

Introduction

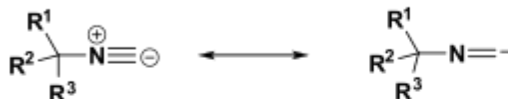
Isonitriles known since 1850s. Their exact structure was solved later with modern abinitio calculations.
 Characteristic hideous smell or pungent stench
 Term "isonitrile" not accepted by IUPAC

Physical data:

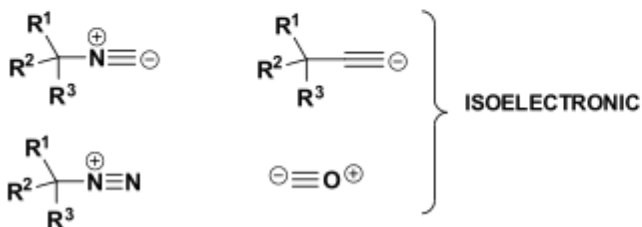
IR: 2150-2110 cm⁻¹ weak-medium intensity
 13C-NMR: 156-170 ppm
 Their carbon atom is formally divalent.

-> Very unusual electronic structure:

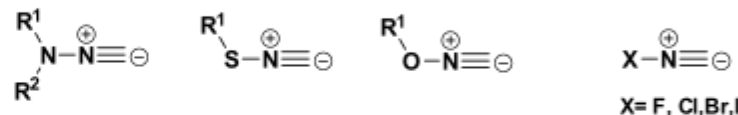
- Reacts as carbene,
- with nucleophiles,
- with electrophiles,
- in radical reactions
- and is isoelectronic with CO therefore a broad organometallic chemistry



a) I. Ugi (Ed.): *Isocyanide Chemistry*, Academic Press, New York 1971.
 b) J. A. Green, P. T. Hoffmann in [1a]; p. 1; G. H. M. Walborsky, M. F. Ferrisamy in S. Patai, Z. Rappaport (Eds.): *The Chemistry of Triple Bonded Functional Groups, Part 2, Supplement*, Wiley-Interscience, New York 1983, p. 875.



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

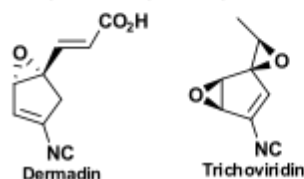
Edenborough, M. S.; Herbert, R. B. *Naturally occurring isocyanides, NPR*, 1988,229-245.

Chang, C. W. J. *Naturally occurring isocyno/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.)

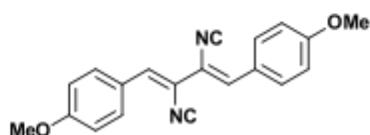
Cyclopentyl isocyanides



Dermadin and trichoviridin soil sample (fungus)
active against staphylococcus aureus

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

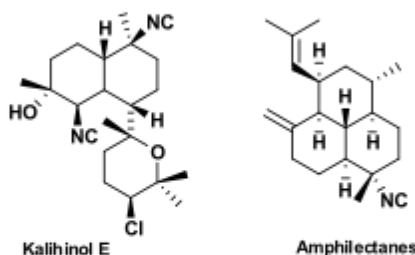
Xanthocillines



xanthocillines soil sample (fungus)
antiviral antibiotics

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

Diterpenes

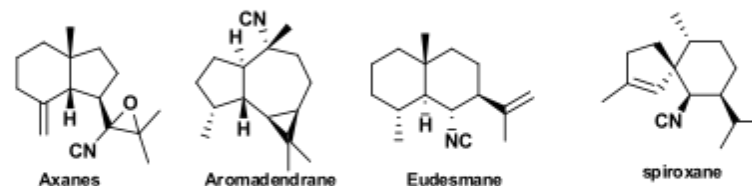


Diterpenes with trans or cis decalin core
Divided in Tetrahydrofuran and -pyran types

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



Skeletal types that contain isocyanides

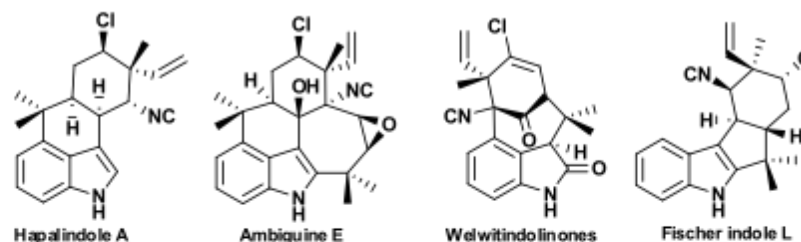
(Eudesmanes, Axanes, Aromadendrane, Epimaaliane, Cadinane, Spiroaxane,
Bisabolane, Pupukeanane, Guaiane.)

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

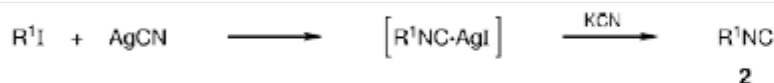


Isolated by cyanobacteria *fischerella* species
prenylated indolalkaloids

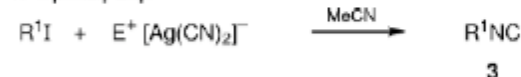
Moore, R. E.; Cheuk, C.; Yang, Xu Q. G.; Patterson, G. M. L.; Bonjouklian, R.; Smitka, T. A.; Mynderse, J. S.; Foster, R. S.; Jones, N. D.; *J. Org. Chem.* 1987, 1036.
Smitka, T. A.; Bonjouklian, R.; Doolin, L.; Jones, N. D.; Deeter, J. B.; Yoshida, W. Y.; Prinsep, M. R.; Moore, Richard E.; Patterson, 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 alkyl iodides with silver salts



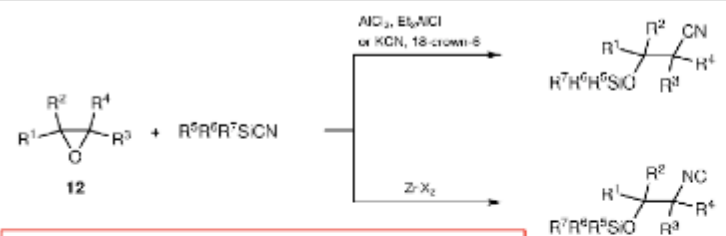
R^1 = primary alkyl



R^1 = Me, CH_2Ar^1 ; E = Me_2N , Ph_3PMe , Ph_4As

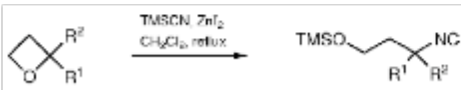
Green, J. A., I. Hoffmann, P. T., In *Isocyanide Chemistry*, Ugi, I., Ed., Academic, New York, (1971), p. 1.
 Gautier, A., *Justus Liebig's Ann. Chem.*, (1867) **142**, 280.
 Hoffmann, A. W., *Justus Liebig's Ann. Chem.*, (1867) **144**, 114.
 Lieke, W., *Justus Liebig's Ann. Chem.*, (1959) **112**, 316.
 Meyer, L., *J. Prakt. Chem.*, (1866) **67**, 147.
 Songstad, J.; Stangland, L. 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



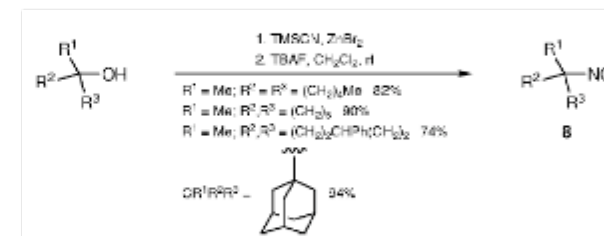
NOTE: $Ti(OiPr)_4, AlCl_3, Et_2AlCl$ lead to CYANIDES
 $ZnI_2, ZnCl_2$ lead to ISOCYANIDES

Gassman, P. G.; Haberman, L. M., *J. Org. Chem.*, (1966) **61**, 5010.
 Gassman, P. G.; Guggenheim, T. I., *J. Am. Chem. Soc.* (1962) **104**, 5849.
 Gassman, P. G.; Gremban, R. S., *Tetrahedron Lett.* (1984) **25**, 3259.



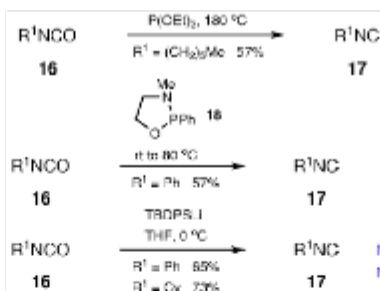
Gassman, P. G.; Haberman, L. M., *Tetrahedron Lett.*, (1985) **26**, 4971.
 Carr, S. A.; Weber, W. P., *Synth. Commun.*, (1985) **15**, 775.

3. Reaction of tertiary alcohols with TMS-cyanide



Sasaki, T.; Nakanishi, A.; Ohno, M., *J. Org. Chem.*, (1981) **48**, 5445.
 Kikano, Y.; Chiba, K.; Tada, M., *Tetrahedron Lett.*, (1999) **38**, 1911.

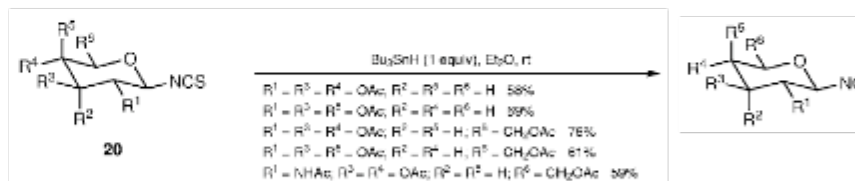
4. From deoxygenation of isocyanates



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.*, (1992) **27**, 3651.
 Mukaiyama, T.; Yokota, Y., *Bull. Chem. Soc. Jpn.*, (1955) **38**, 858.

5. From desulfuration of isocyanates

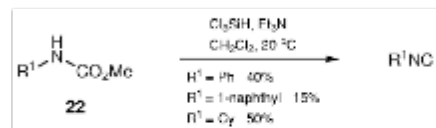


Alternative conditions: $P(OEt)_3$ rt

same principle different name - which ?

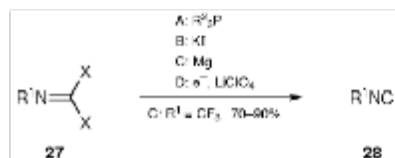
Witezak, Z. J., *Tetrahedron Lett.*, (1986) **27**, 156.
 Lorenz, D. H.; Recker, F. I., *J. Org. Chem.* (1963) **28**, 1707.

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

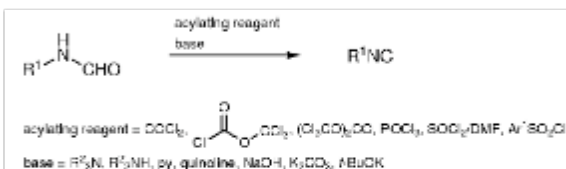


Holtschmidt, H. *Angew. Chem.*, (1952) **74**, 861

Lenka, D., *J. Fluorine Chem.*, (1994) **24**, 923.

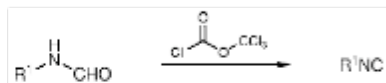
Galindo, A.; Zapata, A.; Forner, M. *Tetrahedron Lett.*, (1992) **33**, 4779.

8. By dehydration of Formamides



Ugi, I.; Meyr, R., *Chem. Ber.*, (1950) **83**, 239.

8a. By dehydration with phosgene or diphosgene



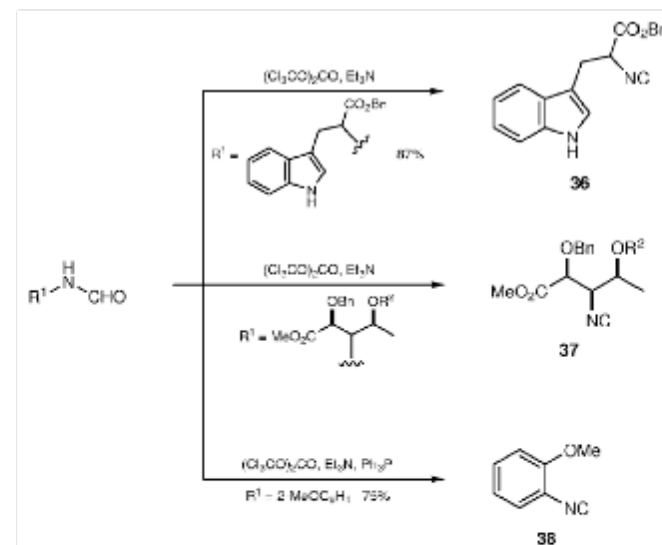
- a. NEt_3 and DCM used at -30°C
 b. NBu_3 as base solvent 1,2-dichlorobenzene
 c. 1,2-dichlorobenzene as solvent
 d. base: 4-methylmorpholine

R ¹	Yield (%)	Ref
	Trichloromethyl Chloroformate ^a	Phosgene
Me	47 ^b	37 [43]
t-Bu	91 ^c	82 [49]
Cy	90	89 [43]
Un	95	92 [43]
4-MeCO ₂ H ₂	95	64 [43]
CH ₂ CO ₂ Me	82	47 [43]
CH ₂ CO ₂ H	75 ^d	51 [49]

Ugi, I.; Feizer, U.; Eholzer, U.; Knupfer, H.; Offermann, K., *Angew. Chem.*, (1965) **77**, 492; *Angew. Chem. Int. Ed. Engl.*, (1965)

Skarna, 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.
 Muzina, M. S.; Pedersen, L. 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.; Alzpurua, J. M.; Urechegui, R.; Garcia, J. M., *J. Org. Chem.*, (1993), **58**, 1646.

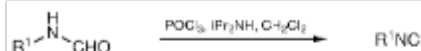
Wells, A., *Synth. Commun.*, (1984), **24**, 1745.

8c. By dehydration with vilsmeier reagent or thionyl chloride

R ¹	Yield (%)	Ref
Tr	95	[50]
OMe, CH ₂ -t-Bu	93	[50]
(R)-(+)-CMeHPh	92	[50]
OMePh ₂	90	[50]
(R)-(-)-2,2-diphenyl-1-methylcyclopropyl	88	[50]
Cy	87	[52]
(F)-CPh=CHPh	84	[52]
(CH ₂) ₅ Me	82	[52]
4-MeOC ₆ H ₄	82	[52]
2,6-Me ₂ C ₆ H 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., II; Walborsky, H. M., *Org. Synth., Coll. Vol. VI*, (1988), 751.



R ¹	Yield (%)	Ref
CH ₂ CO ₂ Me	75	[55]
CH ₂ CO ₂ Et	84	[55]
CH ₂ PhCO ₂ Me	70	[55]
2-Tol	50	[55]
	53-73	[55]
Cy	57-72	[55]
2,4,6-IPr ₂ C ₆ H ₂	90	[55]
4-O ₂ NC ₆ H ₄	77	[55]
4-TBDMSOC ₆ H ₄	56	[55]

Ugi, I.; Meyr, R., *Chem. Ber.*, (1968) **99**, 289.

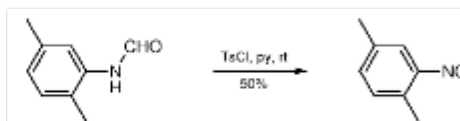
Ugi, I.; Meyr, R., *Angew. Chem.*, (1968) **70**, 702.

Gbrecht, R.; Herrmann, R.; Ugi, I., *Synthese*, (1968), 400.

Ugi, I.; Meyr, R., *Org. Synth., Coll. Vol. V*, (1973), 1000.

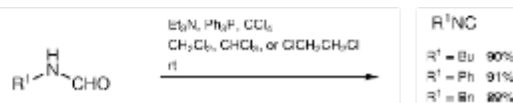
Ugi, I.; Meyr, R.; Lipinski, M., *Org. Synth., Coll. Vol. V*, (1973), 300.

Hoozenboom, B. E.; Oldenziel, O. H.; van Leusen, A. M., *Org. Synth., Coll. Vol. VI*, (1988), 987.

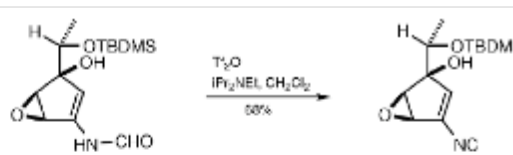
8d. By dehydration with vilsmeier reagent or phosphoryl chloride

Hofker, W. R.; Corey, E. J., *J. Org. Chem.*, (1966) **29**, 1221.

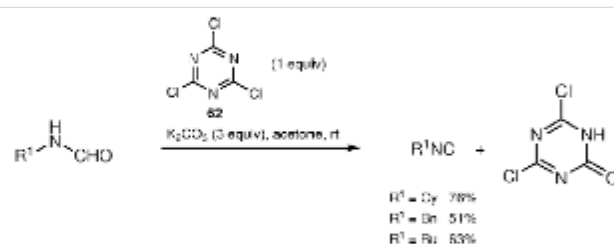
Casanova, J., Jr.; Schuster, R. E.; Werner, N. D., *J. Chem. Soc.*, (1963), 4280.

8e. With other reagents

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



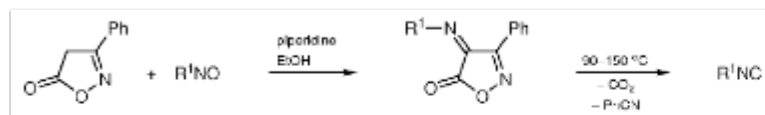
Baldwin, J. E.; Aldous, D. J.; Chan, C.; Harwood, L. M.; O'Neil, I. A.; Peach, J. M., *Synlett*, (1989), 9.



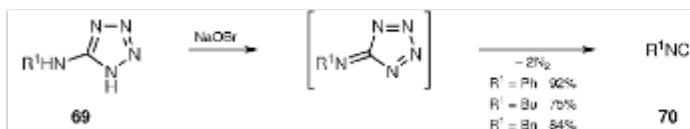
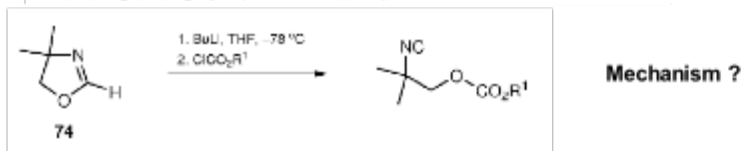
Wittmann, R., *Angew. Chem.*, (1961) **73**, 219.

Mechanism ?

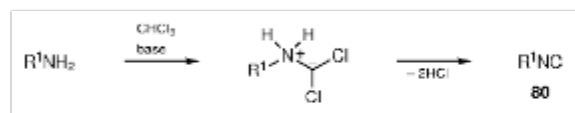
Mechanism ?

R¹ mostly aromatic heterocyclesWentrup, C.; Sturz, U.; Wollweber, H.-J., *Angew. Chem.*, (1978) **90**, 731; *Angew. Chem. Int. Ed. Engl.*, (1978) **17**, 588

Mechanism ?

Hoffe, G.; Lange, B., *Angew. Chem.*, (1976) **88**, 80; *Angew. Chem. Int. Ed. Engl.*, (1976) **15**, 113Hoffe, G.; Lange, B., *Org. Synth., Coll. Vol. VII*, (1990) 27.Gerhart, F.; Schoellkopf, U., *Tetrahedron Lett.*, (1968), 6231Meyers, A. I.; Adkins, H. W., *Tetrahedron Lett.*, (1969), 5151

8f. By the Carbylamine reaction



NOTE: Especially useful for aromatic isocyanides

Gckel, G. W.; Widora, R. P.; Weber, W. P., *Org. Synth., Coll. Vol. VI*, (1988), 232.Krapcho, A. P., *J. Org. Chem.*, (1962) **27**, 1089Sasaki, T.; Fguchi, S.; Katada, T., *J. Org. Chem.*, (1974) **39**, 1238Which other reactions contain α -eliminations??

Reactions of Isonitriles

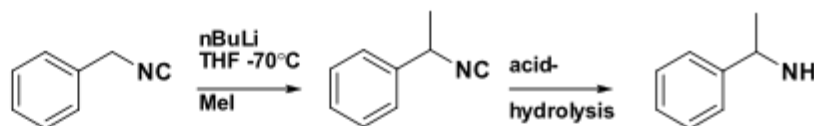
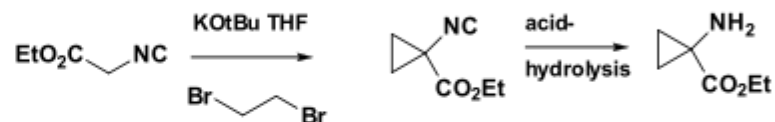
 α -alkali-metalated isocyanides:

react with electrophiles to give, olefines, vinylisocyanides, ketones, 1-amino-alcohols, 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-aza, thia-aza).

Schoellkopf and Gerhart in 1968 found out that isocyanides are α -acidic. Deprotonation is carried out at -70°C with $n\text{BuLi}$ 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 carbanionsSchoellkopf, 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.

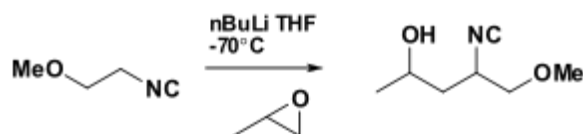
Schoellkopf, U.; Jentsch, R.; Hoppe, D.; *ACIE*, 1971, 10, 331.



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

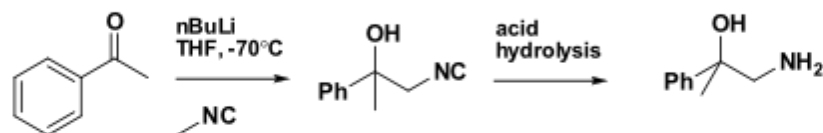
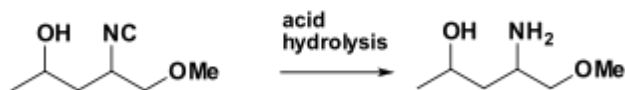
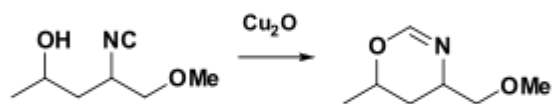
2. γ and β -amino alcohols

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



Problem is stereoselectivity

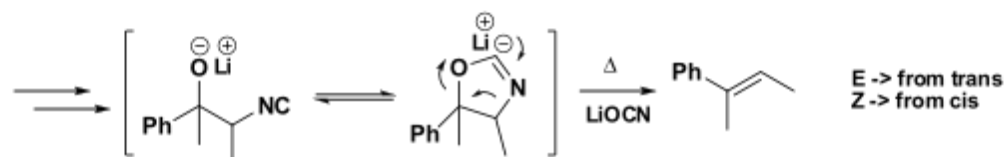
Schoellkopf, U.; Jentsch, R.; *ACIE*, 1973, 12, 323.



Problem is stereoselectivity

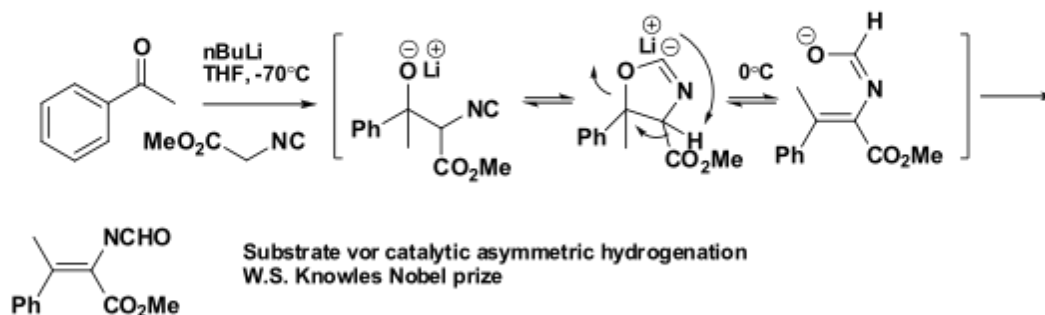
Schoellkopf, U.; Boehme, P.; *ACIE*, 1971, 10, 491

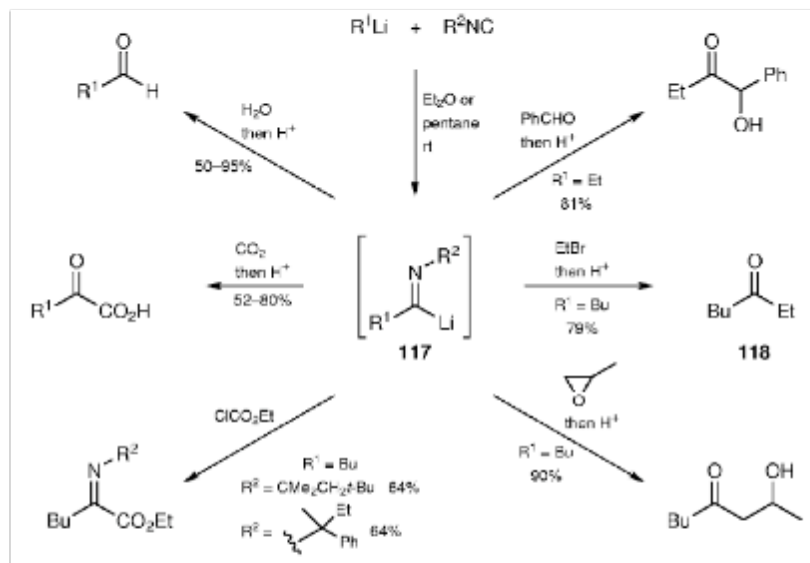
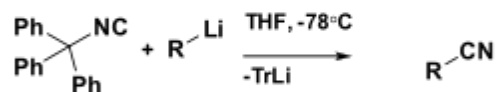
3. Olefination, generation of vinyl-formamides



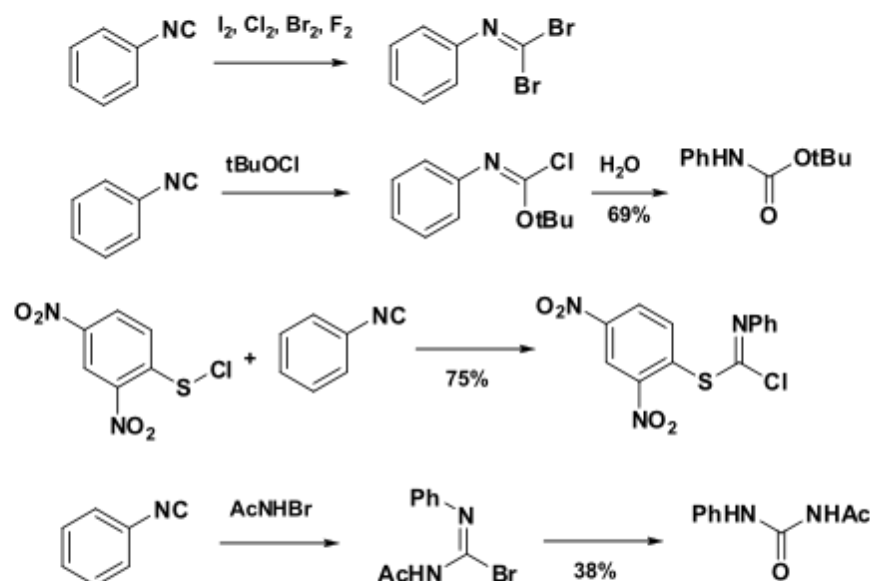
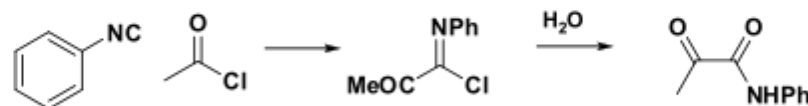
Can be written as [3+2] cycloreversion

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



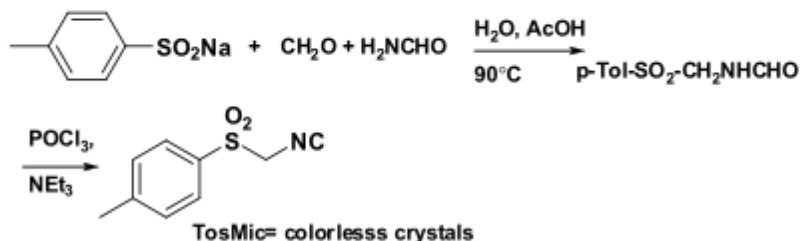
Nucleophilic α -attack on isocyanides - generation of imidoyllithiums:Requirement: No α -protons**Cyanation of organolithiums (with $TrNC$ as reagent)**Walborsky, H. M.; Niznik, G. E., *J. Am. Chem. Soc.*, (1959) **81**, 7778.Niznik, G. E.; Morrison, W. H. III; Walborsky, H. M., *J. Org. Chem.*, (1974) **39**, 600.Perlasamy, 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.*, (1852) **270**, 267.Ruppert, I., *Tetrahedron Lett.*, (1960) **21**, 4993.Ito, Y.; Okano, M.; Oda, R., *Tetrahedron*, (1996) **22**, 447.**Addition of acylchlorides**Ugi, I.; Felzer, U., *Chem. Ber.*, (1951) **84**, 1116.Nef, J. U., *Justus Liebigs Ann. Chem.*, (1854) **280**, 291.

The TosMic-reagent (construction of heterocycles)

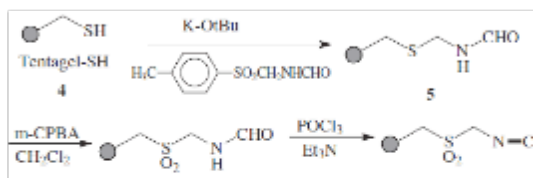
1. Preparation of TosMic



Originally prepared by irradiation of pTsCH_2N_2 in HCN

A.M. VanLeusen (1980). *Leit. 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. Boerms, R.B. Helmholdt, H. Siderius and J. Strating (1972). *Tetrahedron Lett.*, 2367.

Synthesis of TosMic-derivatives

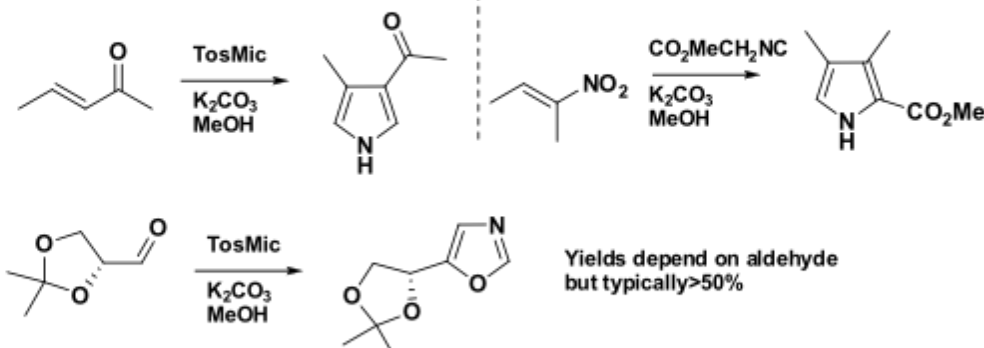


B.A. Kulkarni and A. Ganesh (1999). *Tetrahedron Lett.*, 40, 5633.

Alternatively: alkylation of TosMic

2. Synthesis of oxazoles and pyrroles and imidazoles

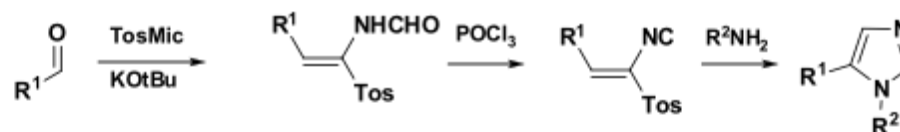
Mechanism ?



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.

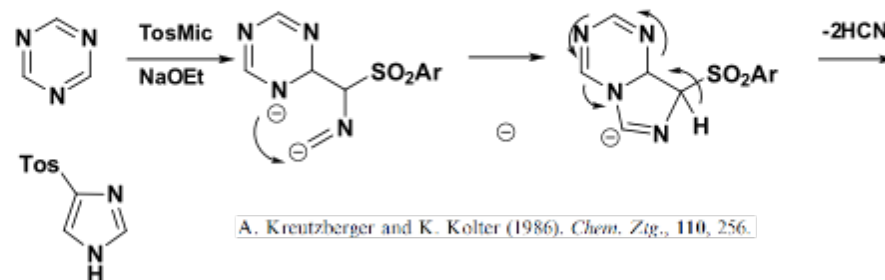
Mechanism ?



A.M. VanLeusen, J. Wildeman and O.H. Oldenzel (1977). *J. Org. Chem.*, 42, 1153.

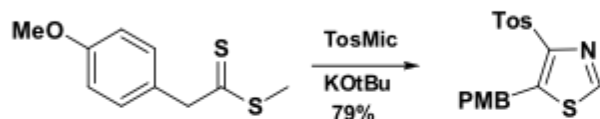
A.M. Van Leusen, F.J. Schaart and D. Van Leusen (1979). *Recl. Trav. Chim. Pays Bas*, 98, 258.

Imidazoles from sym-triazines



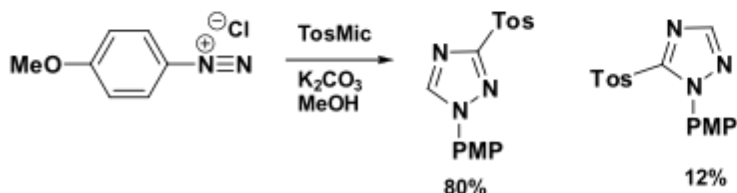
A. Kreutzberger and K. Kolter (1986). *Chem. Ztg.*, 110, 256.

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



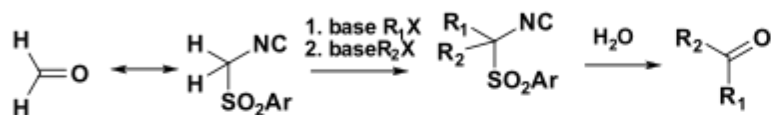
O.H. Oldenzick and A.M. Van Leusen (1972). *Tetrahedron Lett.*, 2777.

How come there are two products ??



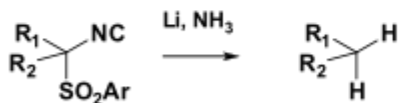
A.M. Van Leusen, B.E. Hoogenboom and H.A. Houwing (1976). *J. Org. Chem.*, 41, 711.

4. TosMic as an umpolungs reagent for formaldehyde



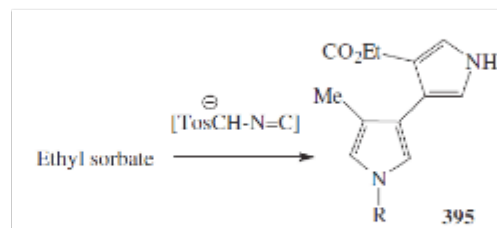
A.M. Van Leusen (1987). In: B. Zwanenburg and A.J. Klunder (Eds.), *Perspectives in the Organic Chemistry of Sulfur*, p. 119. Elsevier, Amsterdam.

5. Synthesis of alkanes



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

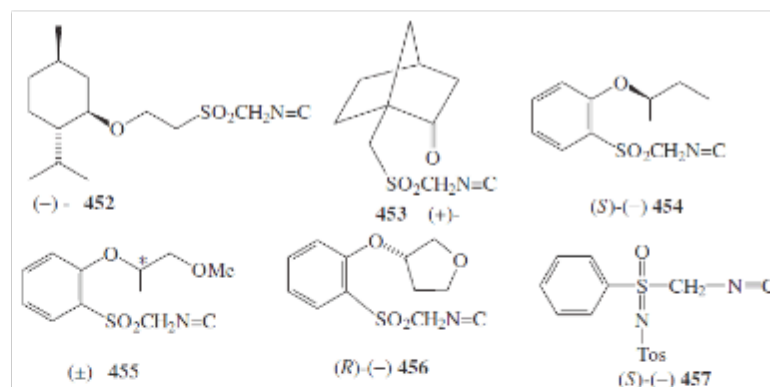
Based on what you've learned before:



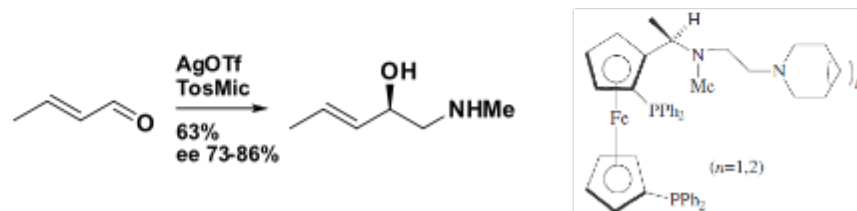
What is the structure of ethyl sorbate ?

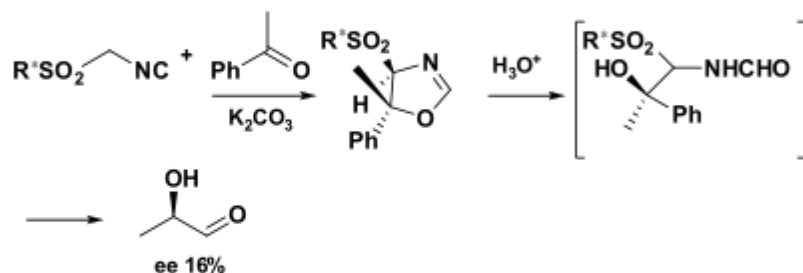
P. Magnus and Y.S. Or (1983). *J. Chem. Soc. Chem. Commun.*, 26.

6. The use of chiral TosMics



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



Synthesis of α -hydroxy aldehydes

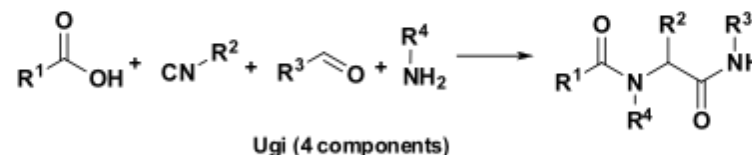
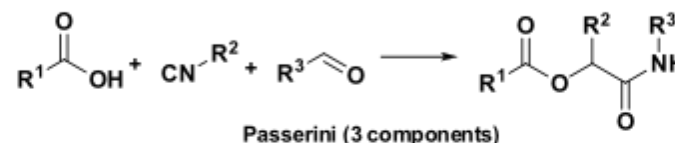
Isocyanides in multicomponent reactions

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



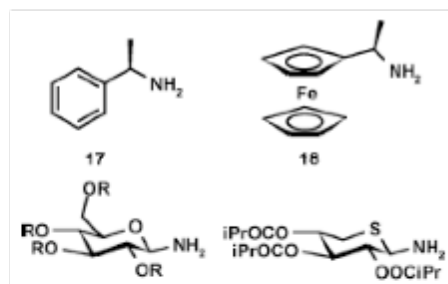
1. The Passerini and Ugi reaction

Mechanism ? and difference in Mechanism ?



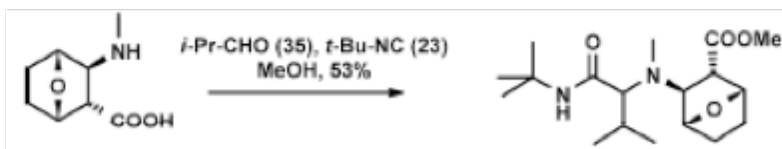
"only 1 new stereocenter formed !!

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.

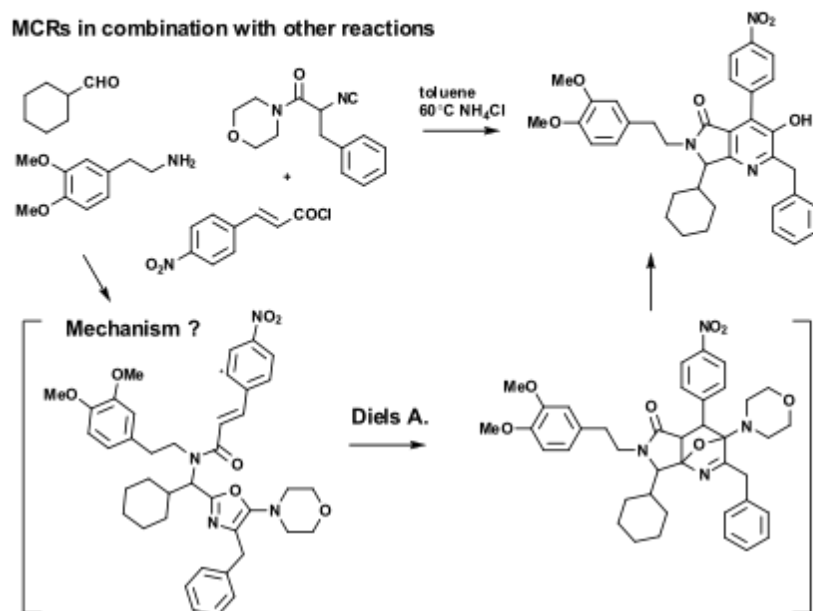


chiral amines suitable for stereinduction in U-MCR and P-MCR
the chiral auxiliary part can be cleaved off after the reaction

Typical reaction:



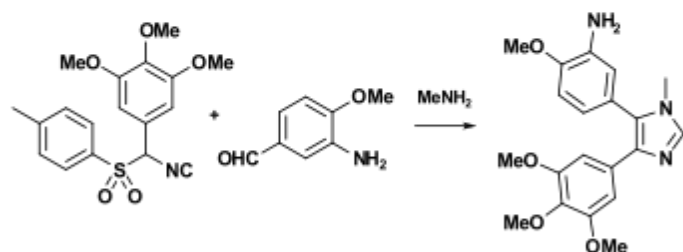
MCRs in combination with other reactions



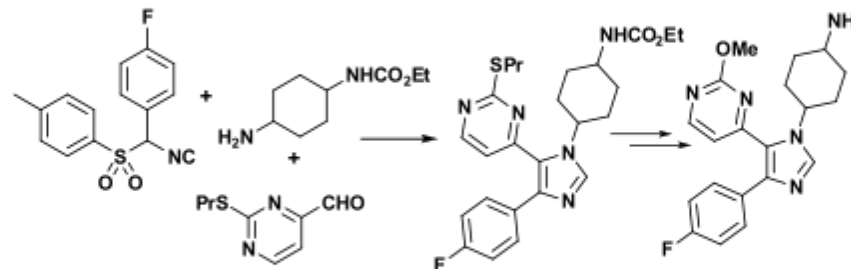
Applications of MCRs in Drug Discovery

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

Abbott scientists:
Tubulin inhibitors same mode of action as Colchicin

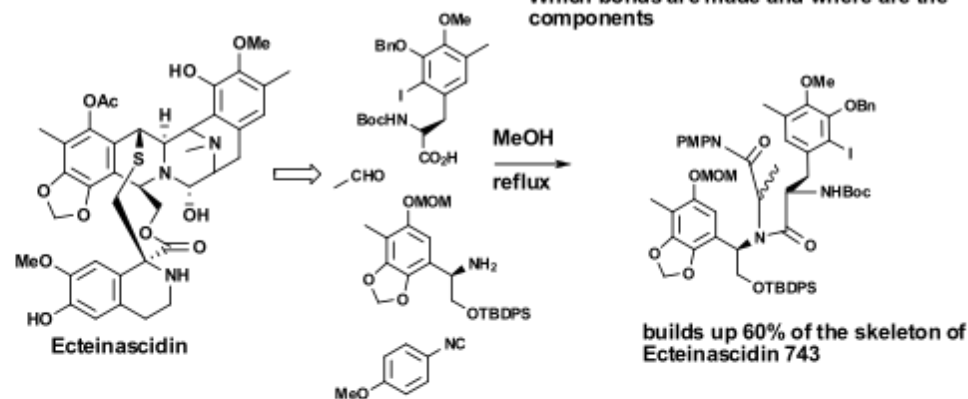


GlaxoSmithKline (GSK):
p38 kinase inhibitor against rheumatoid arthritis
Isonitrile produced on a 500kg scale !!!



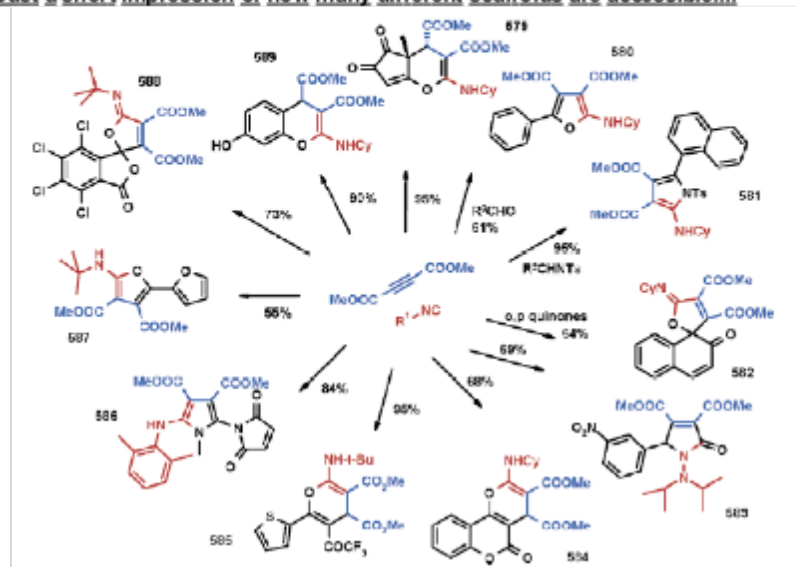
Applications of MCRs in Natural product synthesis

Which bonds are made and where are the components

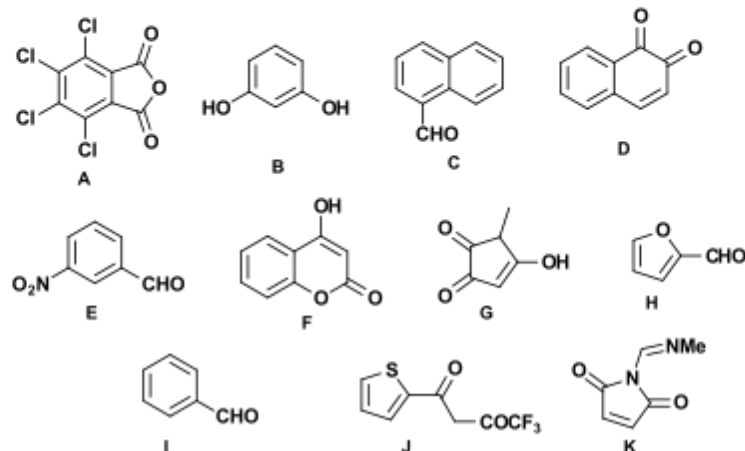


Endo, A.; Yamagisawa, A.; Abe, M.; Thoma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* 2002, 124, 6552.

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



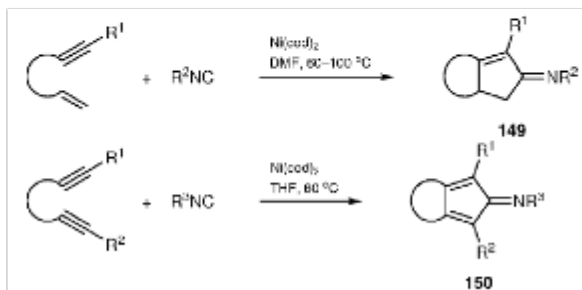
Which belongs to which ??



Organometallic chemistry of isocyanide

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

1. Aza-Pauson-Khand reaction



Tamao, K.; Kobayashi, K.; Ito, Y., *J. Am. Chem. Soc.*, (1988) **110**, 1266.
Tamao, K.; Kobayashi, K.; Ito, Y., *J. Org. Chem.*, (1989) **54**, 3517

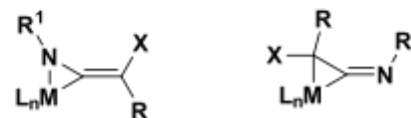
2. Reaction of isocyanides with Carbene complexes



X= O-alkyl, S-alkyl, NR₂, PR₃
R,R¹= alkyl, aryl, alkenyl, alkynyl
M= Cr, Mo, W, Mn, Fe, Os, Th, U
L_n = CO, PR₃, η⁵-C₅H₅

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

Other possibilities of coordination:

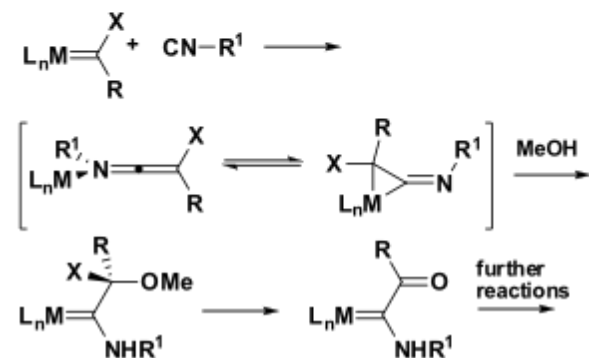


Favoured when M= electron donating

G. R. Knox, *Angew. Chem.* **83** (1971) 455; *Angew. Chem. Int. Ed. Engl.* **10** (1971) 435; M. W. Barker, W. E. McEwen in S. Patai (Ed.), *The Chemistry of Azones, Azides and Related Compounds*, Vol. 2, Wiley, New York 1960, pp. 701-720; N. P. Gunzberg, *Russ. Chem. Rev. Engl. Transl.* **45** (1976) 630; D. Bonmann in Houben-Weyl (Ed.), *Methoden der Organischen Chemie*, Bd. VII/4, Thieme, Stuttgart 1968, p. 323-329; A. Dondoni, *Microscopic* **14** (1988) 1567; L. Ghosez, M. L. O'Donnell in P. Marchand, R. E. Lehr (Eds.), *Inorganic Bioinorganic*, Vol. 2, Academic Press, New York 1971, p. 29.
E. D. Fisher, *Rev. Acc. Appl. Chem.* **35** (1977) 353; K. H. Dawe, H. Fischer, P. Hoffmann, F. K. Krügel, U. Schubert, K. Weiss; *Transition Metal Carbene Complexes*, Verlag Chemie, Weinheim 1983; K. H. Dawe, *Angew. Chem.* **95** (1984) 573; *Angew. Chem. Int. Ed. Engl.* **23** (1984) 587; H. Fischer in S. Patai (Ed.), *The Chemistry of Metal-Carbene Bonds*, Wiley, New York 1983, pp. 181-254; P. L. Pauson in Houben-Weyl (Ed.), *Methoden der Organischen Chemie*, Bd. E/8, Thieme, Stuttgart 1987, p. 2821c.

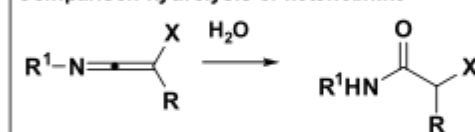
Keteneimines are they chiral ??

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



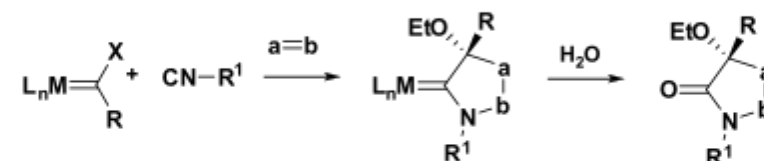
X = O-alkyl, S-alkyl, NR₂, PR₃
R, R¹ = alkyl, aryl, alkenyl, alkynyl
nucleophiles: alcohols, thiols, amines, H₂O
L_nM = [Cr(CO)₅], [Mo(CO)₅], [W(CO)₅], [Mn(CO)₂Cp], [Fe(CO)₄]

Comparison hydrolysis of keteneimine



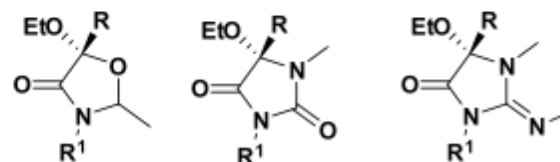
Aumann, R.; Heinen, H. *Chem. Ber.* 120, 1987, 1297.
Aumann, R.; Heinen, H. *Chem. Ber.* 121, 1988.
Aumann, R.; Kuckert, E.; Heinen, H. *Angew. Chem.* 97, 1985, 960;

[3+2]-Cycloadditions



a=b: O=CHR, RN=CO, RN=CNHR,
L_nM = [W(CO)₅], [Mn(CO)₂Cp],

Reaction at room temperature

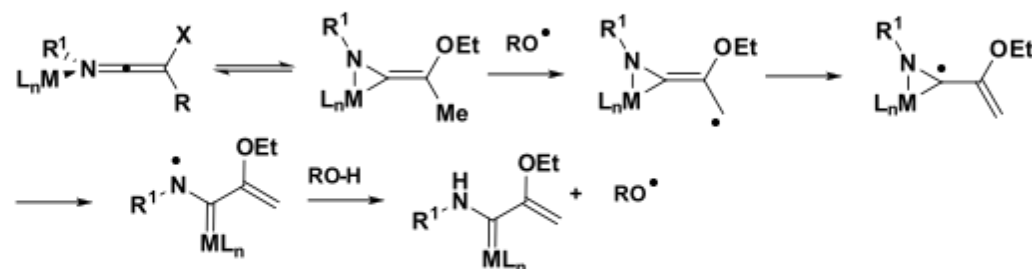


Aumann, R.; Kuckert, E. *Chem. Ber.*, 119, 1986, 156.

Rearrangements of metal-keteneimines

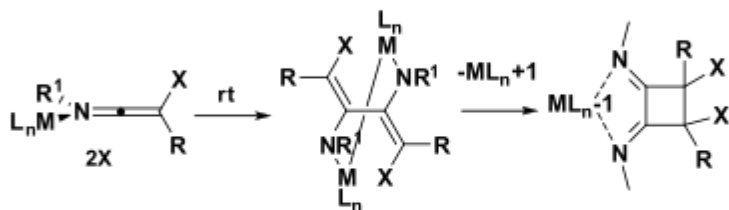
1. Keteneimine aminocarbene rearrangement

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.; Frlisch, D. W.; Lemmon, T. H. *J. Organomet. Chem.* 202, 1980 C77.
Aumann, R.; Fischer, O. *Chem. Ber.* 101, 1968, 954; Kreiter, R.; Aumann *ibid.* 119, 1978, 1223.

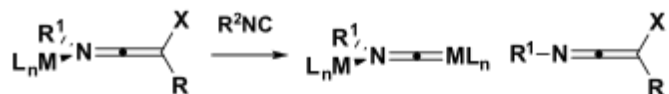
Dimerization of Keteneimine ligands

Reaction at room temperature

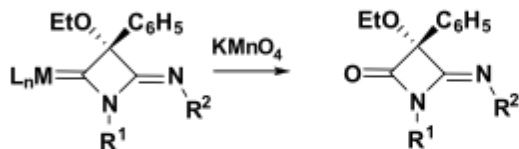
X = OMe

L_nM = [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 keteneimine complexes:

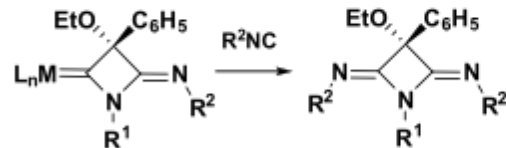
1. Addition of isocyanide to metal with displacement of keteneimine



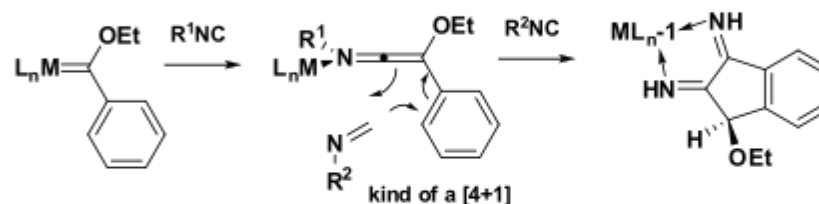
2. [3+1] or [2+2] CA of isocyanides to keteneimine complex



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.

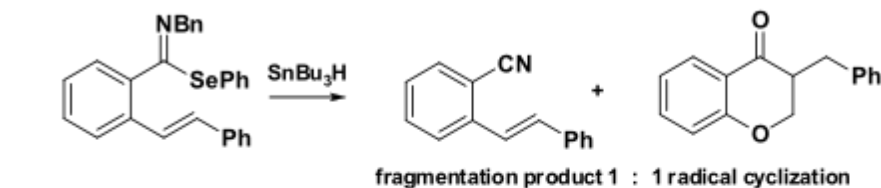
Isocyanides in Radical chemistry

Isocyanides participate in radical additions like CO...(isoelectronic!!)

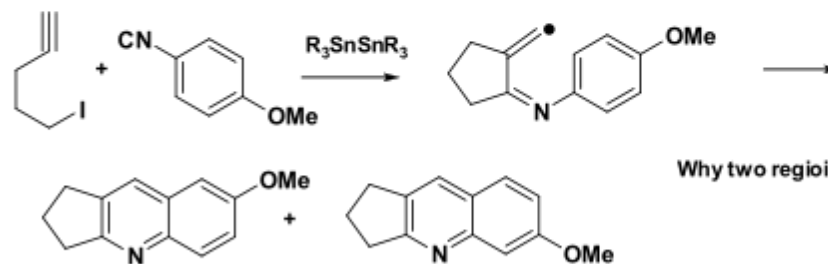
Difference to CO radical addition:

They don't undergo α -fragmentation but β -fragmentation instead to give nitriles.Therefore isocyanides without good β -leaving groups are preferred substrates.

In the process of radical addition the so called imidoyl radical is formed which then undergoes further reactions.



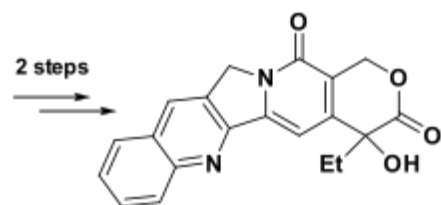
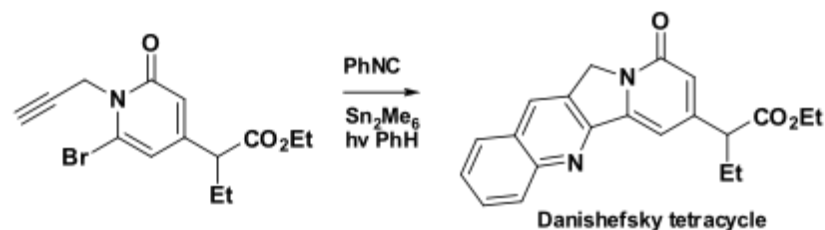
fragmentation product 1 : 1 radical cyclization



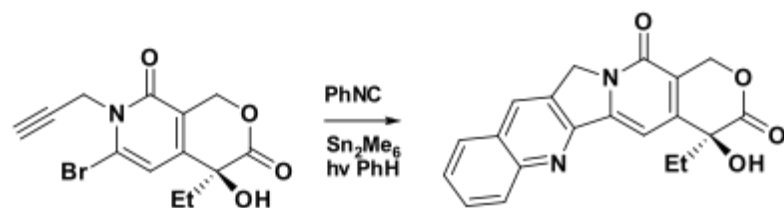
Why two regioisomers ??

See: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* 1991, 113, 2127. (b) Boger, D. L.; Mathwink, 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.

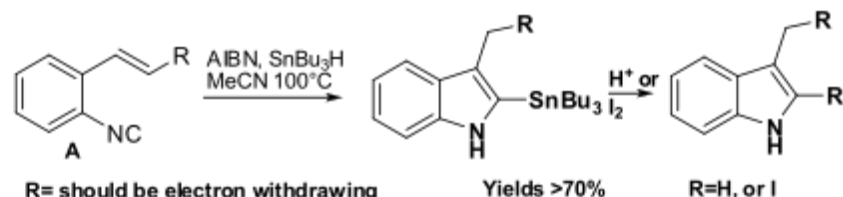


The chemistry is very convergent and therefore gives easy access to analogs.

(a) Danishefsky, S.; Volkman, R. *Tetrahedron Lett.* **1973**, 2521.
 (b) Volkman, 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.

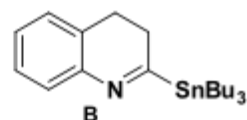
Fukuyama Indole Synthesis:



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

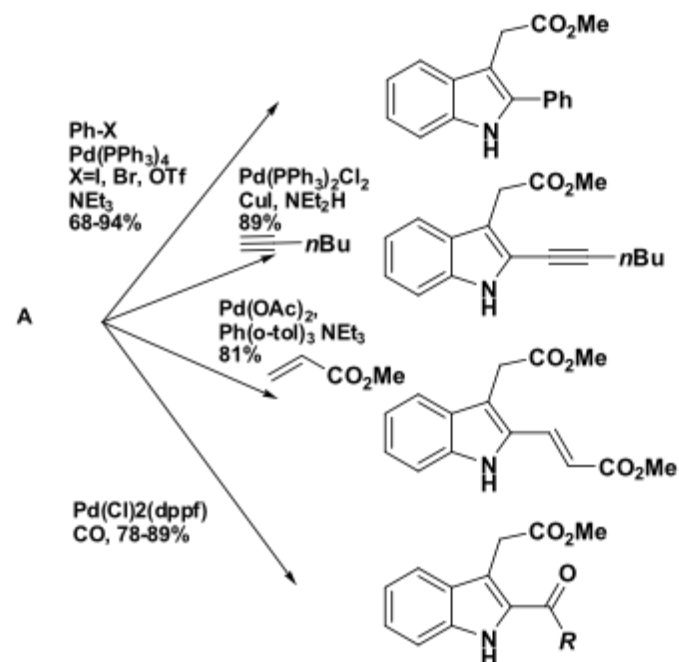
Yields >70%

R=H, or I

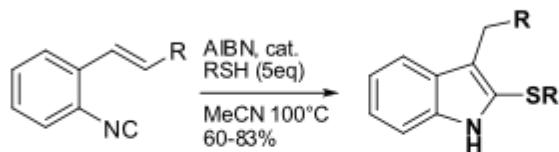


Mechanism of rxn? Why is by-product formed

Further elaboration to yield 2,3 disubstituted indoles

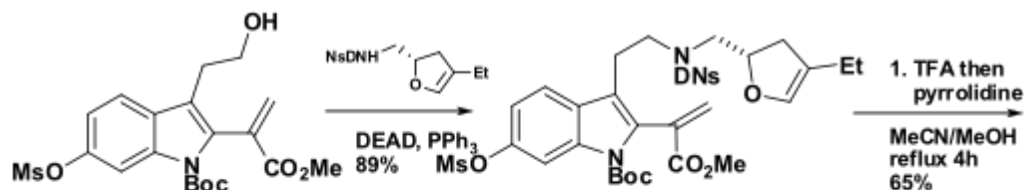
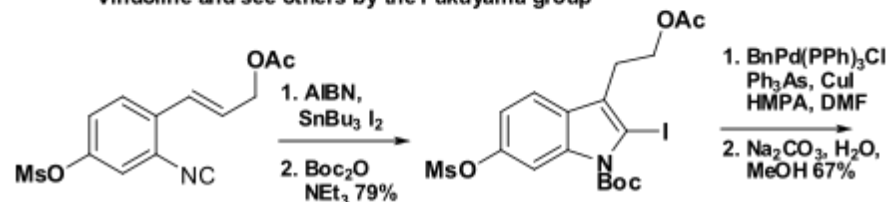


Fukuyama Indole Synthesis:

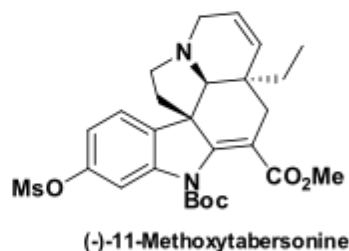


Application to Total Synthesis

Vindoline and see others by the Fukuyama group



Structure ??



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 !!
seleno 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 auxiliary
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.