By the Carbylamine reaction**




**NOTE: Espesially useful for aromatic isocyanides**

Gokel, G. W.; Widera, R. P.; Weber, W. P., *Org. Synth., Coll. Vol. VI*, (1988), 232.
Krapcho, A. P., *J. Org. Chem.*, (1962) **27**, 1669
Sasaki, T.; Eguchi, S.; Kaiada, T., *J. Org. Chem.*, (1974) **39**, 1238

**Which other reactions contain α-eliminations??**

# Reactions of Isonitriles

**α-alkali-metalated isocyanides:**

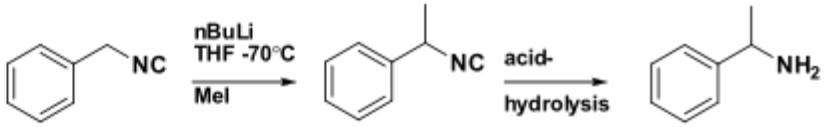
**react with electrophiles to give, olefines, vinylisocyanides, ketones, 1-amino-alkohols, 3-amino-alcohols, straight chain and branched and β-functional α-amino acids.**
**Further a variety of 5,-6,-and 7-membered heterocycles (aza, diaza, oxa-axa, thia-aza).**

**Schoellkopf and Gerhart in 1968 found out that isocyanides are α-acidic. Deprotonation is carried out at -70°C with nBuLi in THF or NaH, NaOEt, KOtBu or DBU depending on the substituents next to the isocyanide functionality.**

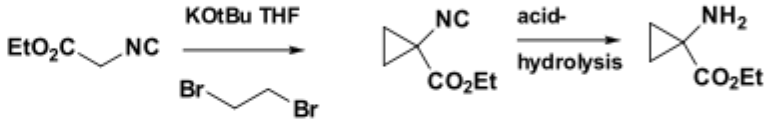
**Schoellkopf, U; Gerhart, F. ACIE,7, 1968 805**

**1. Chainextension of amines**

**Here isocyanides are masked α-amino carbanions**

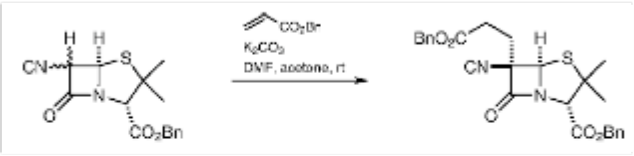



**Schoellkopf, U; Gerhart, F. ACIE,7, 1968 805**




**cyclopropyl amine moiety contained in a variety of drugs, the amino acid is known to induce β-turns, stabilize protein structures and prevent enzymatic hydrolysis**

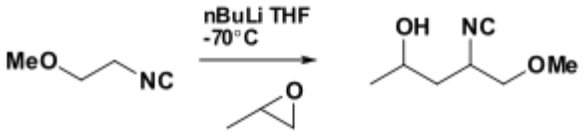
**Schoellkopf, U; Harms, R.; Hoppe, D.; Liebigs Ann. Chem. 1973, 611.**
**Schoellkopf, U.; Jentsch, R.; Hoppe, D.;ACIE, 1971, 10, 331.**




Bentley, P. H., Clayton, J. R., *J. Chem. Soc., Chem. Commun.*, (1974), 278.

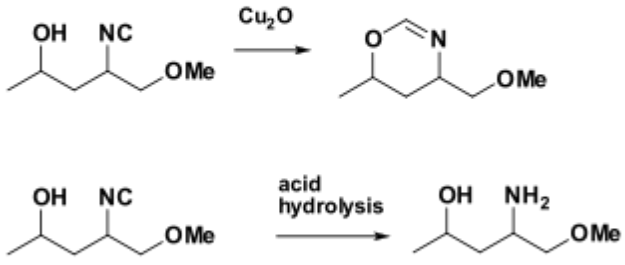
**2. γ- and β-amino alcohols**

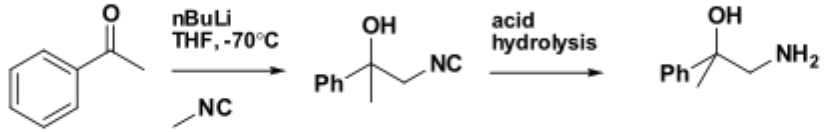
**General: β-amino alcohols from carbonyl addition**
**γ-amino alcohols from epoxide opening**




**Problem is stereoselectivity**

**Schoellkopf, U.; Jentsch, R.; ACIE, 1973, 12, 323.**

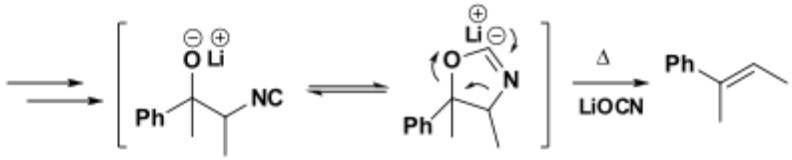



**Problem is stereoselectivity**

**Schoellkopf, U.; Boehme, P.; ACIE, 1971, 10, 491**

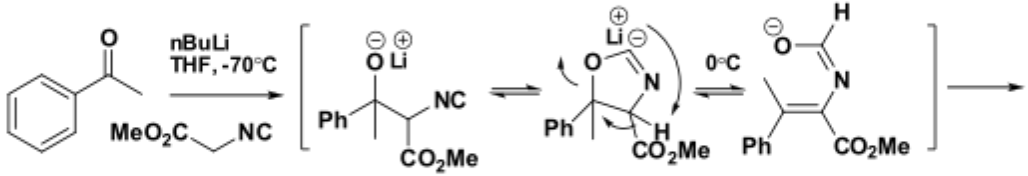
**3. Olefination, generation of vinyl-formamides**

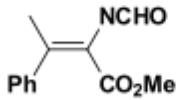



**E -> from trans**
**Z -> from cis**

**Can be written as [3+2] cycloreversion**

**Woodward, R. B.; Hofmann R ACIE, 1969,8, 781**
**Dewar, M. J. S.; ACIE, 1971, 10, 761.**

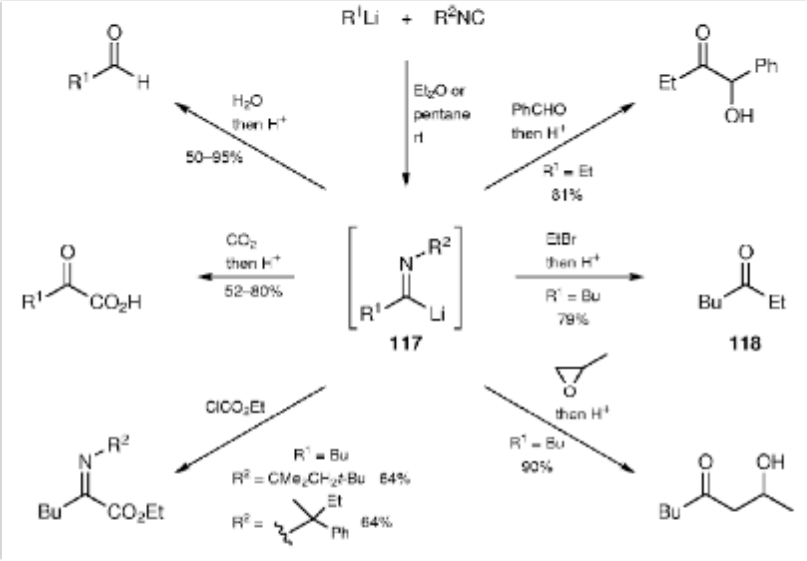


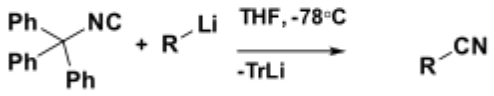

**Substrate vor catalytic asymmetric hydrogenation**
**W.S. Knowles Nobel prize**

**Nucleophilic α-attack on isocyanides - generation of imidoyllithiums:**

**Requirement: No α-protons**



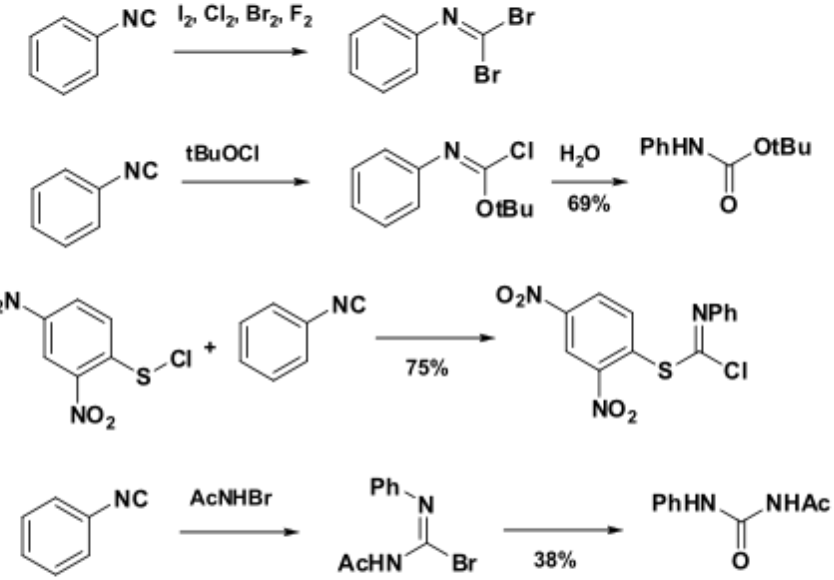

**Cyanation of organolithiums(with TrNC as reagent)**




Walborsky, H. M.; Niznik, G. E., *J. Am. Chem. Soc.*, (1969) **91**, 7778.
Niznik, G. E.; Morrison, W. H. III; Walborsky, H. M., *J. Org. Chem.*, (1974) **39**, 600.
Periasamy, M. P.; Walborsky, H. M., *J. Org. Chem.*, (1974) **39**, 611.

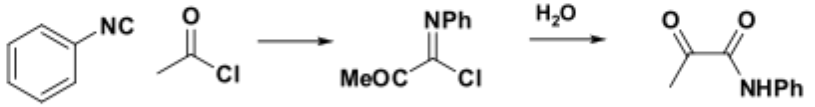
**Oxidative α-addition to isocyanides**

**Isocyanides react violently with halogens !!!**




Nef, J. U., *Justus Liebigs Ann. Chem.*, (1892) **270**, 267.
Ruppert, I., *Tetrahedron Lett.*, (1968) **21**, 4993.
Ito, Y.; Okano, M.; Oda, R., *Tetrahedron*, (1966) **22**, 447.

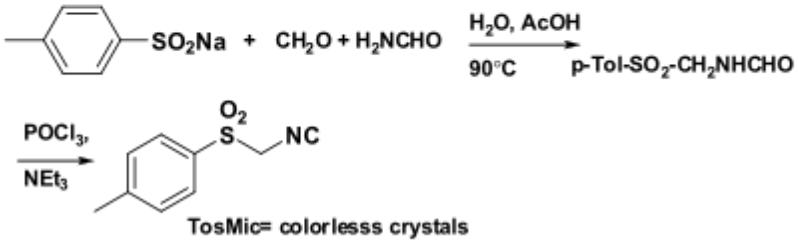
**Addition of acylchlorides**




Ugi, I.; Fetzer, U., *Chem. Ber.*, (1961) **94**, 1116.
Nef, J. U., *Justus Liebigs Ann. Chem.*, (1894) **280**, 291.

# The TosMic-reagent (construction of heterocycles)

## 1. Preparation of TosMic

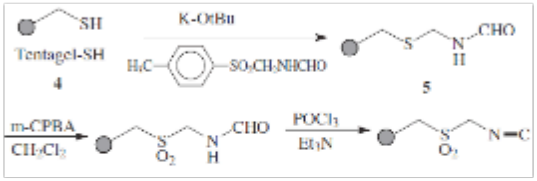



TosMic= colorlesss crystals

**Originally prepaired by irradiation of $pTsCH_2N_2$ in HCN**

A.M. VanLeusen (1980). *Lect. Heterocycl. Chem.*, 5, S111.
A.M. VanLeusen and J. Strating (1977). *Org. Synth.*, 57, 95.
A.M. VanLeusen, R.J. Bouma and O. Possel (1975). *Tetrahedron Lett.*, 3487.
A.M. Van Leusen, G.J.M. Boerma, R.B. Helmholdt, H. Siderius and J. Strating (1972). *Tetrahedron Lett.*, 2367.

**Synthesis of TosMic-derivatives**

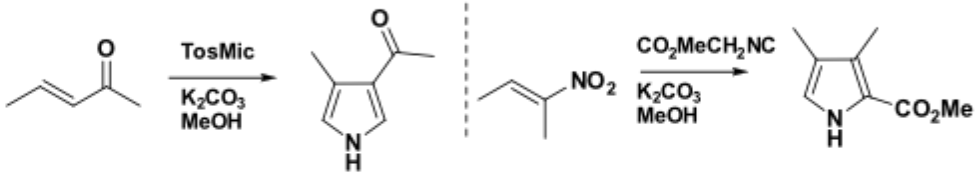



B.A. Kulkarni and A. Ganesh (1999). *Tetrahedron Lett.*, **40**, 5633.

**Alternatively: alkylation of TosMic**

## 2. Synthesis of oxazoles and pyrroles and imidazoles

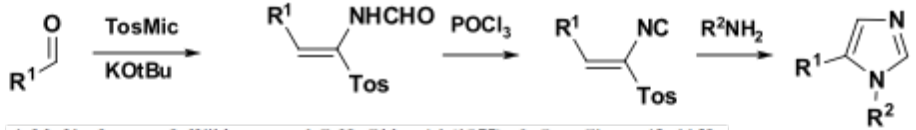
Mechanism ?



**Yields depend on aldehyde but typically>50%**

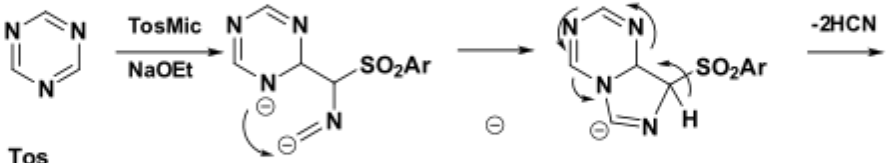
O. Possel and A.M. Van Leusen (1977). *Heterocycles*, 7, 77.
H. Saikachi, T. Kitagawa, H. Sasaki and A.M. Van Leusen (1979). *Chem. Pharm. Bull.*, 27, 793.

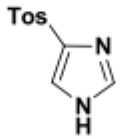
Mechanism ?




A.M. VanLeusen, J. Wildeman and O.H. Oldenziel (1977). *J. Org. Chem.*, **42**, 1153.
A.M. Van Leusen, F.J. Schaart and D. Van Leusen (1979). *Recl. Trav. Chim. Pays Bas*, **98**, 258.

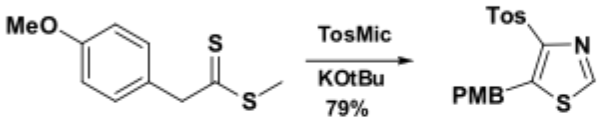
**Imidazoles from *sym*-triazines**



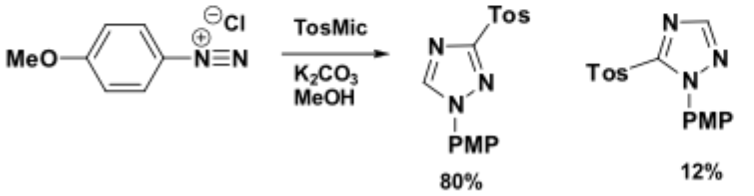

A. Kreutzberger and K. Kolter (1986). *Chem. Ztg.*, **110**, 256.

## 3. Synthesis of thiazoles and 1,2,4-triazoles



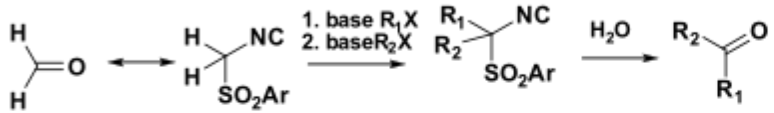

O.H. Oldenziel and A.M. Van Leusen (1972). *Tetrahedron Lett.*, 2777.

**How come there are two products ??**



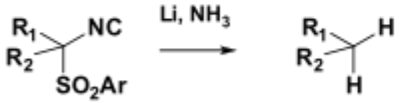

A.M. Van Leusen, B.E. Hoogenboom and H.A. Houwing (1976). *J. Org. Chem.*, 41, 711.

## 4. TosMic as an umpolungs reagent for formaldehyde



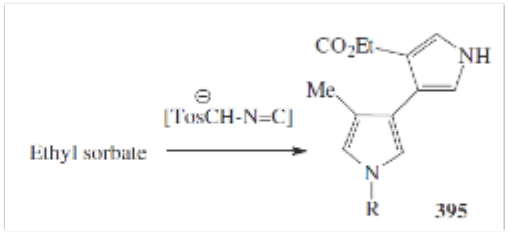

A.M. Van Leusen (1987). In: B. Zwanenburg and A.J. Klunder (Eds.), *Perspectives in the Organic Chemistry of Sulfur*, p. 119. Elsevier, Amsterdam.

## 5. Synthesis of alkanes




J.S. Yadav, P.S. Reddy and B.V. Joshi (1988). *Tetrahedron*, **44**, 7243.

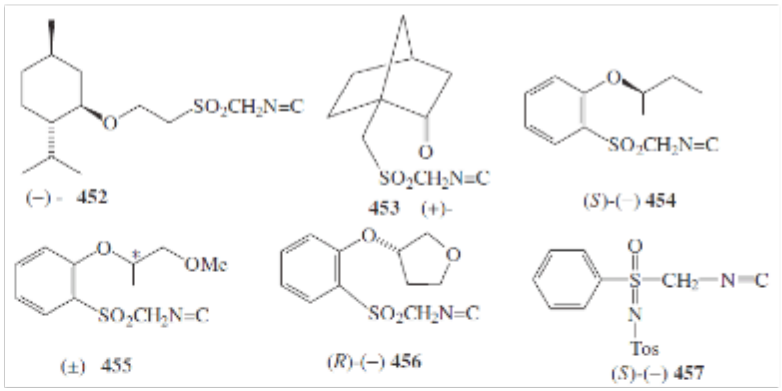
**Based on what you've learned before:**



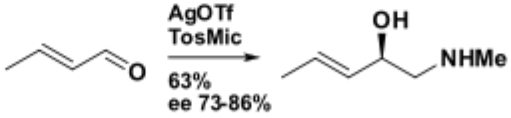

**What is the structure of ethyl sorbate ?**

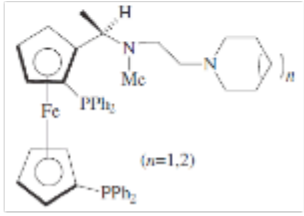
P. Magnus and Y.S. Or (1983). *J. Chem. Soc. Chem. Commun.*, **26**.

## 6. The use of chiral TosMics

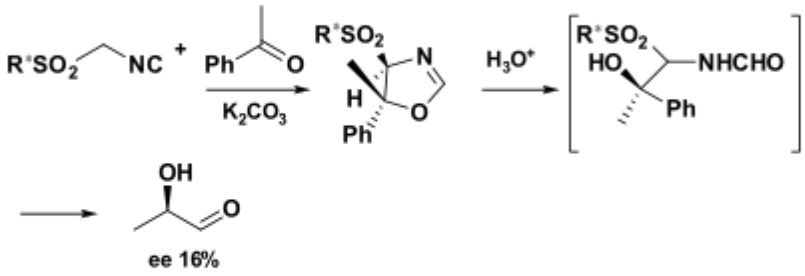



**Silver catalysis:**
**aliphatic and aromatic aldehydes are converted to aminoalcohols.**



Synthesis of α-hydroxy aldehydes



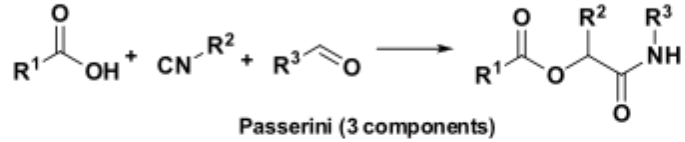

ee 16%

## Isocyanides in multicomponent reactions

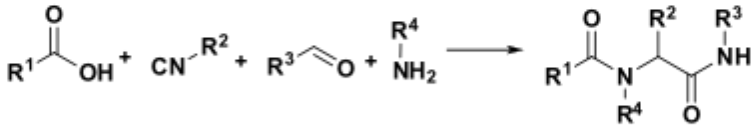
Definition: A multicomponent reaction (MCR) is a reaction where more than two starting materials are INITIALLY reacted together to form one product, and essentially all the atoms are incorporated into the product.
If not put together in the beginning then its "just" a one pot reaction

1. The Passerini and Ugi reaction

Mechanism ? and difference in Mechanism ?



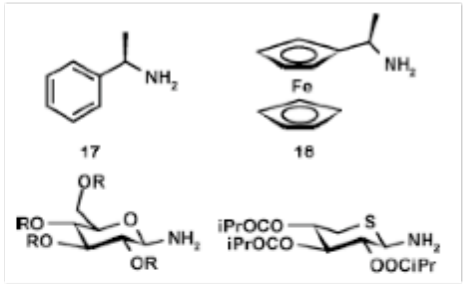

Passerini (3 components)




Ugi (4 components)

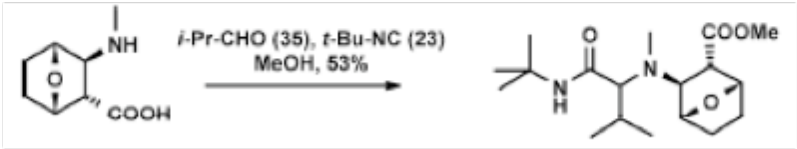
"only 1 new stereocenter formed !!

Stereochemical control gained through the amine or isonitrile component.
The Oxo-component has hardly any influence.
Reactions are typically carried out in alcoholic solutions at rt. or in toluene/benzene at reflux. Sometimes lewis or broensted acids are added in catalytic amounts to facilitate the reaction.

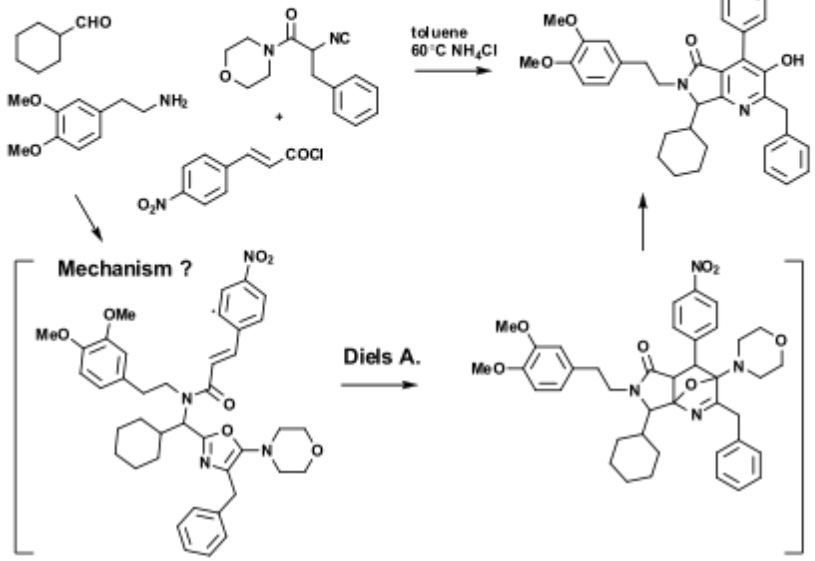



chiral amines suitable for stereoinduction in U-MCR and P-MCR
the chiral auxillary part can be cleaved off after the reaction

Typical reaction:



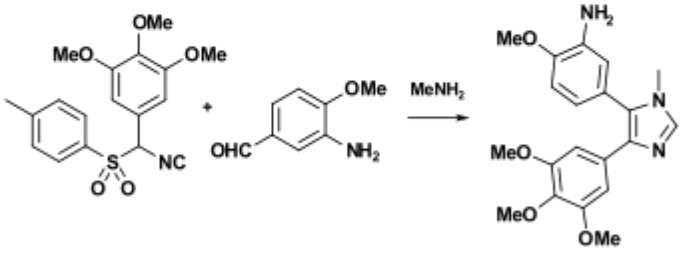
**MCRs in combination with other reactions**



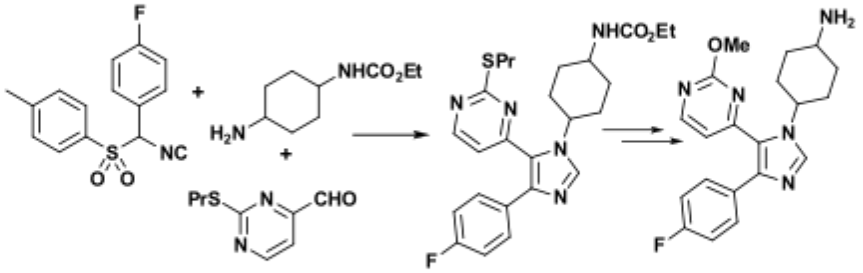

**Applications of MCRs in Drug Discovery**

**A vast number of different structures rapidly accessible => VERY useful in drug discovery**

**Abbott scientists:**
**Tubulin inhibitors same mode of action as Colchicin**

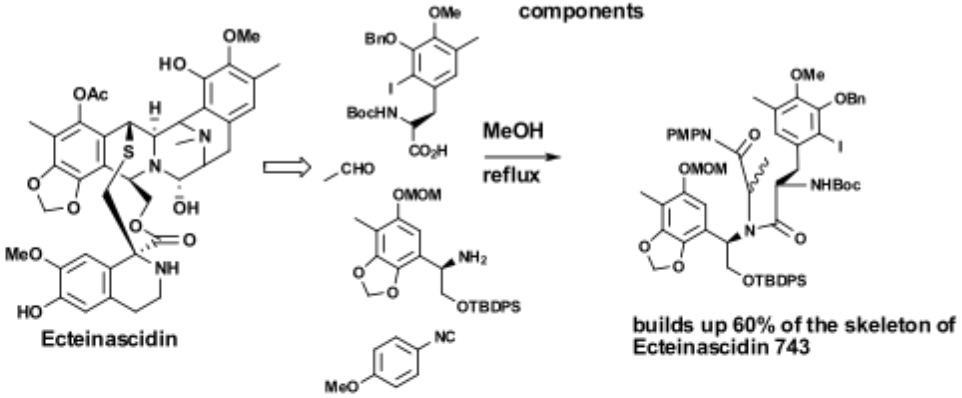



**GlaxoSmithKline (GSK):**
**p38 kinase inhibitor against rheumatoid arthritis**
**Isonitrile produced on a 500kg scale !!!**



**Applications of MCRs in Natural product synthesis**

**Which bonds are made and where are the components**

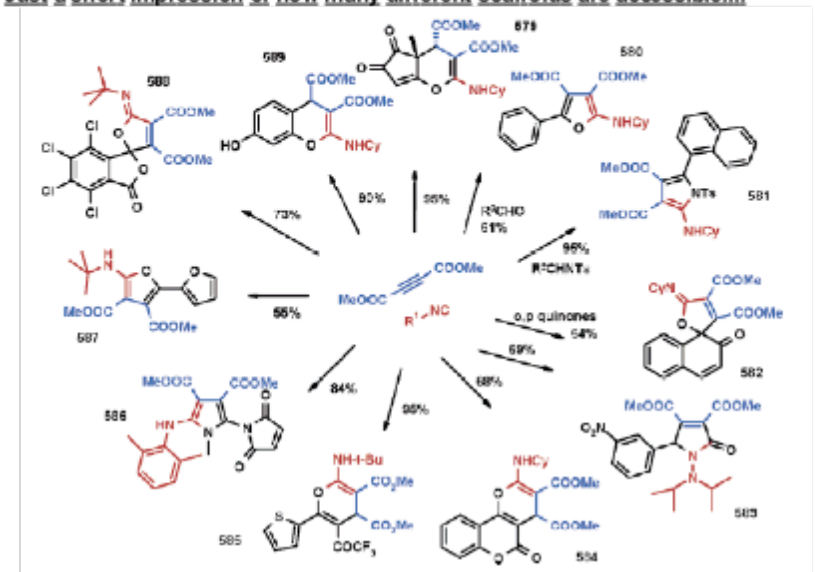



**Ecteinascidin**

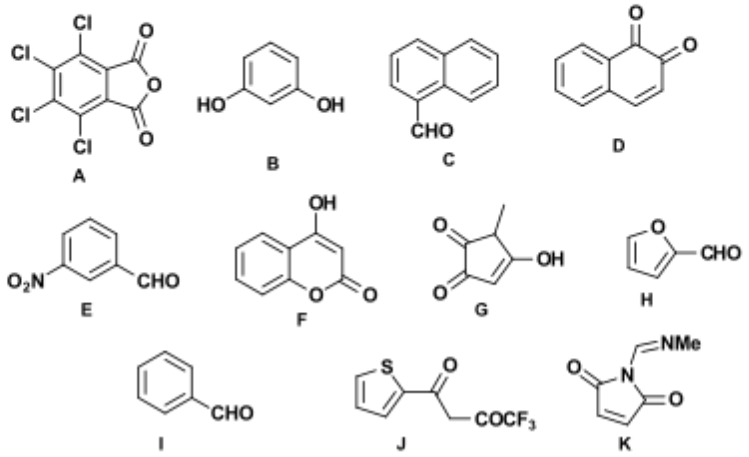
**builds up 60% of the skeleton of Ecteinascidin 743**

Endo, A.; Yamagisawa, A.; Abe, M.; Thoma,S. Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* 2002, 124, 6552.

**Just a short impression of how many different scaffolds are accessible....**



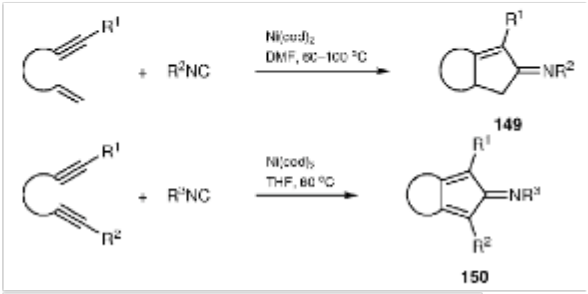
**Which belongs to which ??**




# Organometallic chemistry of isocyanide

**As isocyanides are isoelectronic to carbonmonoxid, they have a ssimilar behaviour towards transition metals**

**1. Aza-Pauson-Khand reaction**



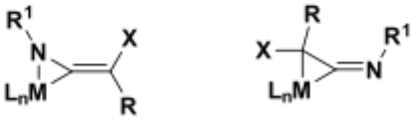

Tamao, K.; Kobayashi, K.; Ito, Y., *J. Am. Chem. Soc.*, (1988) **110**, 1286.
Tamao, K.; Kobayashi, K.; Ito, Y., *J. Org. Chem.*, (1989) **54**, 3517

**2. Reaction of isocyanides with Carbene complexes**

**X= O-alkyl, S-alkyl, $NR_2$, $PR_3$**
**$R,R^1$= alkyl, aryl, alkenyl, alkynyl**
**M= Cr, Mo, W, Mn, Fe, Os, Th, U**
**$L_n$ = CO, $PR_3$, $\eta^5$-$C_5H_5$**

**Keteneiminium complexes are formed. Complexation depends on the type of metal. For the reactivity: Umpolung of ketenimine reactivity**

**Other possibilities of coordination:**

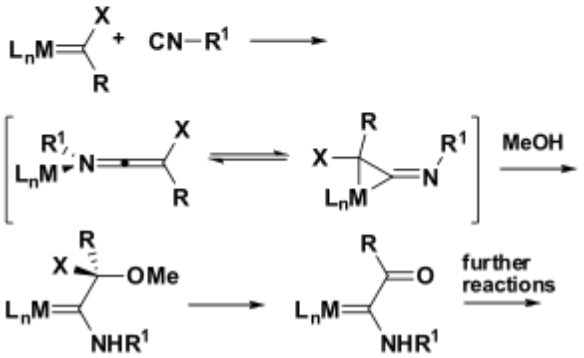


**Favoured when M= electron donating**

G. R. Krow, *Angew. Chem.* 83 (1971) 455; *Angew. Chem. Int. Ed. Engl.* 10 (1971) 435; M. W. Barker, W. E. McHenry in S. Patai (Ed.): *The Chemistry of Ketenes, Allenes and Related Compounds*, Vol. 2, Wiley, New York 1980, pp. 701–738; N. P. Gambaryan, *Russ. Chem. Rev. Engl. Transl.* 45 (1976) 630; D. Bormann in Houben-Weyl (Ed.): *Methoden der Organischen Chemie, Bd. VII/4*, Thieme, Stuttgart 1968, p. 323–339; A. Dondoni, *Heterocycles* 14 (1980) 1547; L. Ghosez, M. L. O'Donnell in P. Marchand, R. E. Lehr (Eds.): *Pericyclic Reactions, Vol. 2*, Academic Press, New York 1977, p. 79.
E. O. Fischer, *Rev. Pure Appl. Chem.* 20 (1970) 353; K. H. Dötz, H. Fischer, P. Hofmann, F. R. Kreissl, U. Schubert, K. Weiss: *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim 1983; K. H. Dötz, *Angew. Chem.* 96 (1984) 573; *Angew. Chem. Int. Ed. Engl.* 23 (1984) 587; H. Fischer in S. Patai (Ed.): *The Chemistry of Metal-Carbon Bonds*, Wiley, New York 1983, pp. 181–224; P. L. Pauson in: Houben-Weyl (Ed.): *Methoden der Organischen Chemie, Bd. E19*, Thieme, Stuttgart 1987, p. 2815.

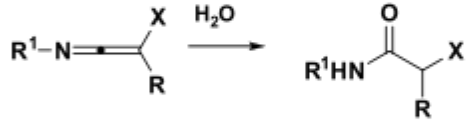
**Keteneimines are they chiral ??**

**In contrast to metal free keteneimines,**
**metal complexed ones react like 1,3 dipoles.**
**The metal undergoes a shift to the central arom !!**
**Protic nucleophiles can attack to give aminocarbene complexes**



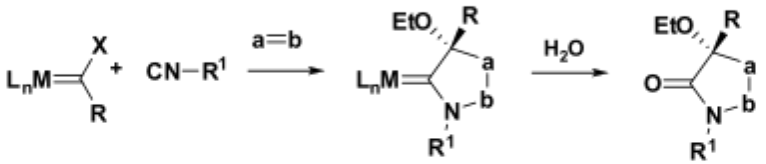

**X= O-alkyl, S-alkyl, $NR_2$, $PR_3$**
**R,$R^1$= alkyl, aryl, alkenyl, alkynyl**
**nucleophiles: alcohols, thiols, amines, $H_2O$**
**$L_nM$= $[Cr(CO)_5]$, $[Mo(CO)_5]$, $[W(CO)_5]$, $[Mn(CO)_2Cp]$, $[Fe(CO)_4]$**

**Comparison hydrolysis of keteneimine**

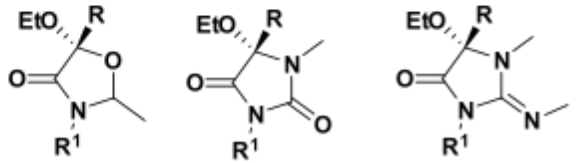



Aumann, R.; Heinen, H. *Chem. Ber.* 120, 1987, 1297.
Aumann, R.; Heinen, H. *Chem. Ber. 121,* 1988.
Aumann, R.; Kuckert, E.; Heinen, H. *Angew. Chem. 97, 1985, 960;*

**[3+2]-Cycloadditions**




**a=b: O=CHR, RN=CO,, RN=CNHR,**
**$L_nM$= $[W(CO)_5]$, $[Mn(CO)_2Cp]$,** **Reaction at room temperature**

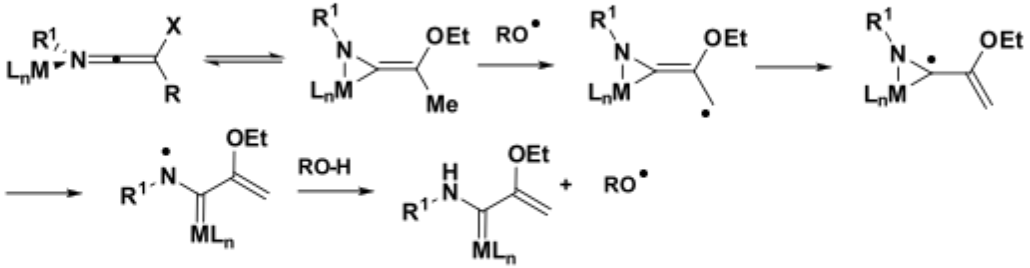


Aumann, R.; Kuckert, E. *Chem. Ber.*, 119, 1986, 156.

**Rearrangements of metal-keteneimines**

**1. Keteneimine aminocarbene rearrangement**

**rearrangement takes place readily. triggered by oxygen/peroxides**



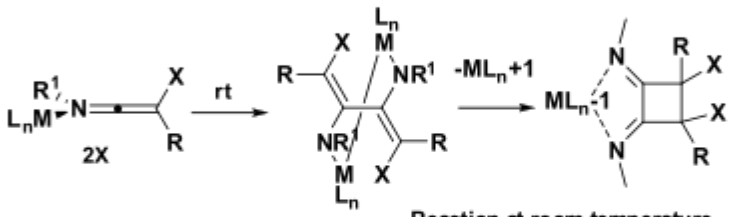

**$L_nM$= $[Cr(CO)_5]$, $[Mo(CO)_5]$, $[W(CO)_5]$**

Aumann, R.; Kuckert, E.; Heinen, H. *Chem. Ber.*, 120,1987, 1293
Ariyaratne, J. K. P.; Green, M. L. H. *J. Chem. Soc., 1963,2976;*
*Treichel, P. M.; Firisch, D. W.; Lemmon, T. H.* J. Organomet. Chem. *202,* 1980 C77.
Aumann, E; Fischer, O. *Chem. Ber. 101,* 1968, 954; Kreiter, R.; Aumann *ibid. 119, 1978,* 1223.

# Isocyanide Chemistry

Tanja Gaich

**Dimerization of Keteneimine ligands**



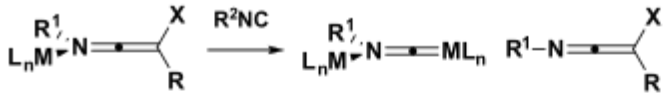

Reaction at room temperature

X= OMe
LnM= [Cr(CO)5], [Mo(CO)5], [W(CO)5]

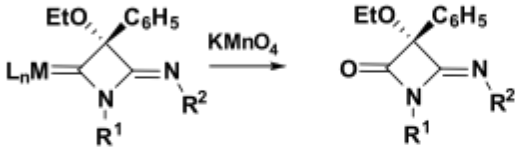
Aumann, R.; Krueger, C.; Heinen, H. *Angew. Chem. Int. Ed*, 24, 1985, 987.
Aumann, R.; Heinen, H. *Chem. Ber.* 118, 1985, 952.

**Addition of isocyanides to ketneimine complexes:**

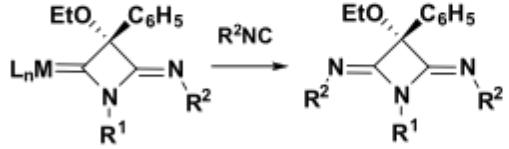
1. Addition of isocyanide to metal with displacement of keteneimine




2. [3+1] or [2+2] CA of isocyanides to keteneimine complex

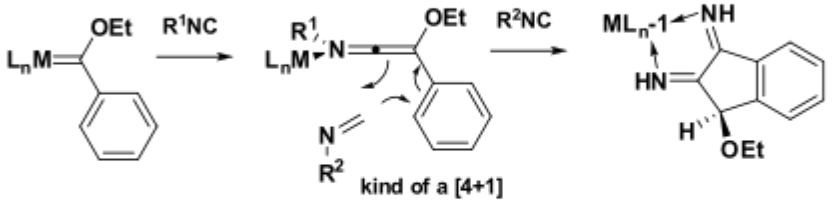



3. [2+1+1] CA of 2 isocyanides to N=C-bond of keteneimine




Moderhack, D. *Synthesis*, 12, 1985, 1083.
Aumann, R.; Krueger, C.; Kuckert, E. Angermund, K. *Angew. Chem. Int. Ed*. 26, 1987, 563.
Aumann, R.; Heinen, H.; *Chem. Ber.* 119, 1986, 2289.

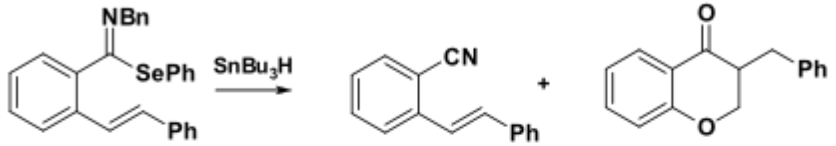
4. [4+1] CA of isocyanides to C-aryl substituted keteneimine



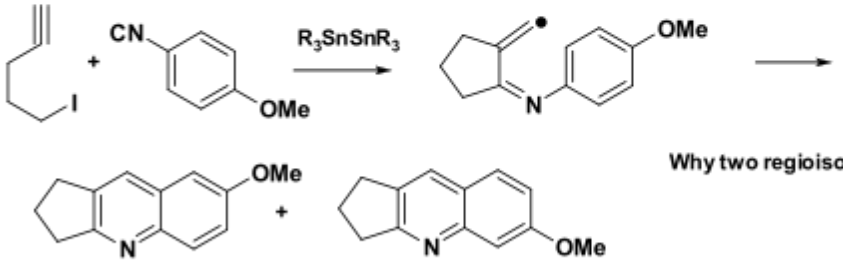

Aumann, R.; Heinen, H. *Chem. Ber.* 118, 1985, 4186.
Aumann, R.; Kuckert, E.; *Chem. Ber.* 119, 1986, 156.
Aumann, R.; Heinen, H. *Chem. Ber.* 121, 1988, 1085.

## Isocyanides in Radical chemistry

Isocyanides participate in radical additions like CO...(isoelectronic!!)
Difference to CO radical addition:
They don't undergo $\alpha$-fragmentation but $\beta$-fragmentation instead to give nitriles.
Therefore isocyanides without good $\beta$-leaving groups are preferred substrates.
In the process of radical addition the so called imidoyl radical is formed which then undergoes further reactions.



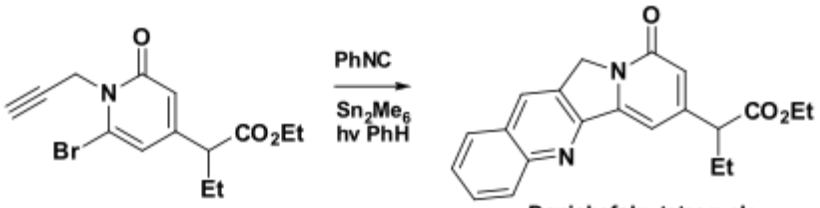

fragmentation product 1 : 1 radical cyclization

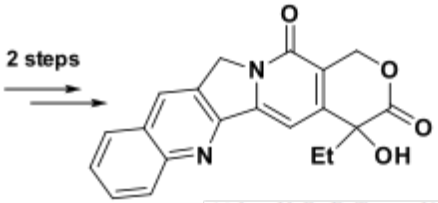



Why two regioisomers ??

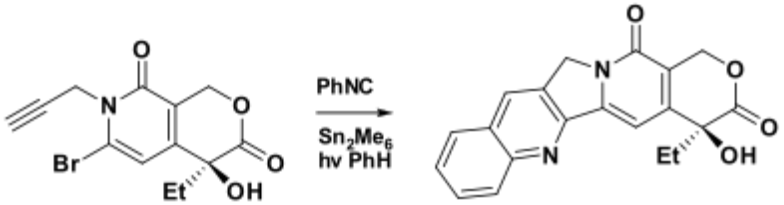
See: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1991**, *113*, 2127. (b) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1988**, *53*, 3377. (c) Patel, V. F.; Pattenden, G. *Tetrahedron Lett.* **1988**, *29*, 707.

**The total synthesis of Camptothecin**




(a) Liu, H. Ph.D. Thesis, University of Pittsburgh, 1994. (b) Ko, S.-B. University of Pittsburgh. Unpublished results.

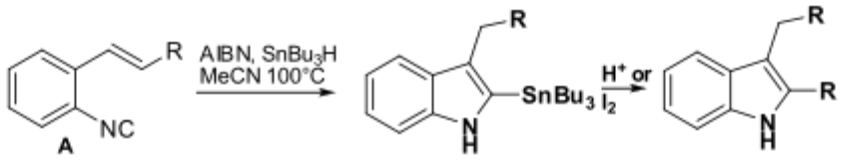



**The chemistry is very convergent and therefore gives easy access to analogs.**

(a) Danishefsky, S.; Volkmann, R. *Tetrahedron Lett.* **1973**, 2521. (b) Volkmann, R.; Danishefsky, S.; Eggler, J.; Solomon, D. M. *J. Am. Chem. Soc.* **1971**, *93*, 5576.
Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863.

(a) Curran, D. P.; Ko, S. B. *J. Org. Chem.* **1994**, *59*, 6139. (b) Fang, F. G.; Xie, S. P.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142.

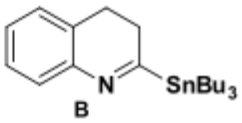
**Fukuyama Indole Synthesis:**




**R= should be electron withdrawing**
**if R= alkyl then by-product B formed**

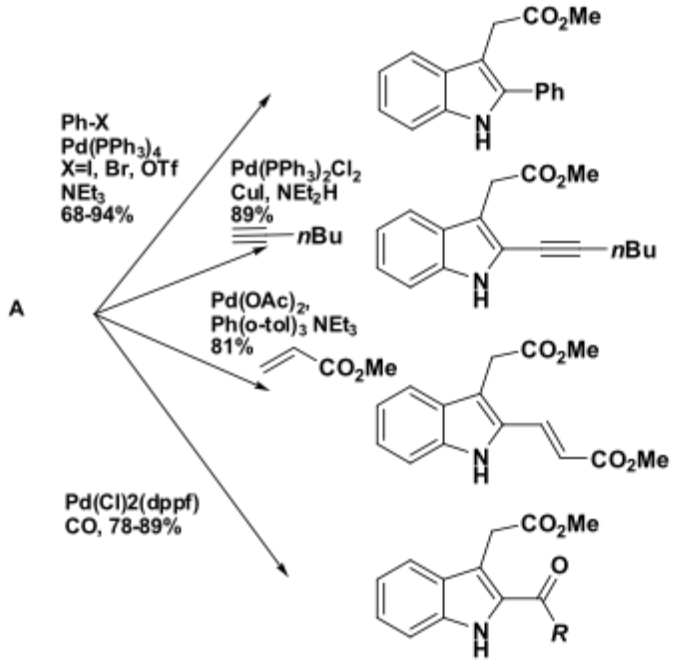
**Yields >70%**

**R=H, or I**

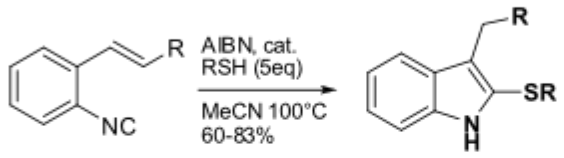



**Mechanism of rxn ? Why is by-product formed**

**Further elaboration to yield 2,3 disubstituted indoles**

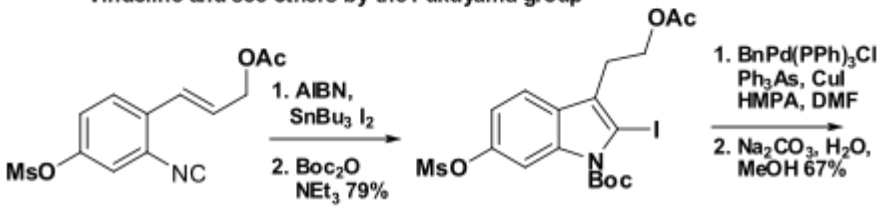


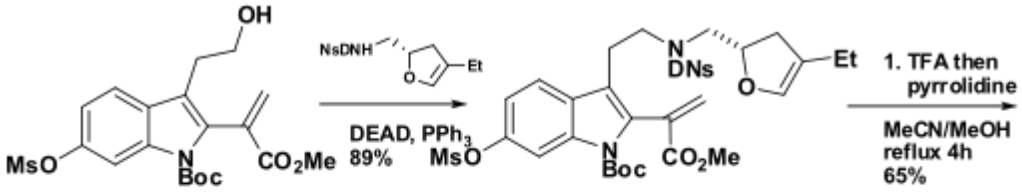
**Fukuyama Indole Synthesis:**



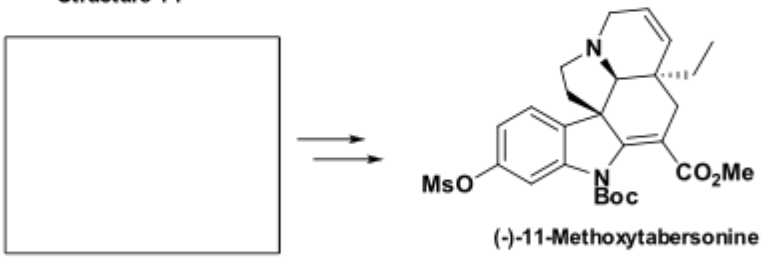

**Application to Total Synthesis**

**Vindoline and see others by the Fukuyama group**




**Structure ??**




**(-)-11-Methoxytabersonine**

Fukuyama, T. et al. Chem. Record 2002, 37.
Fukuyama, T. et al. Synlett, 2000, 883.

## Conclusions:

For the making of isocyanides:

There is a variety of different reagents available which show different reactivities check carefully which one suits your substrate !!

For α-anion chemistry of isocyanides:

Alkylation takes place stepwise (no problem of double alkylation)
It represents the umpolung of a carbonyl functionality
A variety of different functionalities are accessible.

For α–addition chemistry of isocyanides:

Two ways: 1. generation of imidoyllithium and addition of electrophile
2. Oxidative

TosMic-reagent for construction of all kinds of heterocycles !!

MCRs:

Wide applications in drug-design couple with other reactions and you get a dramatic increase in molecular complexity

Organometallic chemistry:

No broad application so far, huge variety of different structures

Radical chemistry:

Problem of β-elimination !!
selene or stannylimidates as analog starting units

## Needs for Development:

General problem of reactions where isocyanides participate is the stereoselectivity. There are some specific solutions but nothing general like the Evans auxillary
MCRs, chiral TosMic give ee's to some extent but a large range of improvement exists.
Organometallic chemistry there is no chiral transition metal complex in application
In Organometallic chemistry of isocyanides there is probably the most chance to discover something new.