

## Definition

Multicomponent reactions (MCRs) are those reactions in which three or more reactants come together in a single reaction vessel to form a new product which contains portions of all the components

"MCRs convert more than two educts directly in to their product by one-pot reactions"- Ivar Ugi

Several MCRs involve isonitriles- their unique structural features and chemical properties make them suited for such reactions

Isoyanide multicomponent reaction methodologies have applications in most stages of the drug discovery process spanning lead discovery, lead optimization and final drug manufacture

**This presentation focuses on the construction of heterocycles**

Hulme, C.; Gore, V. *Current. Med. Chem.* **2003**, 10(1), 51. Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, D. A.; Keating, T. A. *Acc. Chem. Res.* **1996**, 29, 123. Ugi, I. *Pure Appl. Chem.* **2001**, 73(1), 187.

## History of MCRs

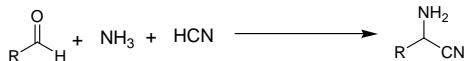
First 'officially' reported MCR was the Strecker synthesis of  $\alpha$ -amino nitrile in 1850

A large portion of MCR chemistry has developed from isocyanides

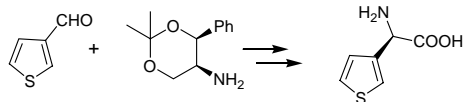
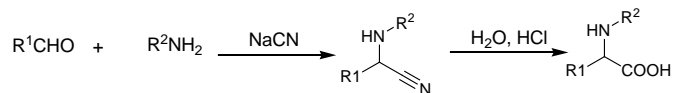
Pioneering contribution by Ivar Ugi with his discovery of the Ugi four component reaction

Other contributors to report heterocycles from Ugi reaction include Bienayme, Weber, Schreiber, Armstrong, Bossio

## Strecker Synthesis (1838 first reported by Laurent &amp; Gerhardt, 1850 by Strecker)

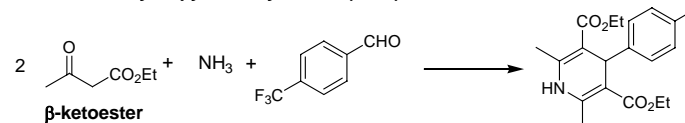


Strecker, A. *Liebigs Ann. Chem.* **1850**, 75, 27.



Arend, B. Westermann, N.; Risch, N. *Angew. Chem.* **1998**, 110, 1096.  
Arend, B. Westermann, N.; Risch, N. *Angew. Chem. Int. Ed.* **1998**, 37, 1044.

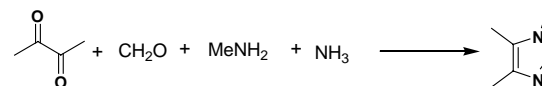
## Hantzsch Dihydropyridine synthesis (1882)



$\beta$ -ketoester

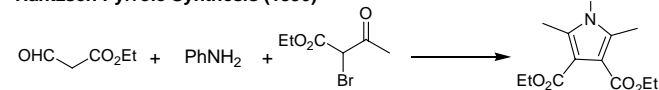
Hantzsch, A. *Justus Liebigs Ann. Chem.* **1882**, 215, 1.

## Radziszewski Imidazole Synthesis (1882)



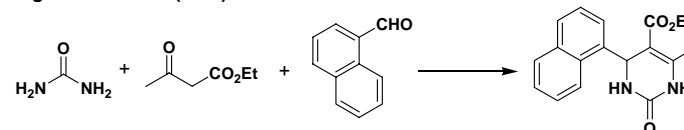
Radziszewski, B. *Ber. Dtsch. Chem. Ges.* **1882**, 15, 1499.

## Hantzsch Pyrrole Synthesis (1890)



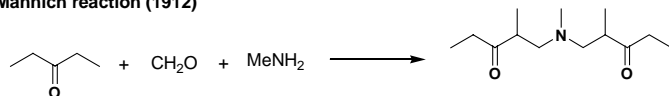
Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, 23, 1474.

## Biginelli Reaction (1891)



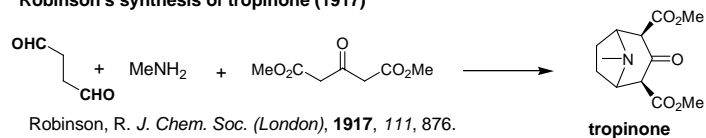
Kappe, O. *Acc. Chem. Res.* **2000**, 33, 879.  
Baran Lab group meeting presentation by Mike DeMartino

## Mannich reaction (1912)



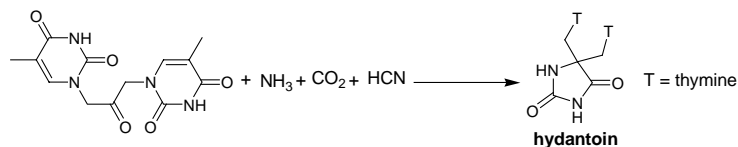
Mannich, C.; Krosche, W. *Arch. Pharm.* **1912**, 250, 647.  
 Bur, S. K.; Martin, S. F. *Tetrahedron*, **2001**, 57, 3221 (Review).  
 Martin, S. F. *Acc. Chem. Res.* **2002**, 35, 895.

## Robinson's synthesis of tropinone (1917)



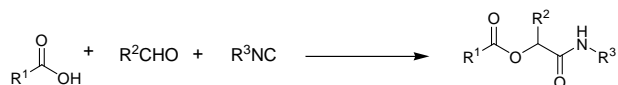
Robinson, R. *J. Chem. Soc. (London)*, **1917**, 111, 876.

## Bucherer-Bergs hydantoin Synthesis (1929)



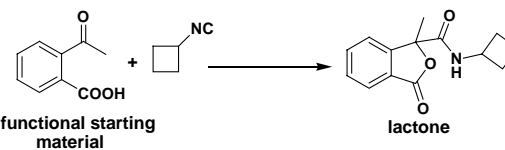
Bucherer, T.; Barsch, H.; *J. Prakt. Chem.* **1934**, 140, 151.  
 Kubik, S.; Meisner, R. S.; Rebek, J. *Tetrahedron Lett.* **1994**, 36, 6635.

## Passerini Reaction (1921)

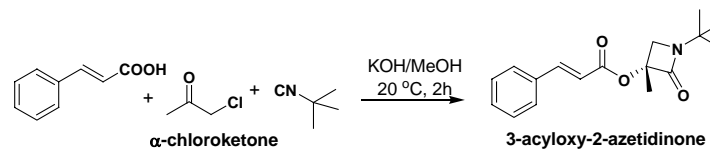


**α-acyloxy carboxamide**-commonly encountered motif in natural products and pharmacologically interesting peptides

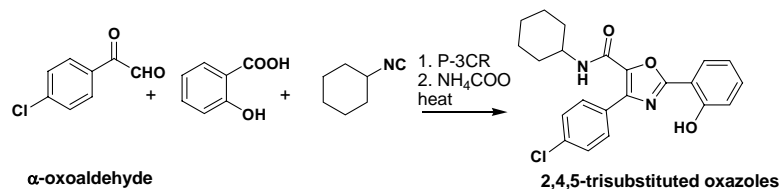
## Cyclic variations of the Passerini reaction



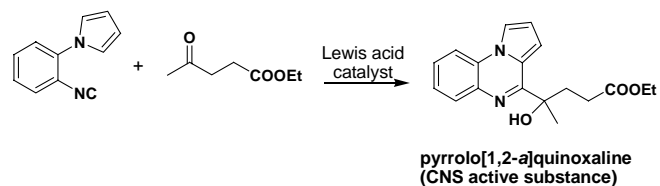
Passerini, M. *Gazz. Chim. Ital.* **1923**, 53, 331.



Sebti, S.; Foucand, A. *Synthesis*, **1983**, 546.  
 Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1997**, 38, 2519.

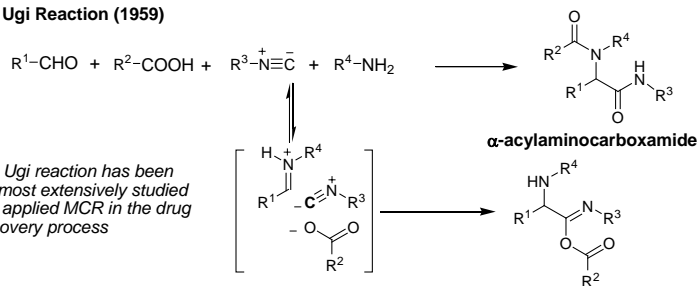


Such oxazoles can be generated smoothly, with high diversity with all three positions variable  
 Bossio, R.; Marcaccini, S.; Pepino, R.; Torroba, T. *Liebigs Ann. Chem.* **1991**, 1107.



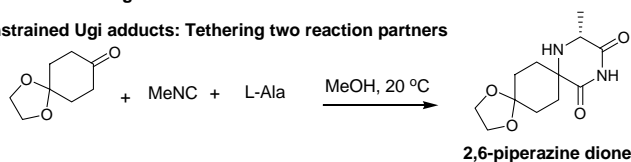
Kobayashi, K.; Matoba, T.; Susumu, I.; Takashi, M.; Konishi, H. *Chem. Lett.* **1998**, 551.

## The Ugi Reaction (1959)

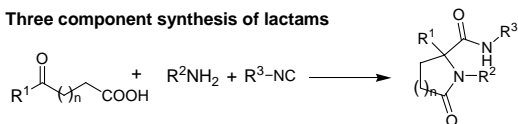


## Variations of the Ugi Reaction

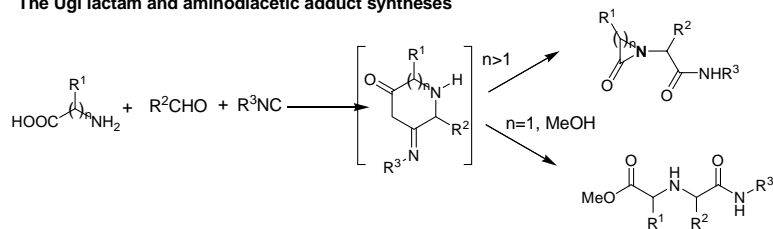
## Constrained Ugi adducts: Tethering two reaction partners

Ugi I.; Hori, W.; Hanusch, C.; Schmid, T.; Herdtweck, E. *Heterocycles*, **1998**, *47*, 985.

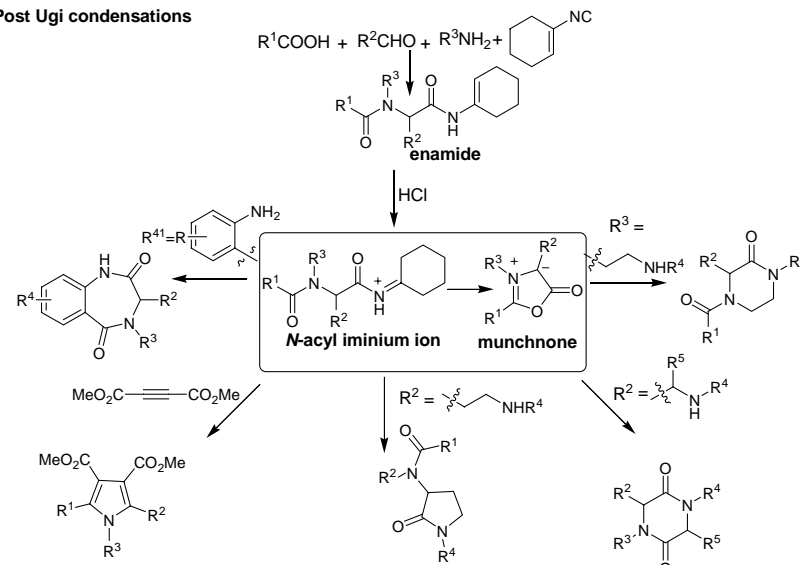
## Three component synthesis of lactams

Hanusch-Kompa, C. Ugi, I. *Tetrahedron Lett.* **1998**, *39*, 2725.  
Harriman, G. C. B. *Tetrahedron Lett.* **1997**, *38*, 5591.

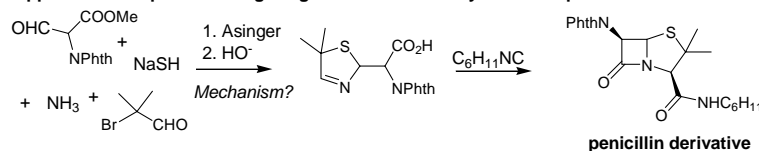
## The Ugi lactam and aminodiacetic adduct syntheses

Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Lee, D. H. *Tetrahedron Lett.* **1998**, *39*, 7109.  
Ugi, I.; Hori, W.; Hanusch-Kompa, C.; Schmid, T.; Herdtweck, E. *Heterocycles*, **1998**, *47*, 965.

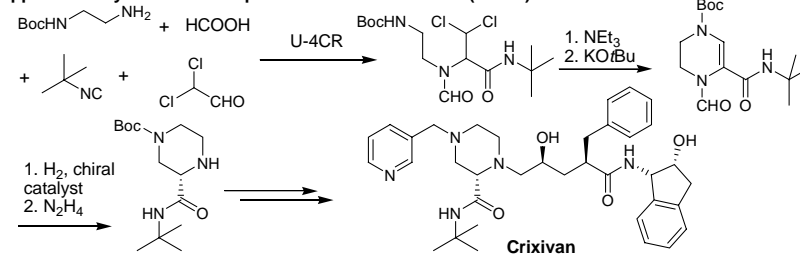
## Post Ugi condensations

Bienayme, H.; Hulme, C.; Odon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*(10), 3321.

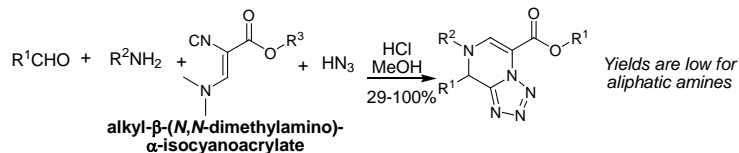
## Application: sequential Asinger Ugi Reactions in the synthesis of penicillin derivatives

Ugi, I.; Wishofer, E. *Chem. Ber.* **1962**, *95*, 136.

## Application: synthesis of HIV protease inhibitor crivivan (Merck)

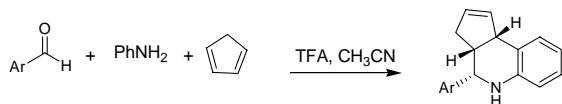
Rossen, K.; Pye, P. J.; Di Michele, L. M.; Volante, K.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823.

## A 'two-step one-pot' fused tetrazole synthesis (Ugi variation)



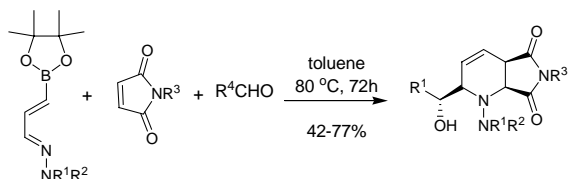
Bienayme, H.; Bouzid, K. *Tetrahedron Lett.* **1998**, 39, 2735.

## Grieco three component synthesis of piperidines



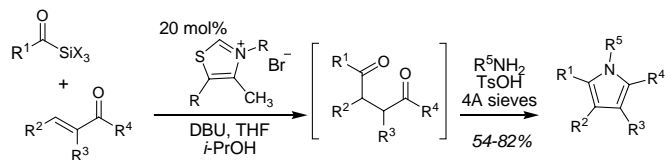
Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, 107, 1768.  
Grieco, P. A.; Bahsas, A. *Tetrahedron Lett.* **1988**, 29, 5855.

## Three component tandem aza [4+2]/allylboration reactions in the diversity oriented synthesis of polysubstituted piperidines



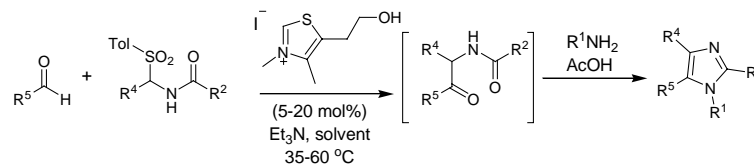
Toure, B. B.; Hoveyda, H. R.; Tailor, J.; Agnieszka, U.-L.; Hall, D. *Chem. Eur. J.* **2003**, 9, 466.

## One-pot synthesis of pyrroles catalyzed by thiazolium salts



Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* ASAP.

## Synthesis of Imidazoles via organocatalysis

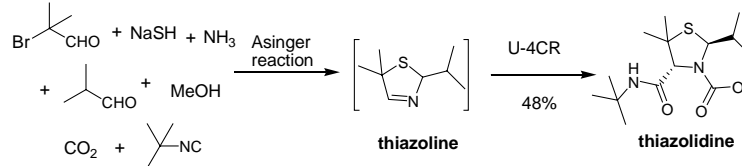


Based on the same strategy synthesis of oxazoles and thiazoles has also been reported.

Frantz, D. E.; Morency, L.; Soheili, A.; Murry, J. E.; Grabowski, E. J. J.; Tillyer, R. D. *Org. Lett.* **2004**, 6, 843.

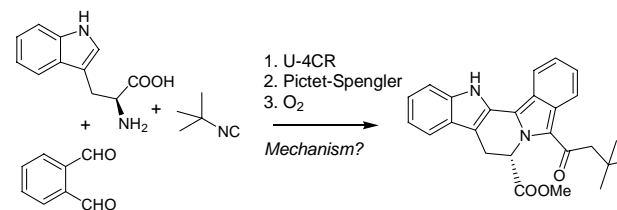
## Combination of MCRs

## A seven component reaction



Domling, A.; Ugi, I. *Angew. Chem.* **1993**, 105, 634.  
Domling, A.; Ugi, I. *Angew. Chem. Intl. Ed.* **1993**, 32, 563.  
Review on the Asinger Reaction: Asinger, F.; Offermanns, H. *Angew. Chem. Intl. Ed.* **1967**, 6, 907.

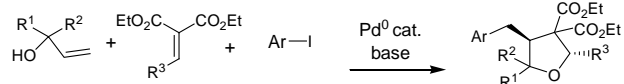
## Ugi + Pictet-Spengler Reaction



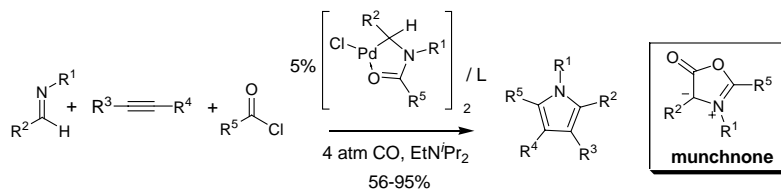
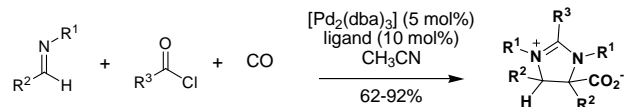
Domling, A.; Ugi, I. *Angew. Chem. Intl. Ed.* **2000**, 39, 3168.

## Organometallic Multicomponent Reactions

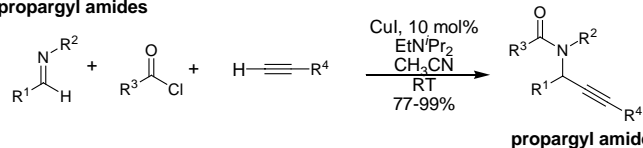
## Pd catalysed multi-component tetrahydrofuran synthesis

Cavicchioli, M.; Sixdenier, E.; Derrey, A.; Bouyssi, D.; Balme, G. *Tetrahedron. Lett.* **1997**, 38, 1763.

## Pd catalyzed multicomponent coupling of alkynes, imines and acid chlorides via munchnones (1,3-oxazolium-5-oxides) in the synthesis of pyrroles

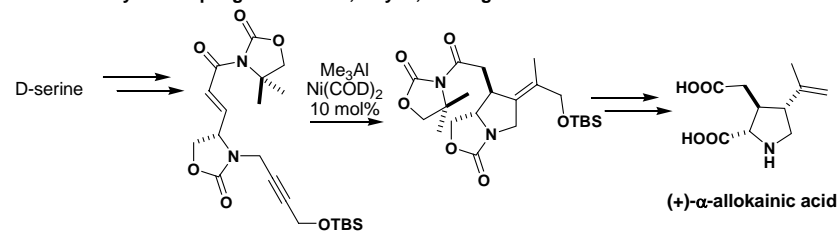
Pd catalyzed of  $\alpha$ -amino acid derived imidazolines

## Cu catalyzed multicomponent of imines, acid chlorides and alkynes in the synthesis of propargyl amides

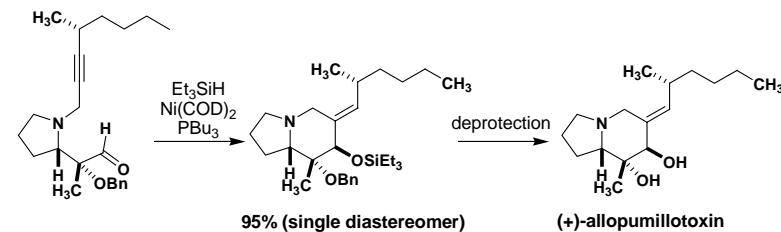


Dhawan, R.; Dghaym, R. D.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, 125, 1474.  
 Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, 6, 1107.  
 Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, 126, 468.  
 Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem. Int. Ed.* **2001**, 40, 3228.

## Ni catalyzed coupling of an enone, alkyne, and organozinc

Chevliakov, M. V.; Montgomery, J. *Angew. Chem. Int. Ed. Eng.* **1998**, 37, 3144.

## Ni catalyzed coupling of an aldehyde, alkyne and organozinc or silane

Tang, X. Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, 121, 6098.

Some Useful Reviews on MCRs

Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168.

Bienayme, H.; Hulme, C.; Odon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321.

Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.

Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.

Armstrong, R. M.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123.

Dax, S. L.; McNally, M. A.; Youngman, M. A.; *Curr. Med. Chem.* **1999**, *6*, 255.

Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363.

Ugi, I. *Pure and Appl. Chem.* **2001**, *73*, 187.

Williams, T. J.; Zhang, L. *Pure Appl. Chem.* **2002**, *74*, 25.

Domling, A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 318.