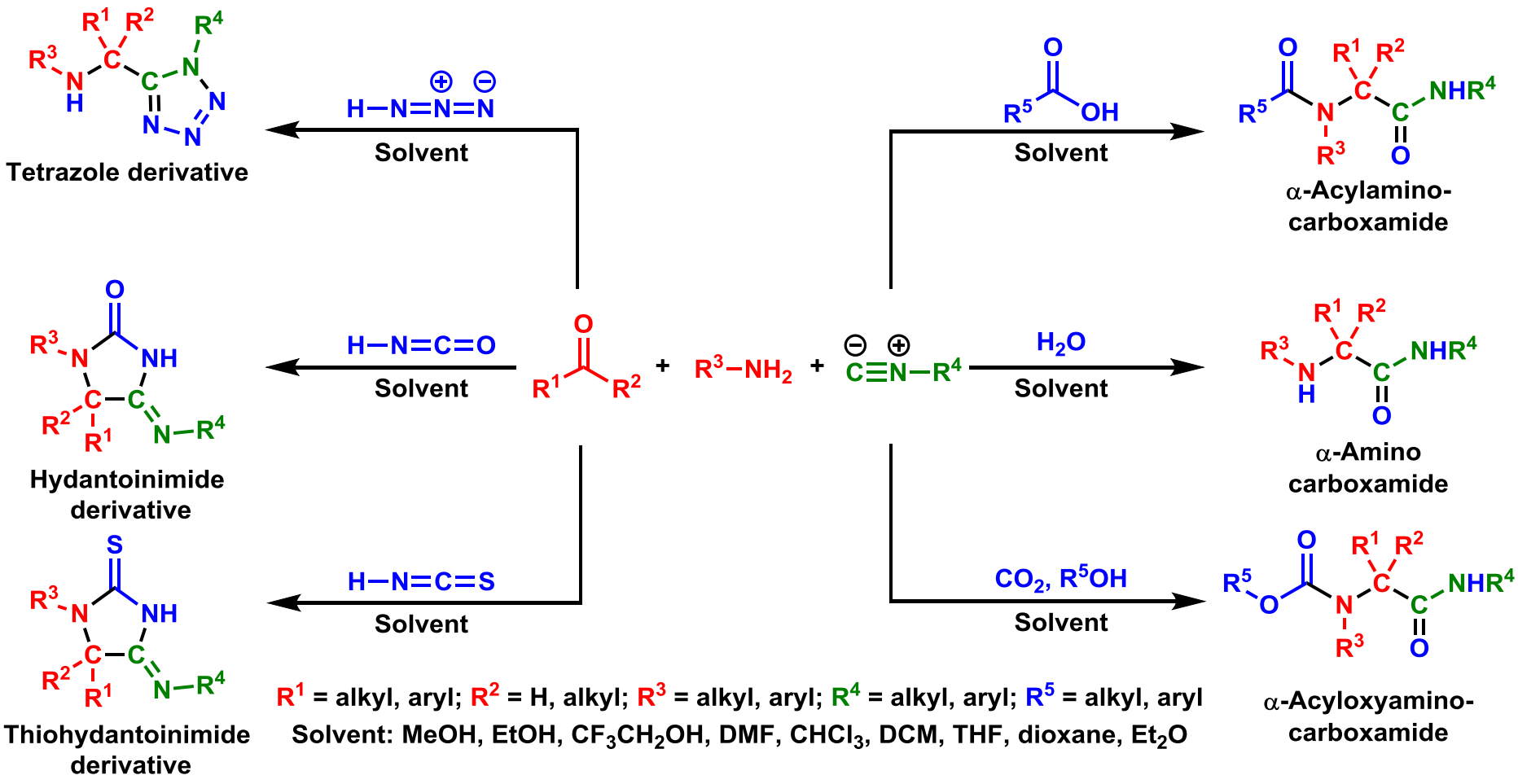
May Lab Ugi Multicomponent Reaction *Jian-Yuan Li 8/5/2015*



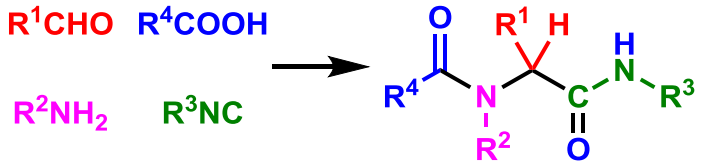
R^1 = alkyl, aryl; R^2 = H, alkyl; R^3 = alkyl, aryl; R^4 = alkyl, aryl; R^5 = alkyl, aryl

Solvent: MeOH, EtOH, CF_3CH_2OH, DMF, $CHCl_3$, DCM, THF, dioxane, Et_2O

Reviews: (a) Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.
(b) Ramon, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.
(c) Kurti, L.; Czako, B. (2005) *Strategic applications of named reactions in organic synthesis: Background and detailed mechanisms.* Amsterdam: Elsevier Academic Press.

Outline:

- Ugi Reaction
- Variations of Ugi Reaction
- Catalytic Ugi Reaction
- Asymmetric Ugi Reaction
- Natural Product and Drug Synthesis via Ugi Reaction



A. Domling I. Ugi

- Born on September 5, 1930 in Estonia
- Studied chemistry and mathematics at University of Tubingen (1949-51)
- Obtained his PhD degree under Dr. Rolf Huisgen at University of Munchen (1954)
- His Habilitation in isocyanides followed in 1959
- A member of Bayer AG (1962-1968)
- Professor at University of Southern California (1968-1971)
- Professor at Technical University of Munich from 1971 to 1999, was an emeritus from 1999 until his death in 2005

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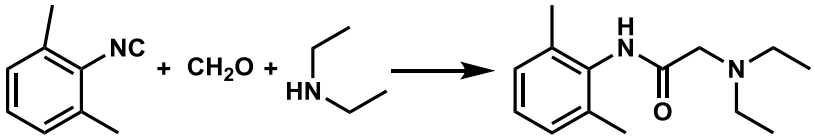
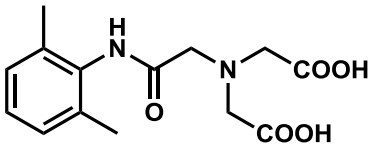
Anesthetic agent



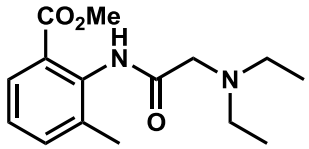
Xylocain (A. B. Astra)

Ugi, I.; Steinbruckner, C. DE-B 1,103,337, **1959.**

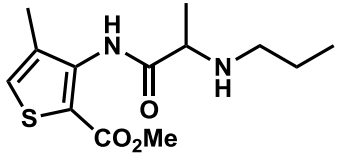
Other analogues



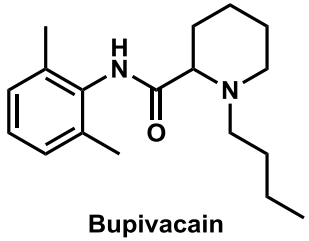
Lidofenin



Tylocain



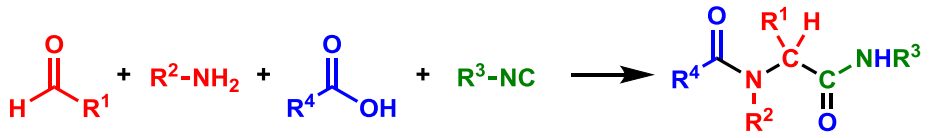
Articain



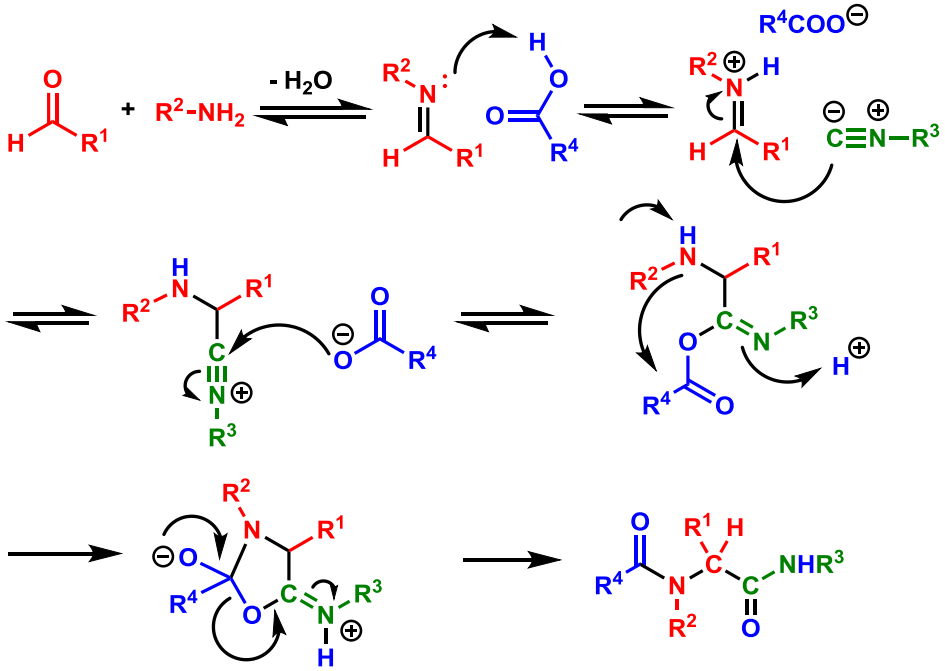
Bupivacain

- Synthesized different a-amino amides via U-4CR and screened their anesthetic effect.
- Xylocain analogs were developed and marketed by various pharmaceutical companies.

Ugi Four Component Reaction (U-4CR)



Plausible Mechanism

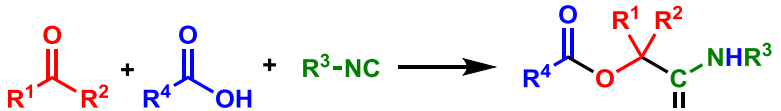


Ugi, I. *et al. Angew. Chem.* **1959**, *71*, 386.
Ugi, I. *et al. Angew. Chem.* **1960**, *72*, 267.

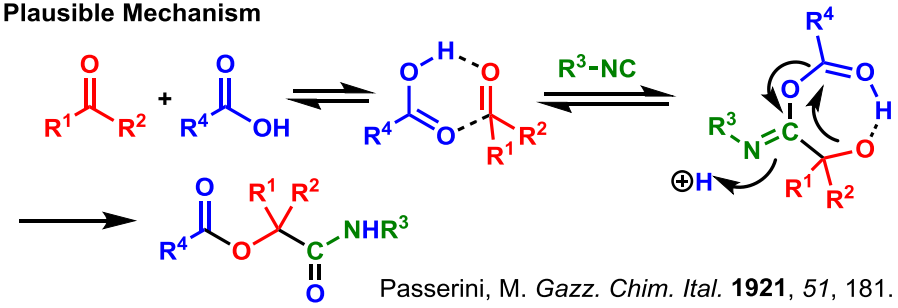
Ugi Multicomponent Reaction

Jian-Yuan Li 8/5/2015

Passerini Three Component Reaction (P-3CR)

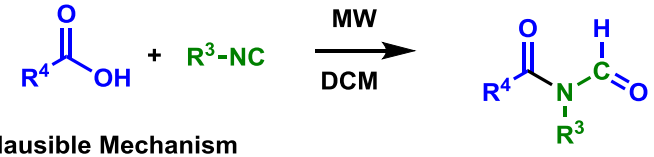


Plausible Mechanism

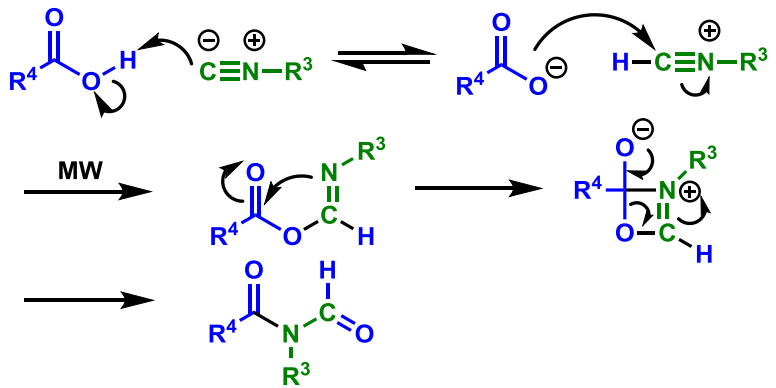


Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.

Danishefsky Two Component Reaction (D-2CR)

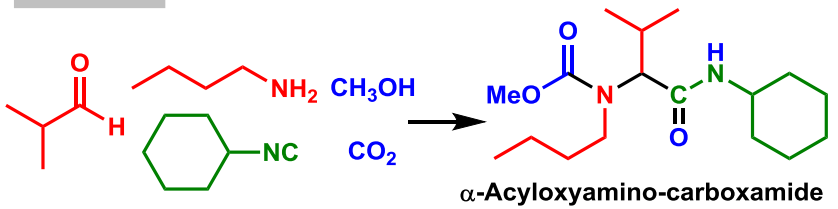


Plausible Mechanism



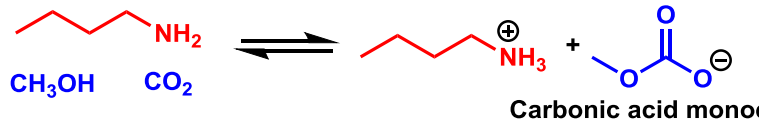
Li, X. *et al. J. Am. Chem. Soc.* **2008**, *130*, 5446.
Li, X. *et al. J. Am. Chem. Soc.* **2008**, *130*, 13222.

CO_2, ROH

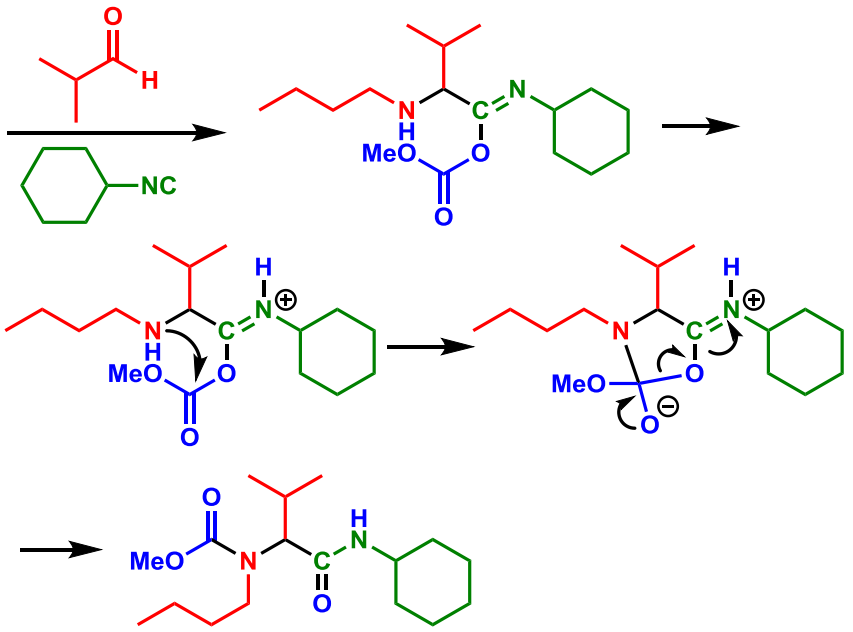


α-Acyloxyamino-carboxamide

Plausible Mechanism



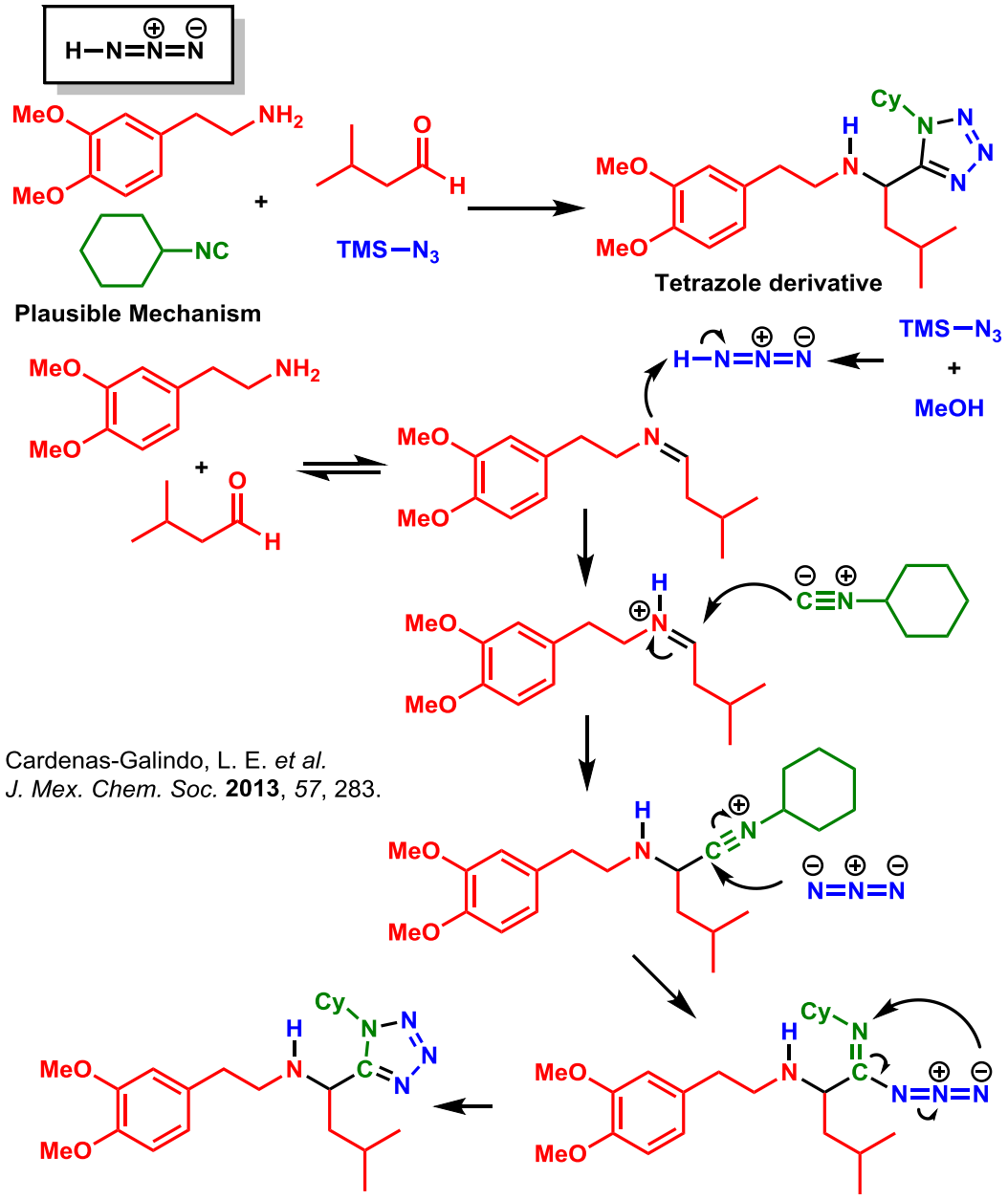
Carbonic acid monoester



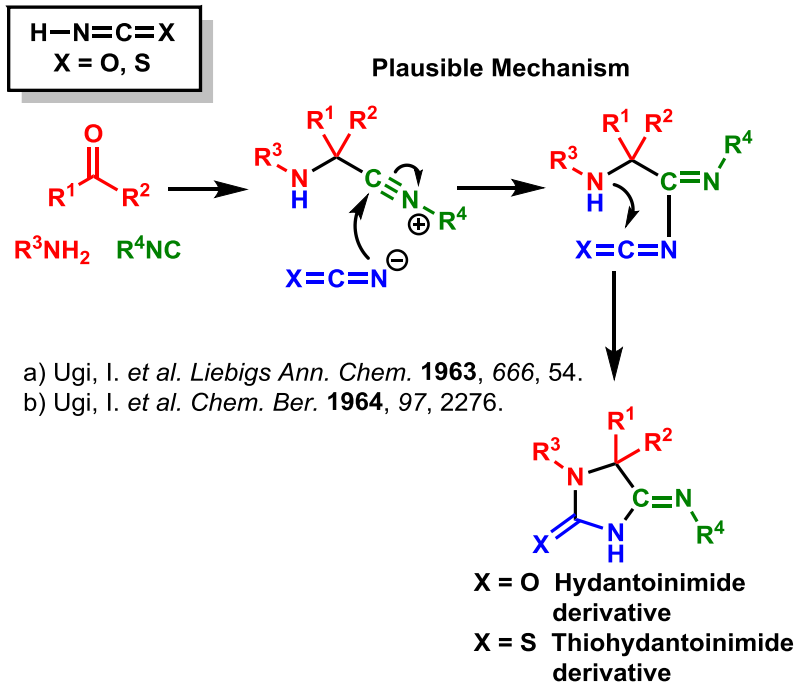
Ugi, I. *et al. Chem. Ber.* **1961**, *94*, 2802.

Ugi Multicomponent Reaction

Jian-Yuan Li 8/5/2015

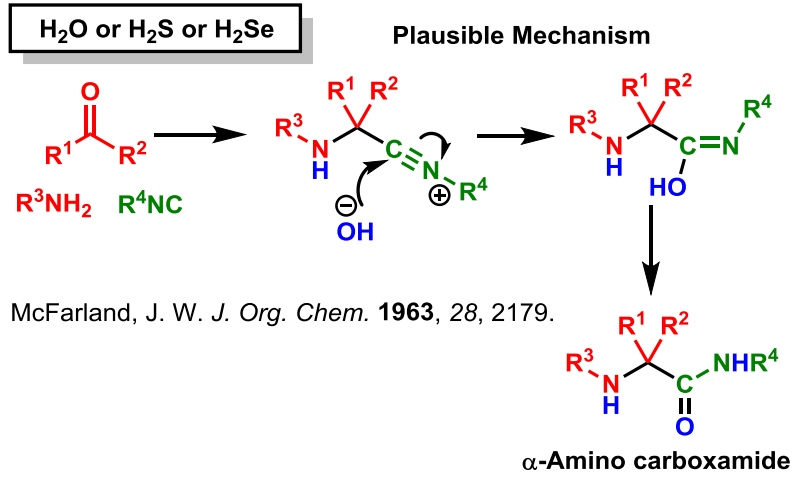


Cardenas-Galindo, L. E. *et al.* *J. Mex. Chem. Soc.* **2013**, *57*, 283.



a) Ugi, I. *et al. Liebigs Ann. Chem.* **1963**, *666*, 54.
b) Ugi, I. *et al. Chem. Ber.* **1964**, *97*, 2276.

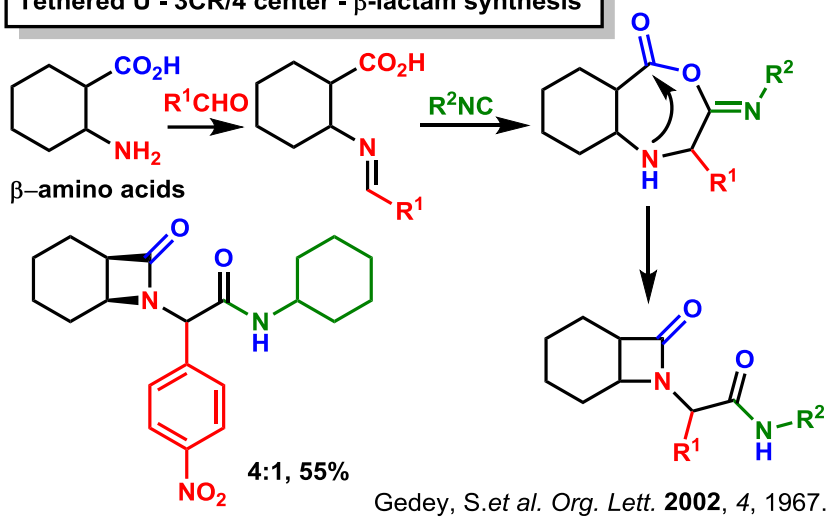
X = O Hydantoinimide derivative
X = S Thiohydantoinimide derivative



McFarland, J. W. *J. Org. Chem.* **1963**, *28*, 2179.

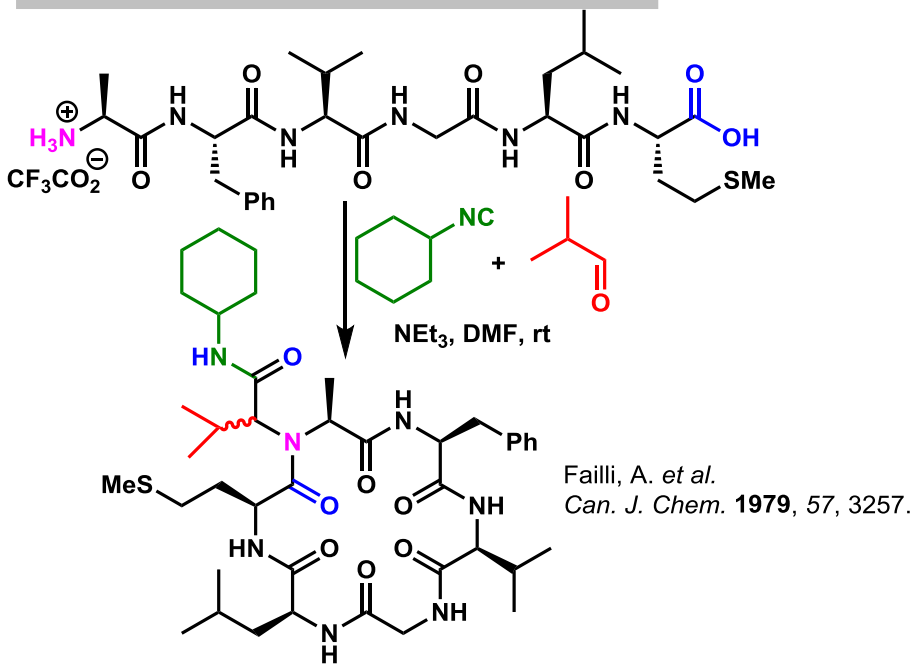
α-Amino carboxamide

Tethered U - 3CR/4 center - β-lactam synthesis



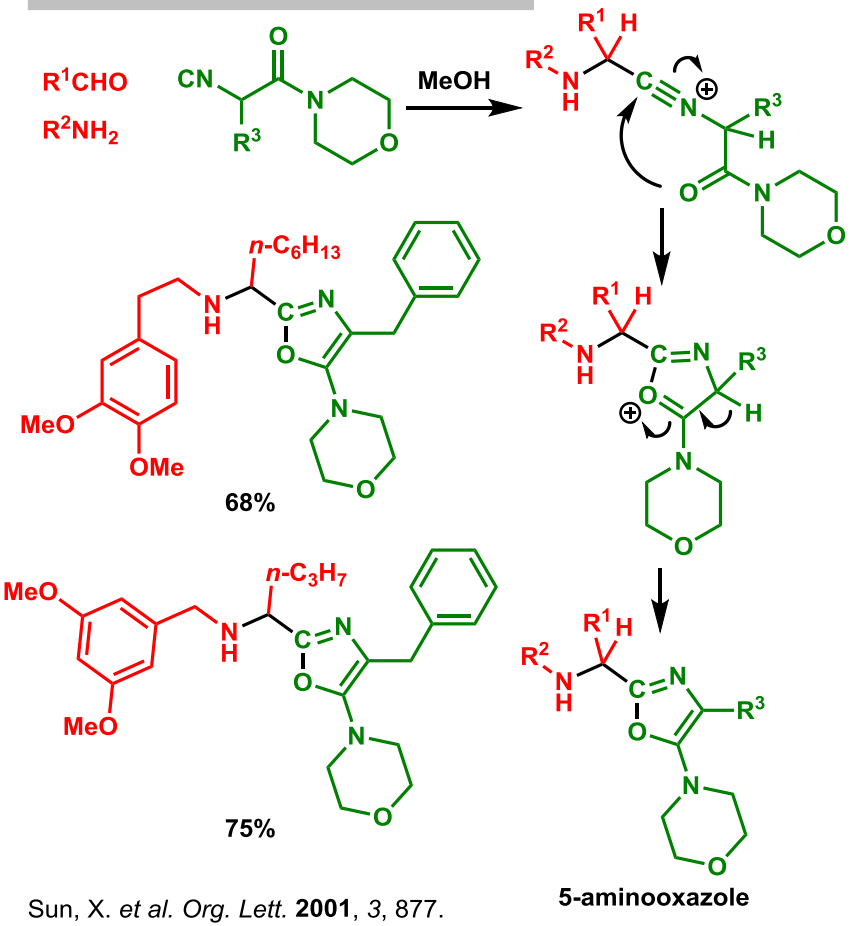
Gedey, S.*et al. Org. Lett.* **2002**, *4*, 1967.

Tethered U - 3CR/4 center - Cyclopeptide synthesis



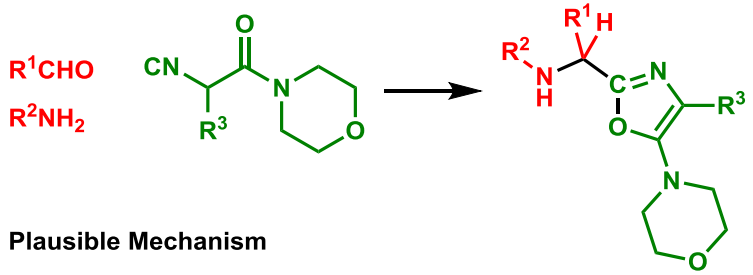
Failli, A. *et al.*
Can. J. Chem. **1979**, *57*, 3257.

U - 3CR - Synthesis of 5-aminooxazole

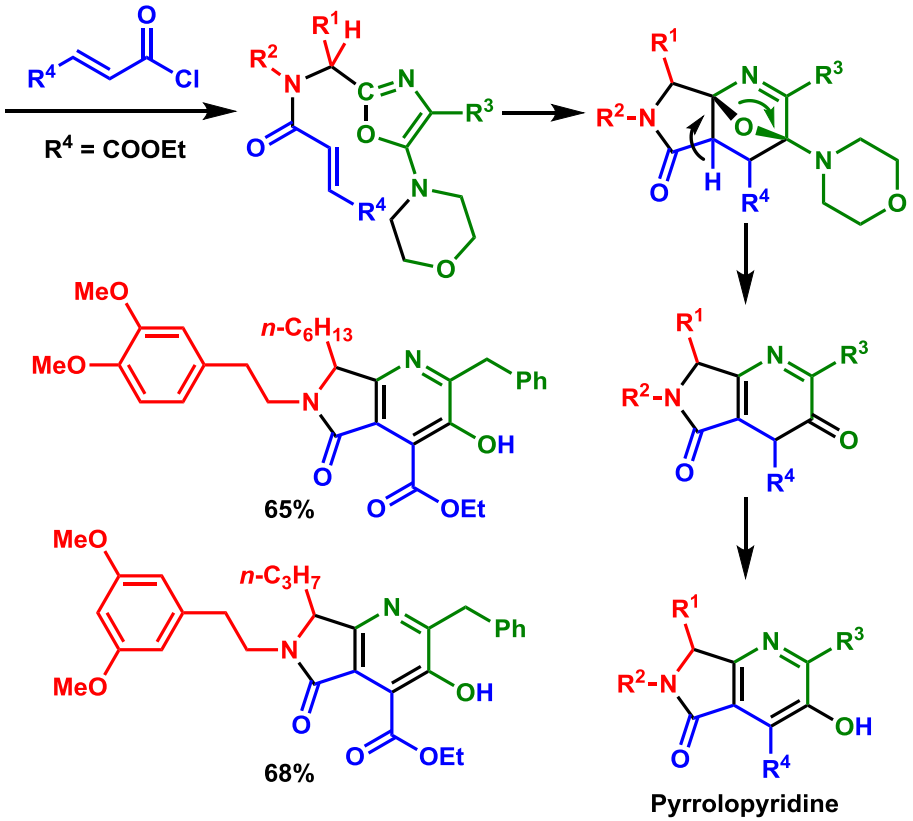


Sun, X. *et al. Org. Lett.* **2001**, *3*, 877.

U - 3CR + DA - Synthesis of pyrrolopyridines

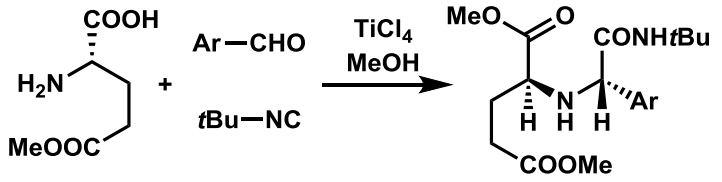


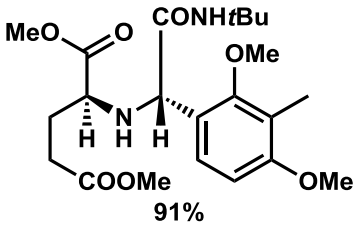
Plausible Mechanism

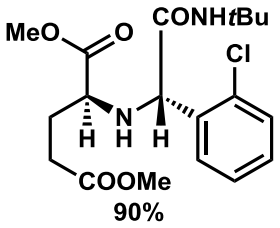


Sun, X. *et al. Org. Lett.* **2001**, *3*, 877.

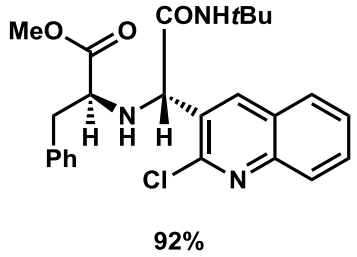
$TiCl_4$ catalyzed Ugi reaction

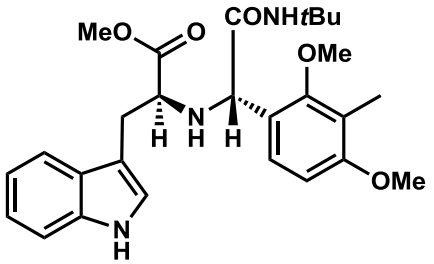






From rther amino acid

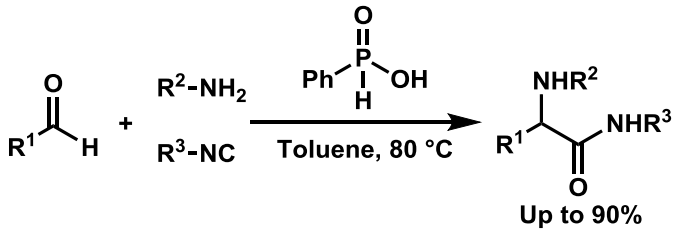




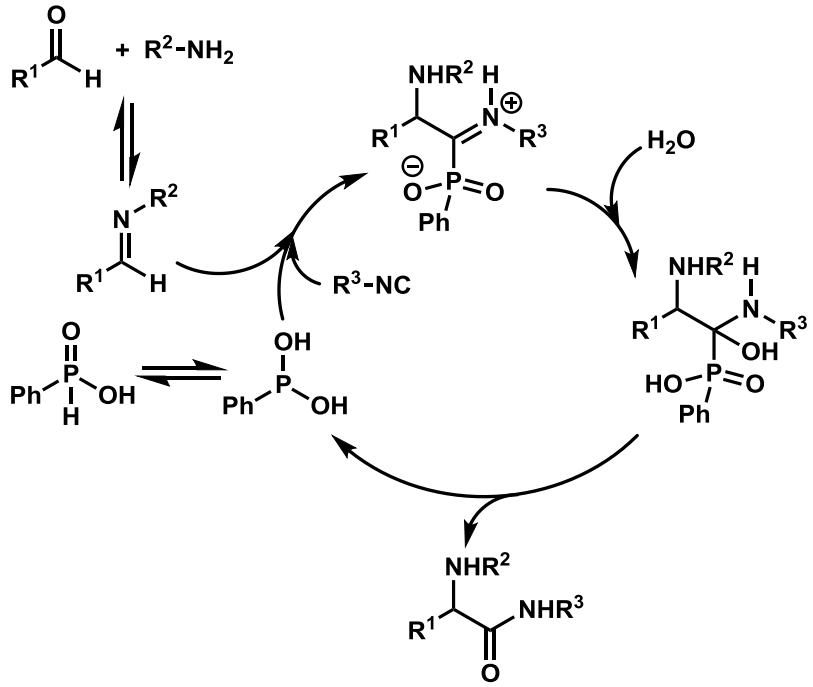
Godet, T. *et al. Org. Lett.* **2004,** *6*, 3281.

Lewis acid catalyzed U-3CR/4 centers with aromatic aldehyde

Phenyl phosphonic acid catalyzed Ugi reaction

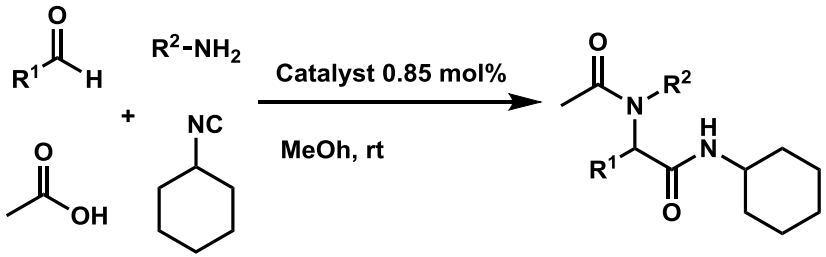


Plausible Mechanism

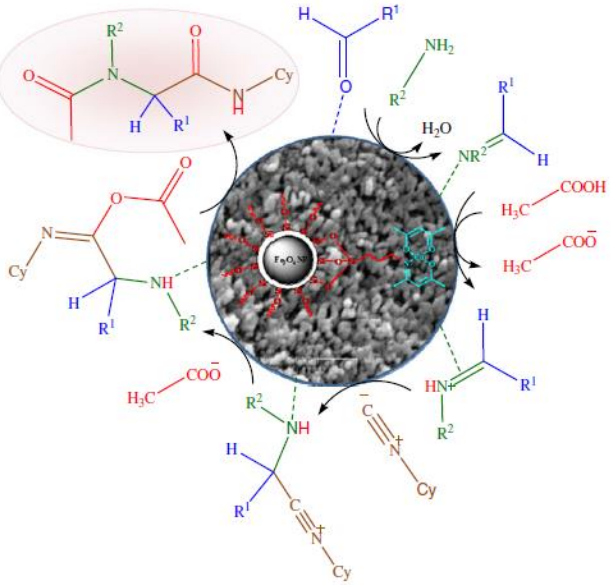


Pan, S. C. *et al. Angew. Chem. Int. Ed.* **2008**, *47*, 3622.

Use of nanocatalyst



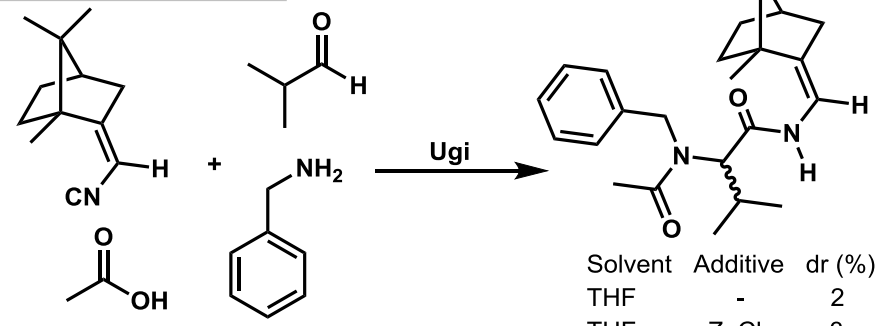
Catalyst = $Cu(acac)_2/NH_2$-T/SiO_2@Fe_3O_4 nanoparticles (Magnetically recoverable)



Ghavami, M. *et al. J. Chem. Sci.* **2013**, *125*, 1347.

May Lab **Ugi Multicomponent Reaction** *Jian-Yuan Li 8/5/2015*

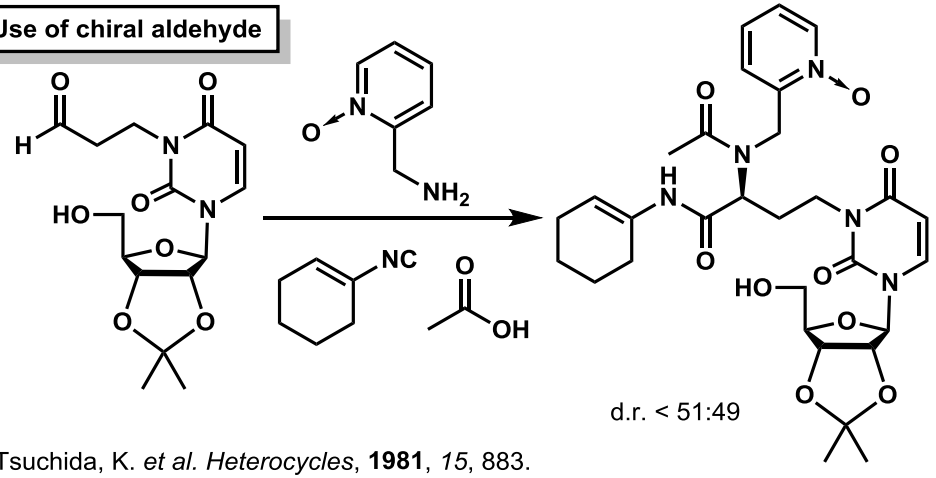
Use of chiral isocyanide



Solvent	Additive	dr (%)
THF	-	2
THF	$ZnCl_2$	3
THF	$CoCl_2$	3
MeOH	$LiClO_4$	3

Bock, H. *et al. J. Prakt. Chem.* **1997**, *339*, 385.

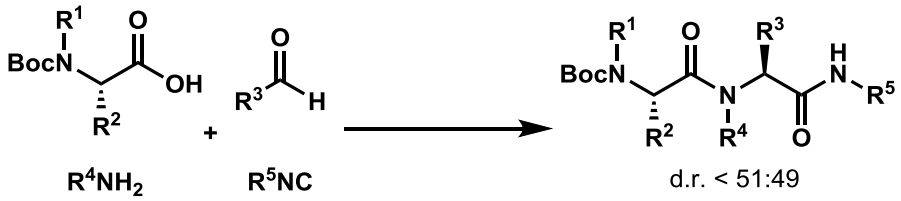
Use of chiral aldehyde



d.r. < 51:49

Tsuchida, K. *et al. Heterocycles*, **1981**, *15*, 883.

Use of chiral acid

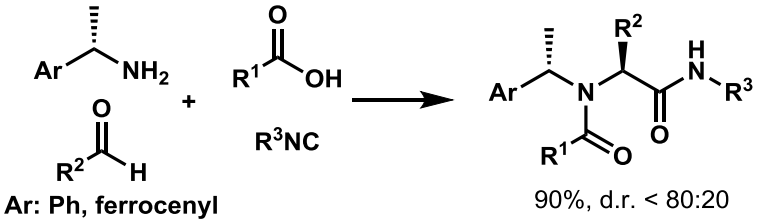


R^4NH_2 **R^5NC**

d.r. < 51:49

Hulme, C. *et al. Tetrahedron Lett.* **1998**, *39*, 1113.

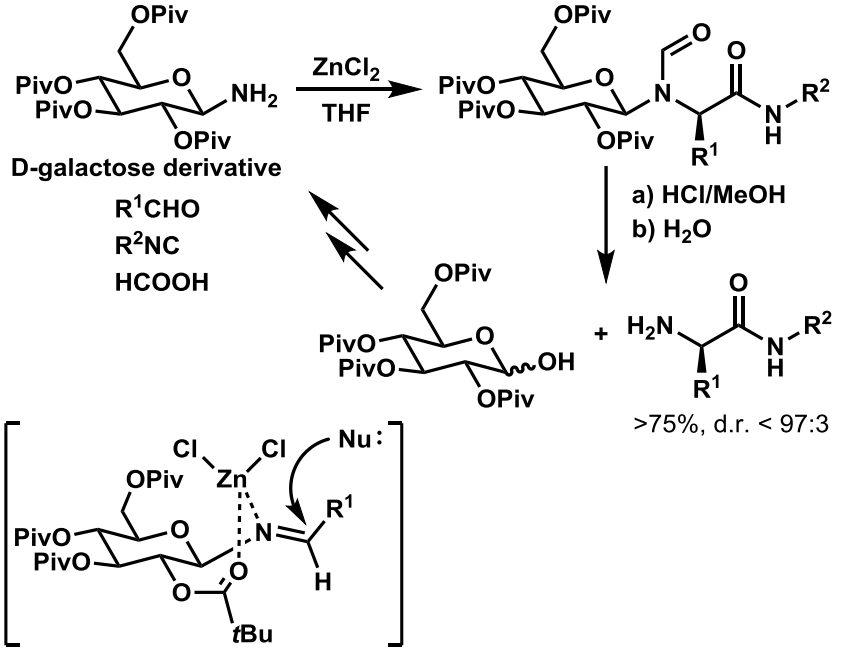
Use of chiral amine



Ar: Ph, ferrocenyl

90%, d.r. < 80:20

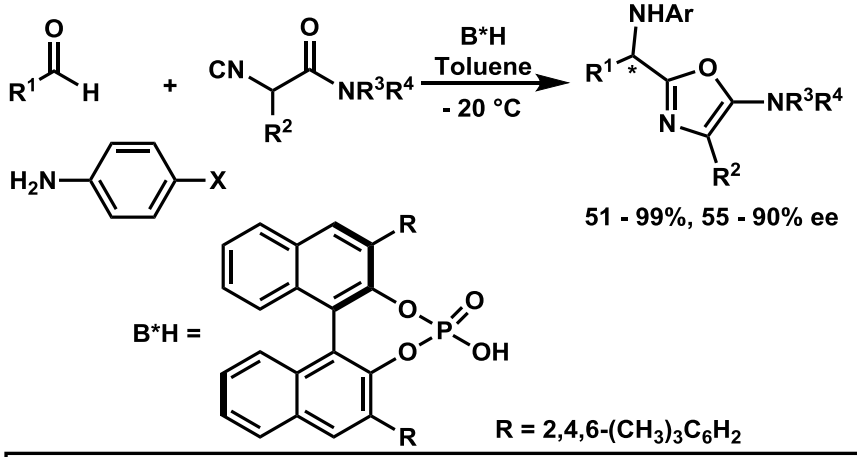
Ugi, I. *et al. Angew. Chem. Int. Ed.* **1963**, *2*, 624.
Marquarding, D. *et al. J. Am. Chem. Soc.* **1970**, *92*, 1969.
Eberle, G. *et al. Angew. Chem. Int. Ed.* **1976**, *15*, 492.



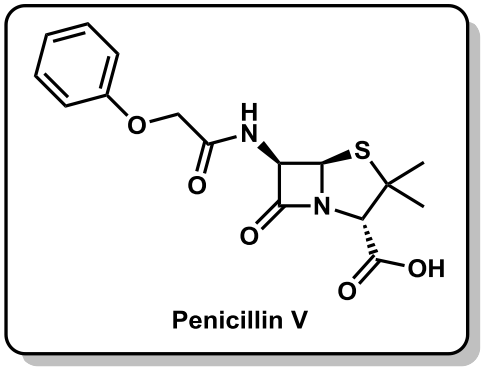
>75%, d.r. < 97:3

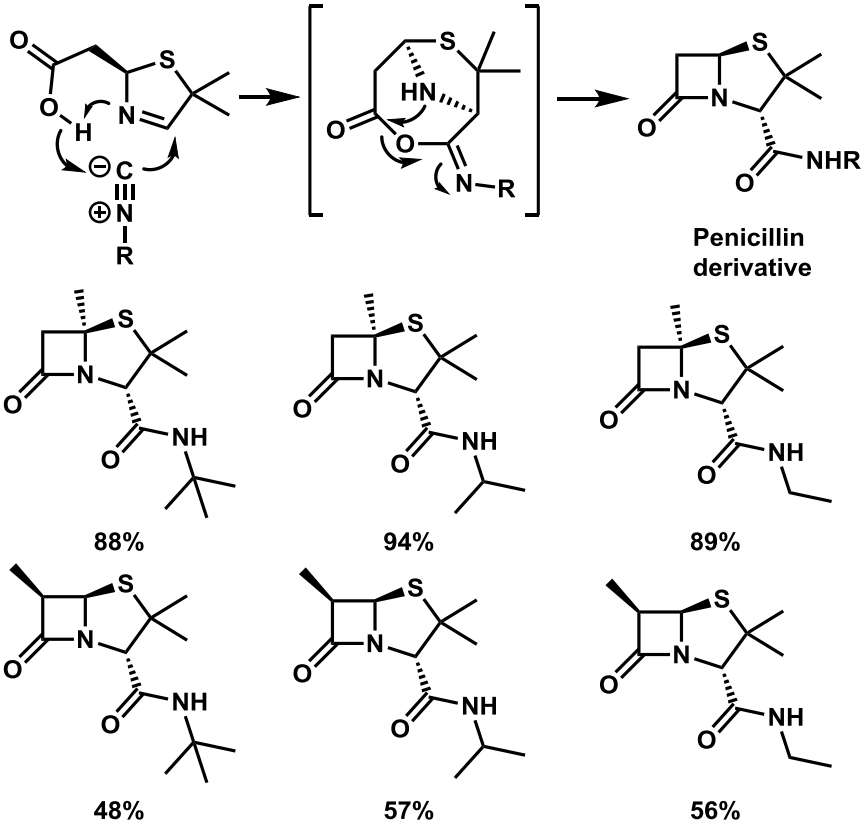
Kunz, H. *et al. J. Am. Chem. Soc.* **1988**, *110*, 651.
Kunz, H. *et al. Tetrahedron*, **1988**, *44*, 5487.
Ross, G. F. *et al. Tetrahedron*, **2002**, *58*, 6127.

Bronsted acid catalyzed enantioselective U - 3CR



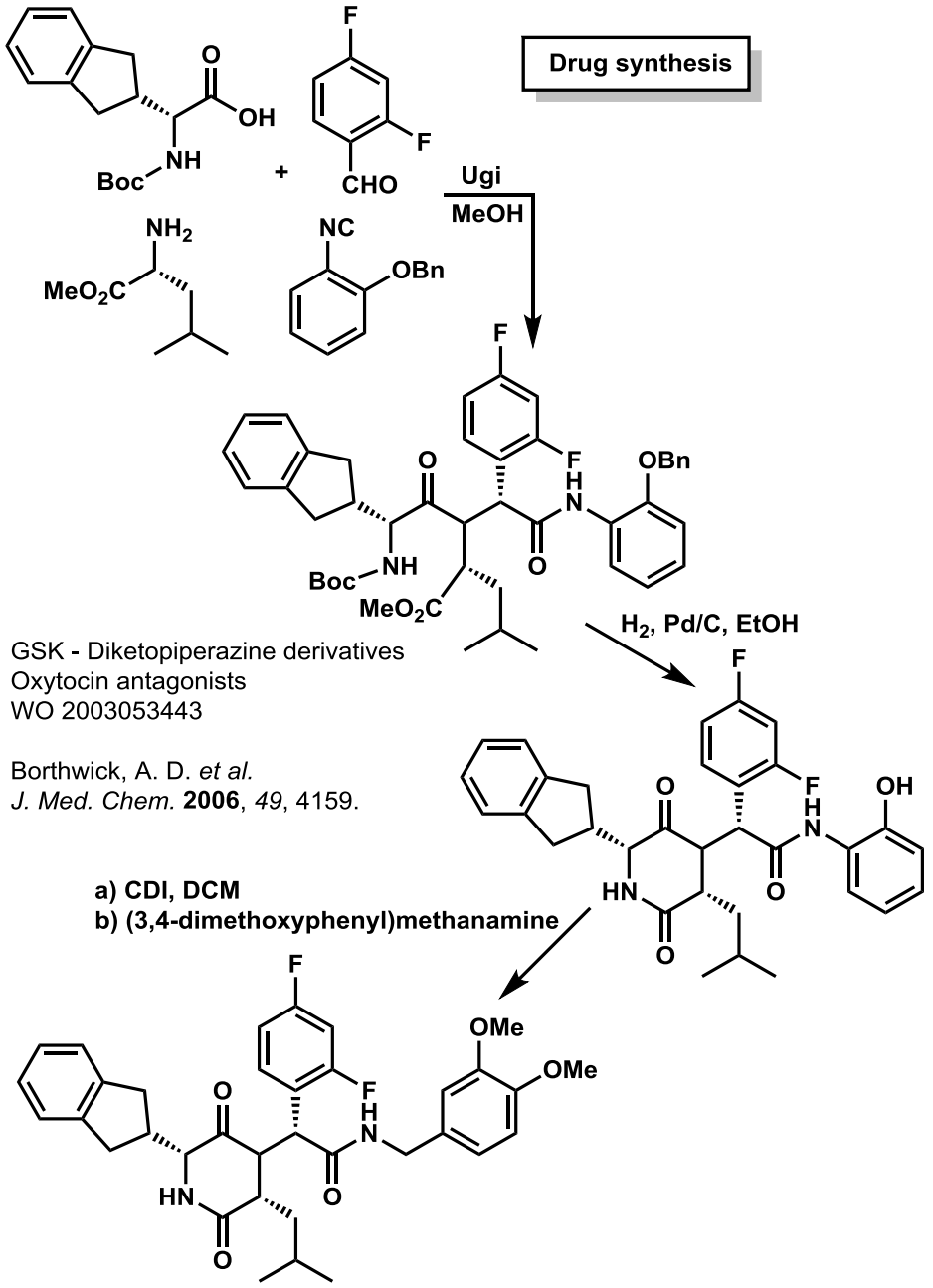
Yue, T. *et al. Angew. Chem. Int. Ed.* **2009**, *48*, 6717.





Ugi, I. *et al. Angew. Chem. Int. Ed.* **1962**, *1*, 8.
Asinger, F. et al. *Angew. Chem.* **1958**, *70*, 667.

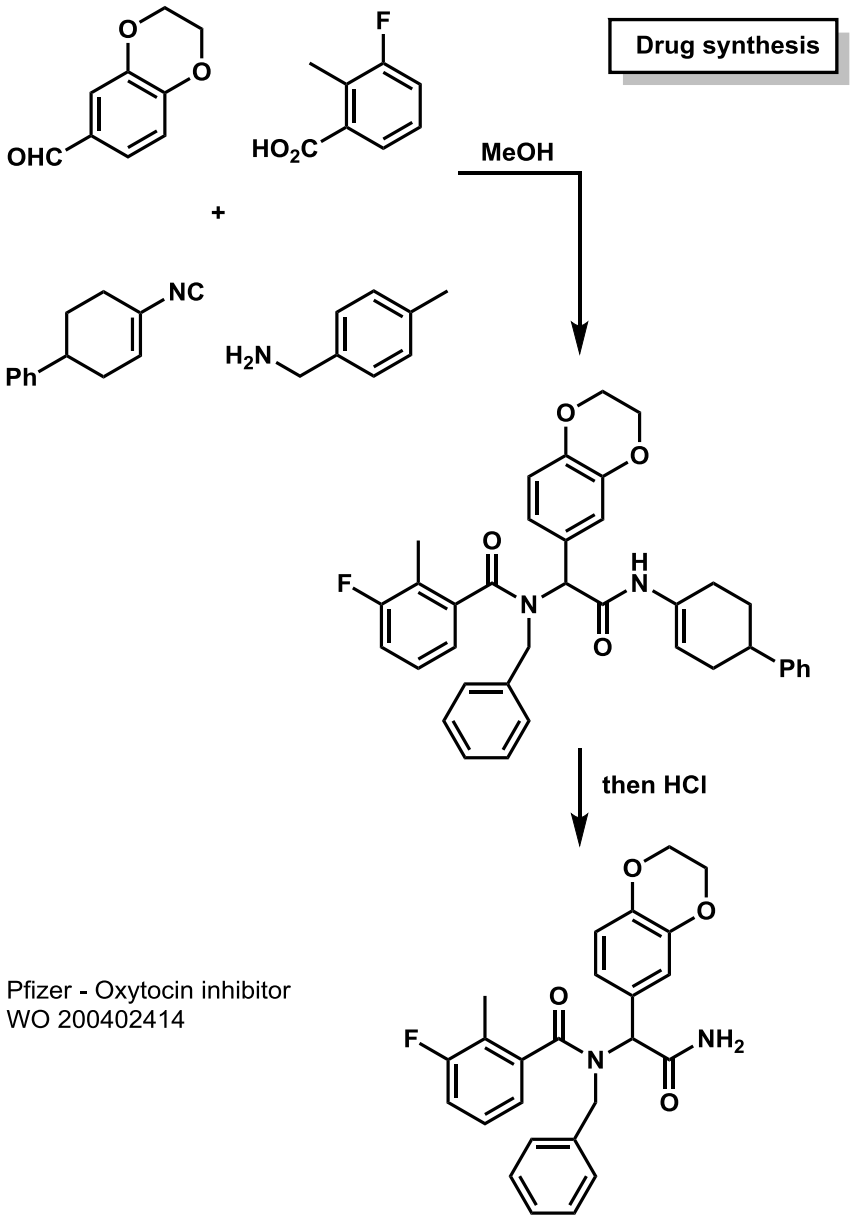
Drug synthesis



GSK - Diketopiperazine derivatives
Oxytocin antagonists
WO 2003053443

Borthwick, A. D. *et al.*
J. Med. Chem. **2006**, *49*, 4159.

Drug synthesis



Pfizer - Oxytocin inhibitor
WO 200402414

Ugi Multicomponent Reaction

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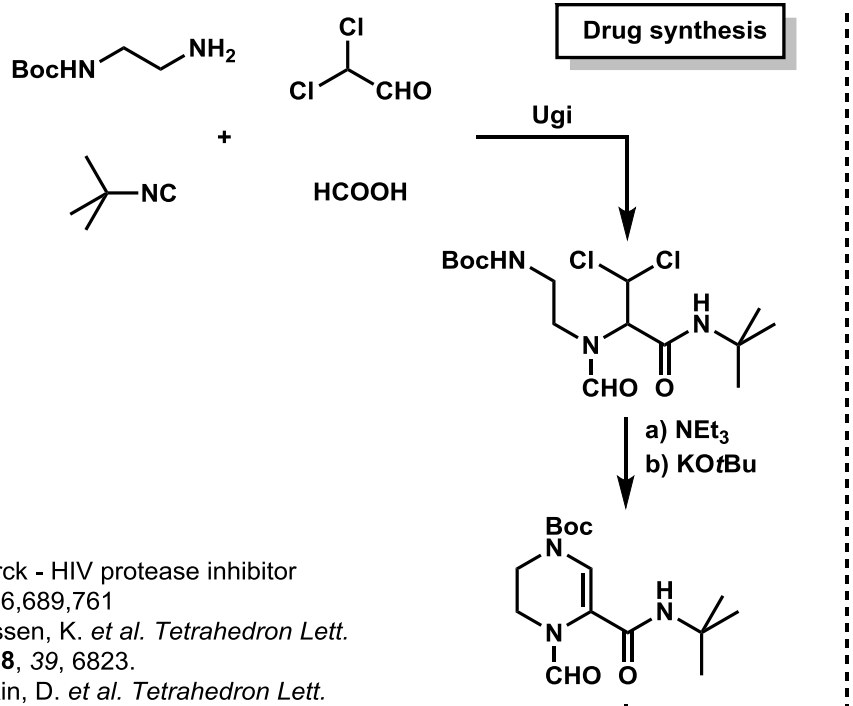
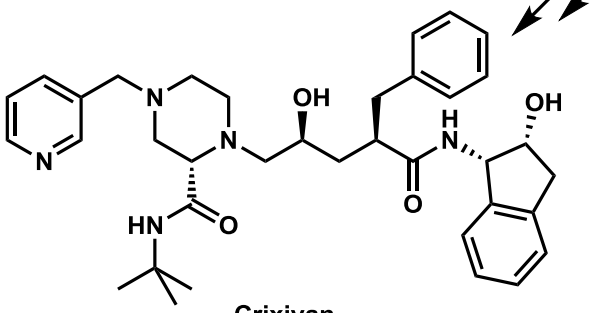
Drug synthesis



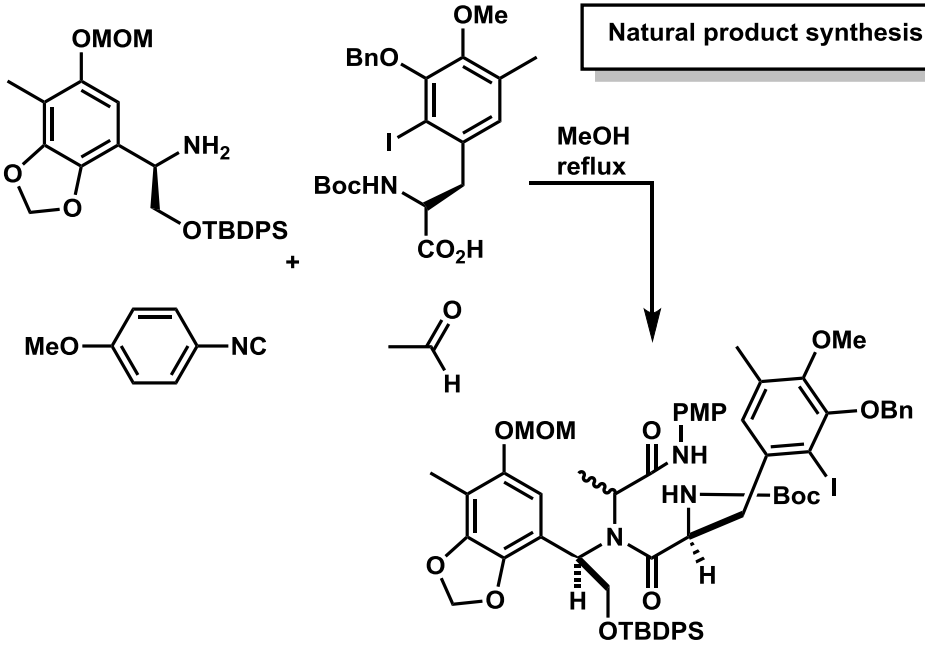
Merck - HIV protease inhibitor
US 6,689,761
Rossen, K. *et al. Tetrahedron Lett.* **1998**, *39*, 6823.
Askin, D. *et al. Tetrahedron Lett.* **1994**, *35*, 673.

Improved yield from 26% to 91%



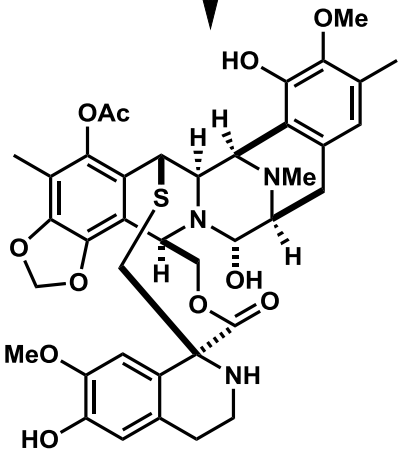
Crixivan

Natural product synthesis



Ecteinascidin 743 (ET 743)
Fukuyama group
Endo, A. *et al.*
J. Am. Chem. Soc. **2002**, *124*, 6552

steps



Strategic applications of named reactions in organic synthesis are important to us!!!