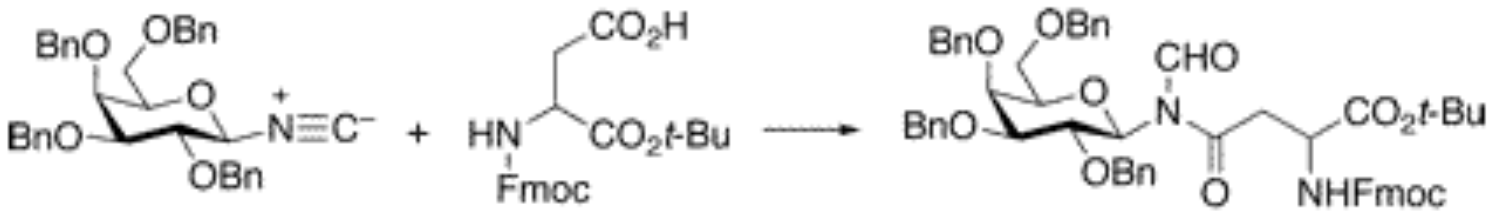
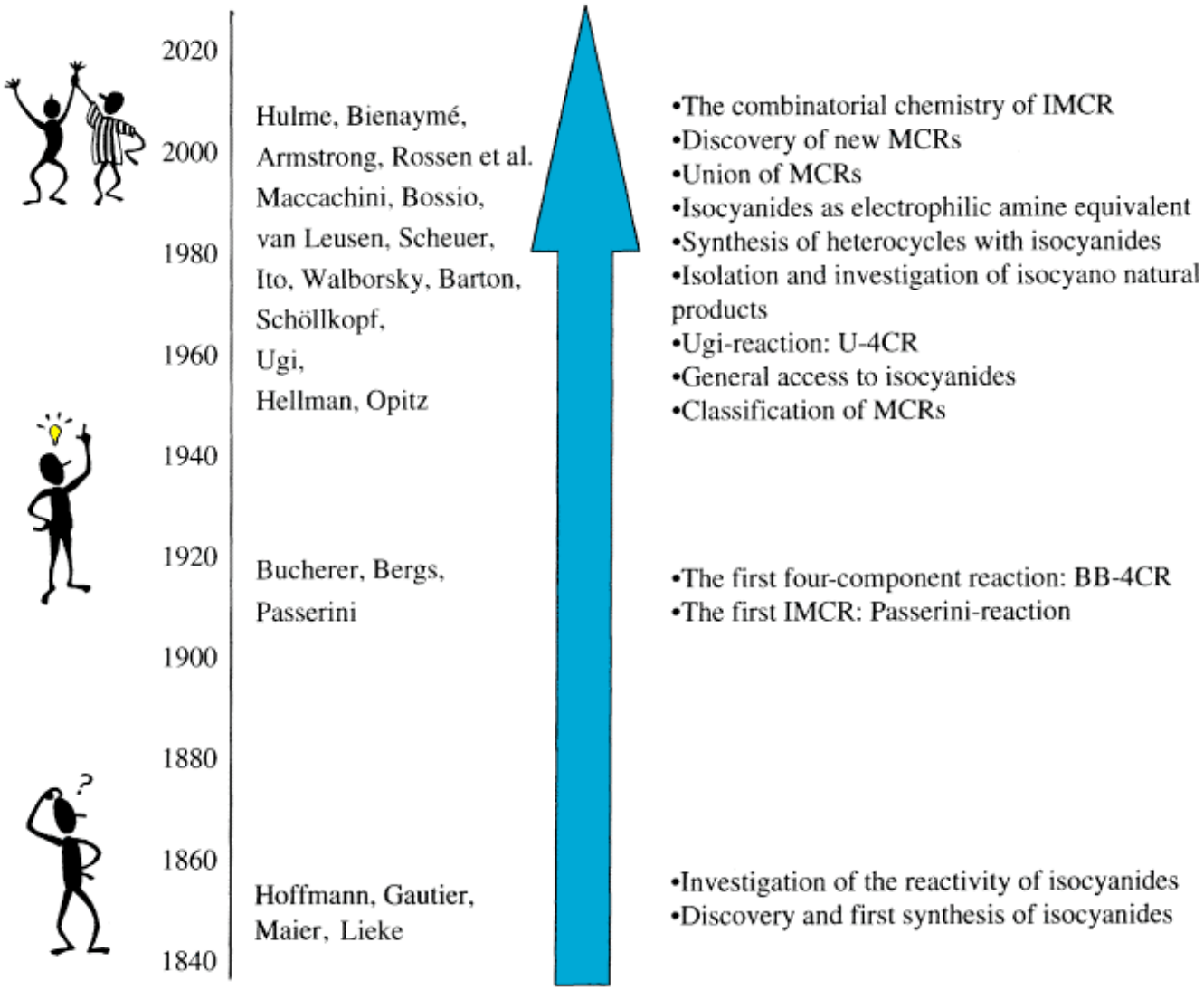
New Chemistry with Old Functional Groups: On the Reaction of Isonitriles with Carboxylic Acids-A Route to Various Amide Types

Li, X.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2008**, *130*, 5446.



Zhiyong Wang
Wipf Group
Current Literature Presentation
April 26th, 2008

Isocyanide-An Old and Versatile Functional Group



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

Properties of Isocyanides

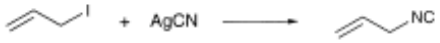
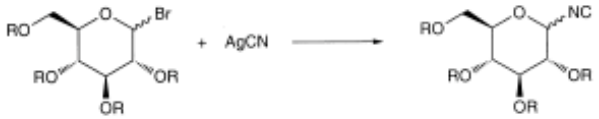
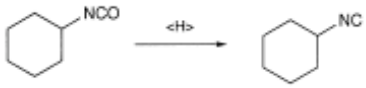
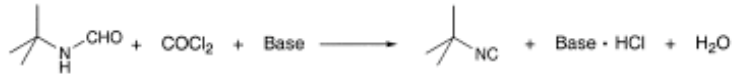
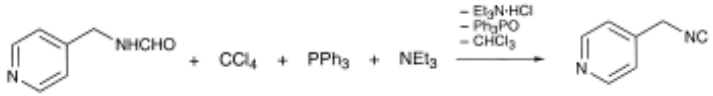
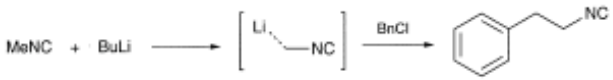
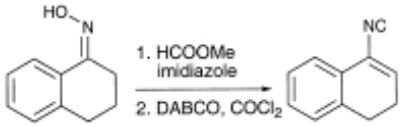
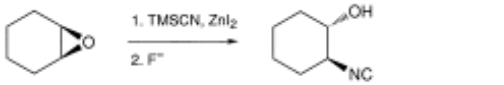
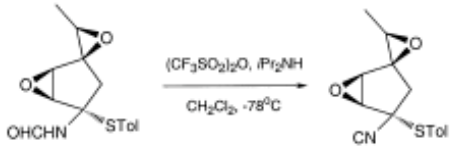
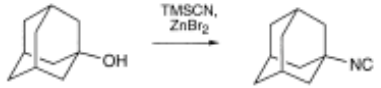
- Most commercially available simple alkyl isocyanides carry a repulsive odor which is reminiscent of artichokes and phosphorus at the same time.
- Long term inhalation of volatile isocyanides might cause the sensory perception of the smell of hay and increase the intensity of dreams at night.
- Structurally more complex isocyanides are generally solid, odorless and of low toxicity.

LD_{50} < 10mgkg^{-1} for mouse

Gautier, A. *Ann. Chim. (Paris)* **1869**, *17*, 618.

Preparation of Isonitriles

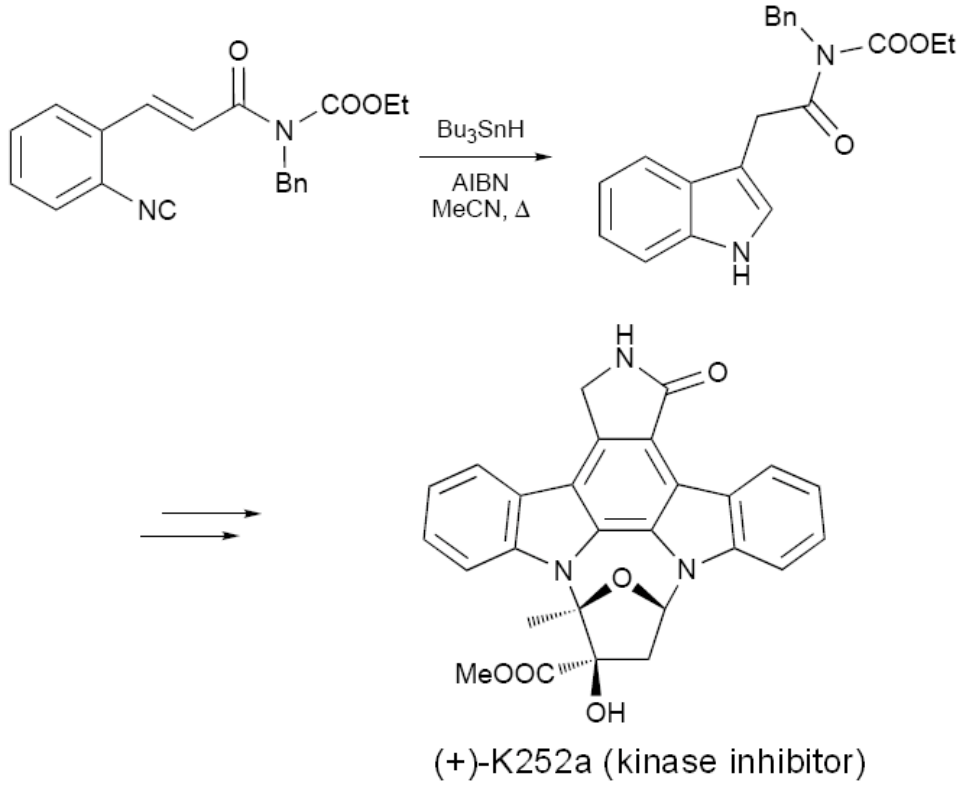
Important preparative isocyanide syntheses with examples.

Method	Example[a]
Lieke, 1859	
Meyer, 1866	
Gautier, 1867	the silver cyanide method, often referred to as the Gautier method, was first described by Lieke and Meyer.
Hoffmann, 1867	
Hoffmann, 1870	
Ugi, 1958	
Ugi, Weber, Gockel, 1972	improved Hoffmann carbylamine method, in $CH_2Cl_2/CHCl_3/H_2O$ with phase transfer catalyst
Appel, 1972	
Schöllkopf, 1971	
Barton, 1988	
Gassman, 1982	
Baldwin, 1990	
Kitano, 1998	

[a] DABCO = 1,4-diazabicyclo[2.2.2]octane, TMS = Me_3Si, Tol = tolyl.

Chemical Reactivity of Isocyanide

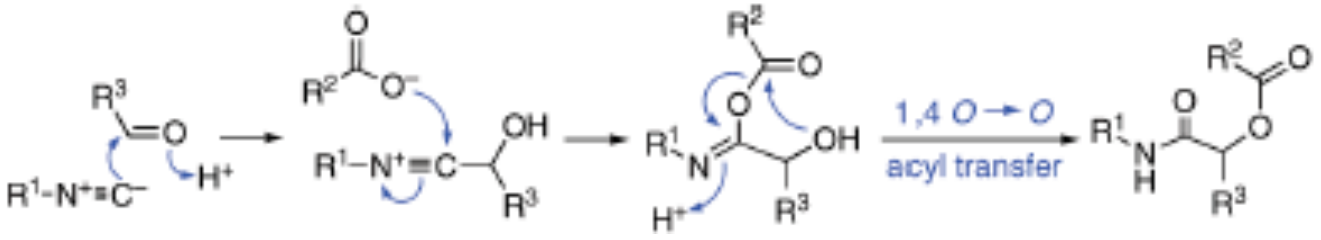
- α-Acidity: heterocycles formation
- α-Addition: multicomponent reactions (MCRs)
- Radical formation

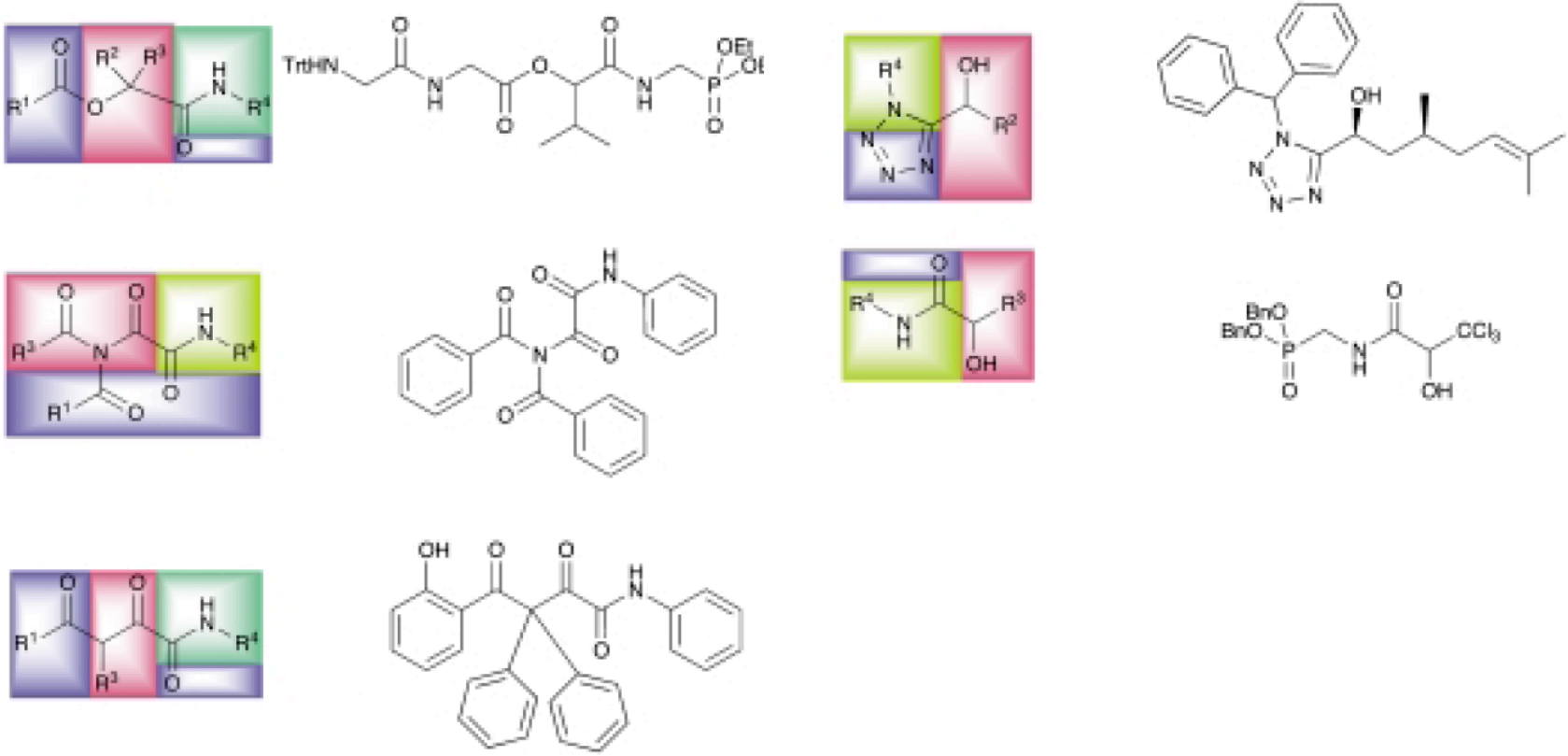


(+)-K252a (kinase inhibitor)

Kobayashi, Y.; Fukuyama, T. *J. Heterocycl. Chem.* **1998**, *35*, 1043.

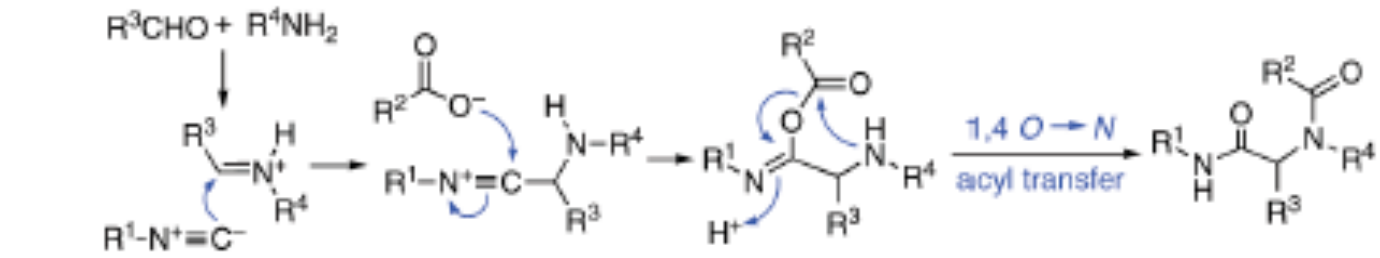
Passerini Reaction

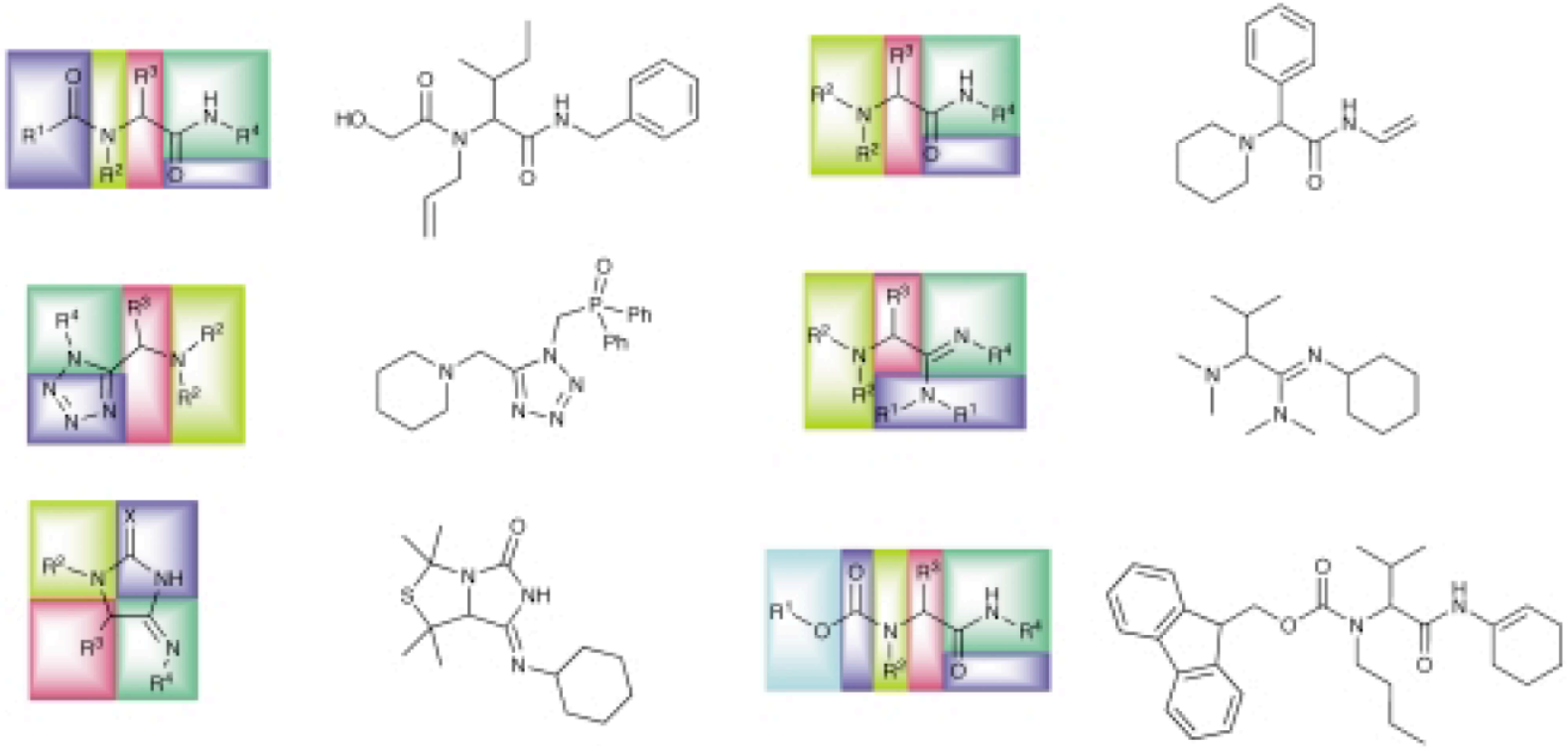




Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.
Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1.

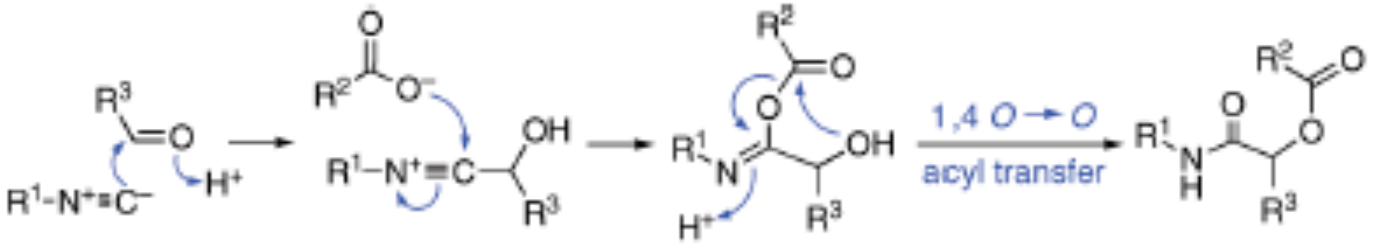
Ugi Four-Component Reaction (U-4CR)



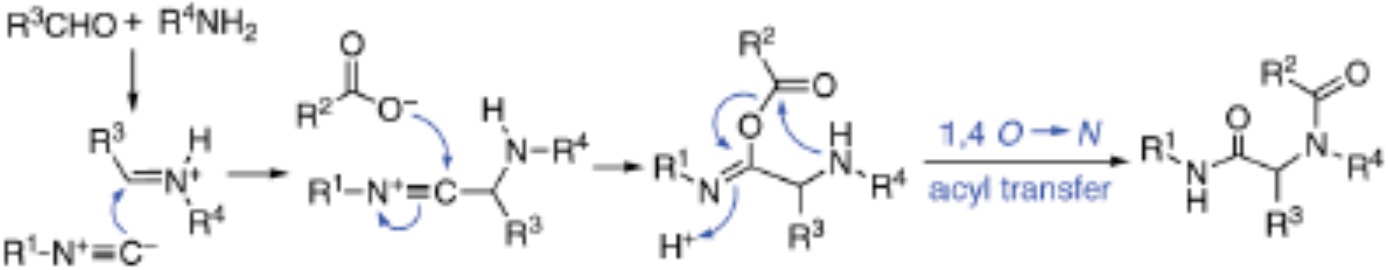


Ugi, I.; Meyr, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386.
Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

Current Paper: Do Ordinary Carboxylic Acids React with Isonitriles?



Scheme 1a: *Passerini reaction.*



Scheme 1b: *Ugi four-component coupling reaction.*

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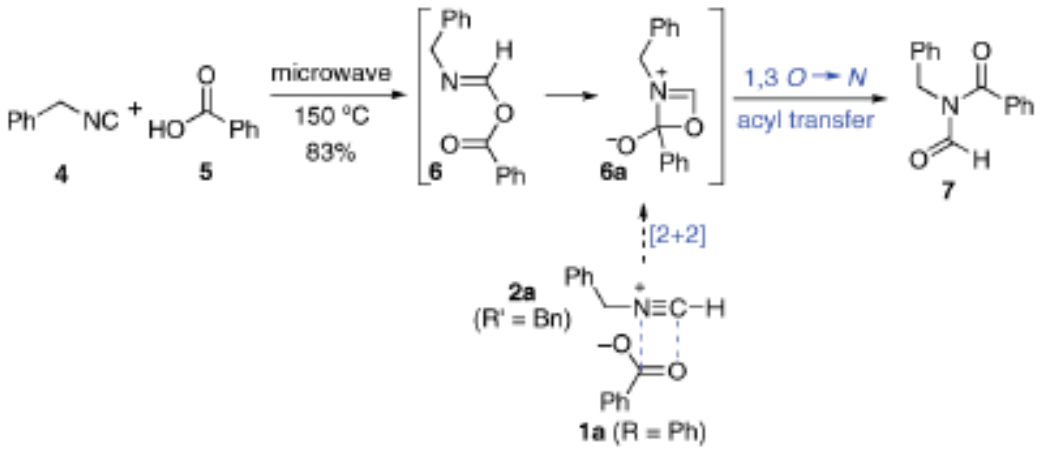
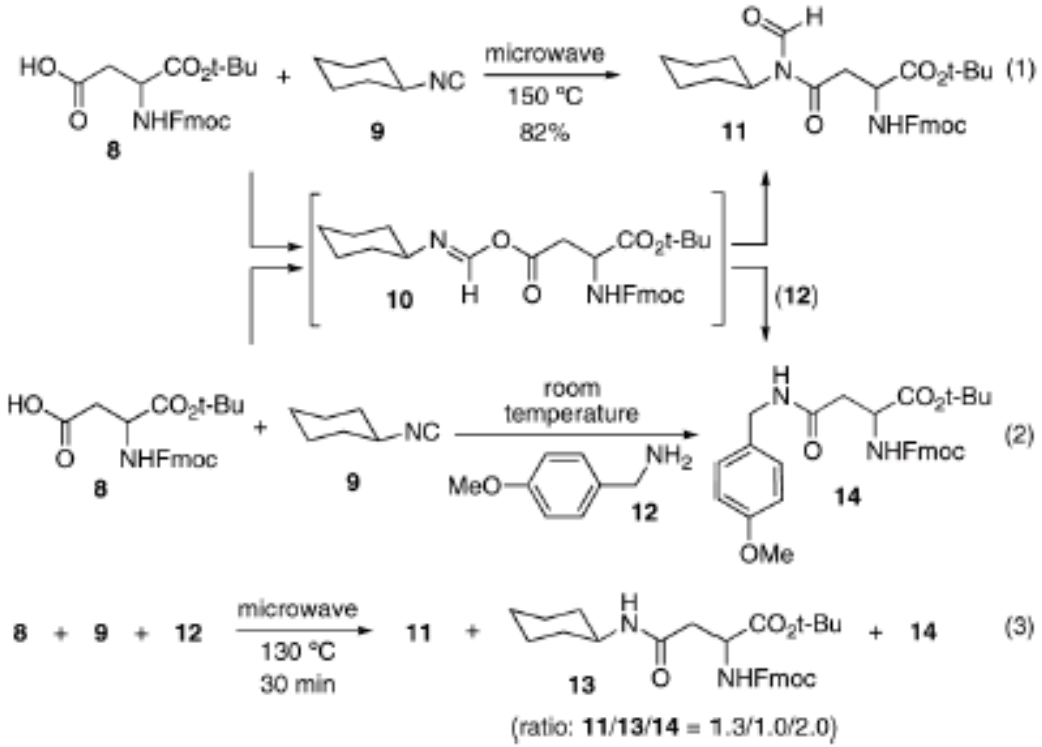
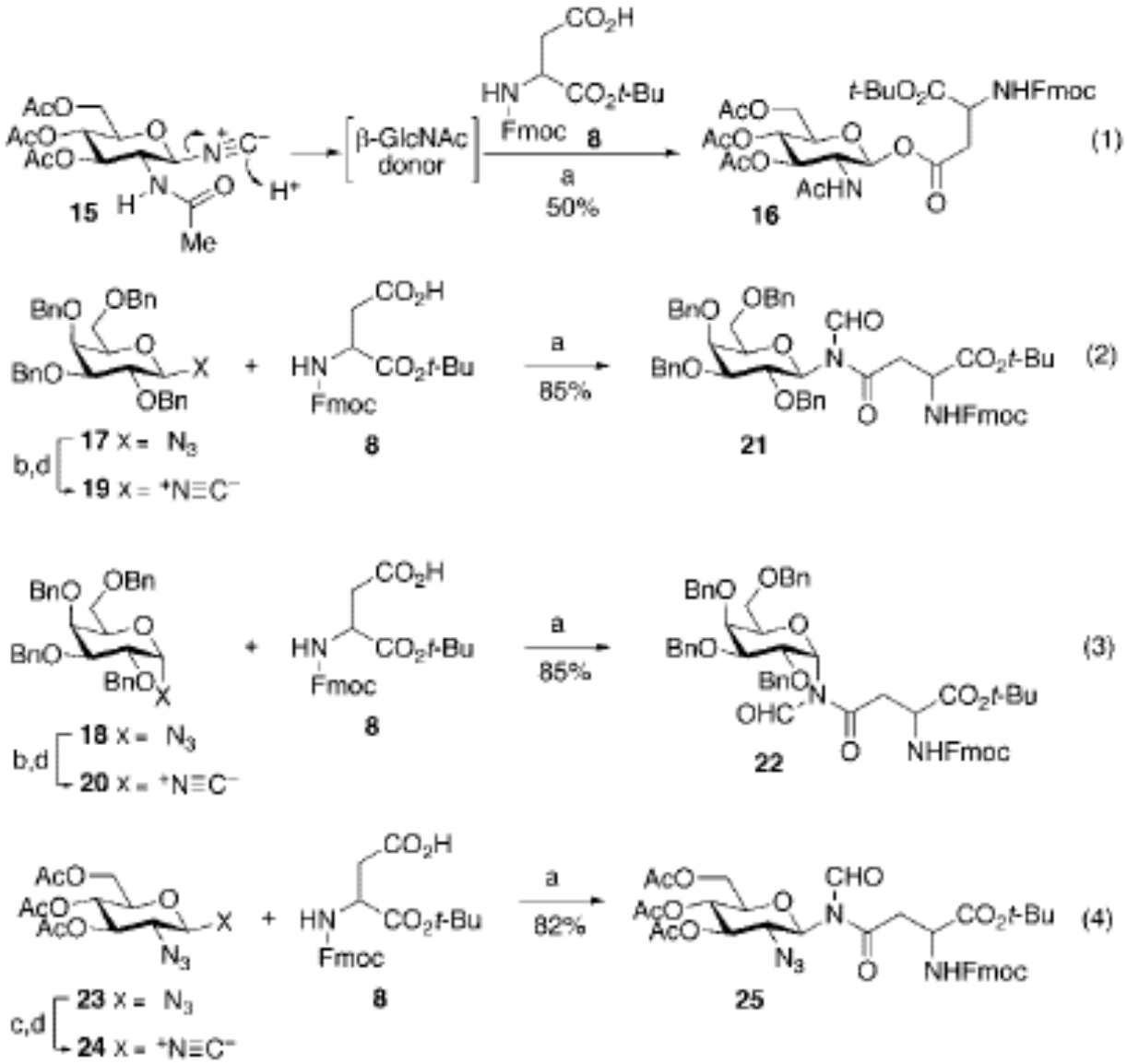
Exploration



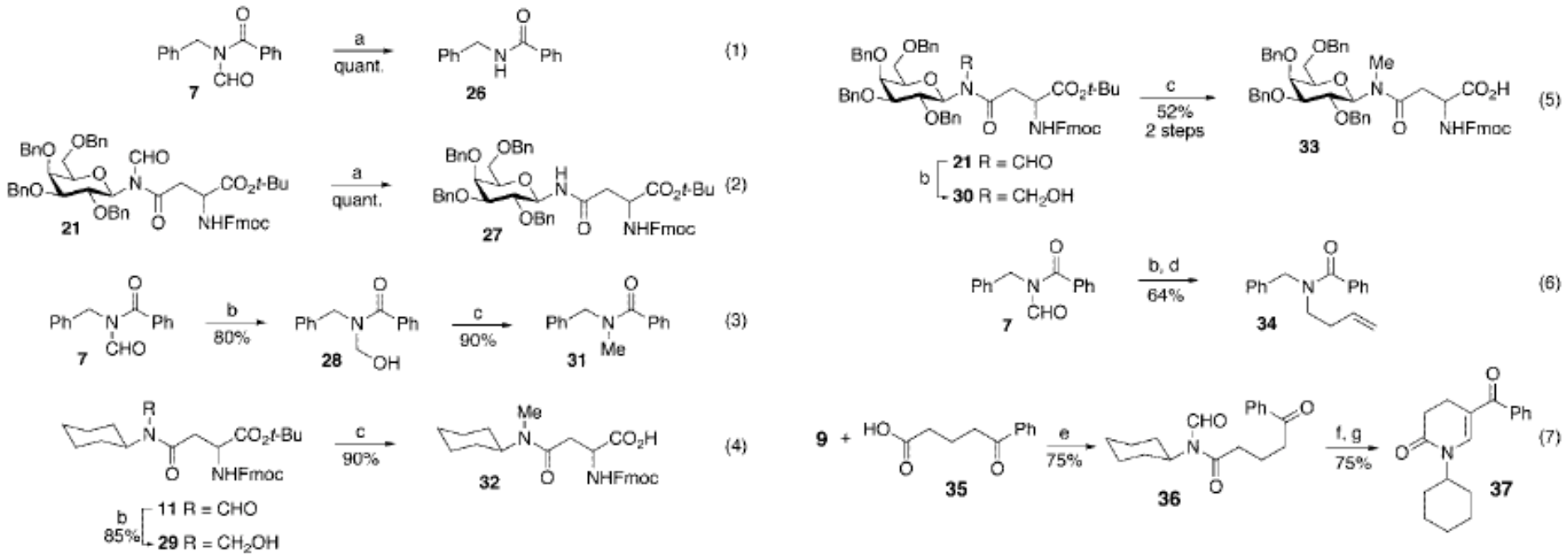


Application to Glycopeptide Formation



[a] Key: (a) $CHCl_3$, 150 °C (microwave), 30-45 min; (b) (1) Pd/C, H_2, Et_3N, EtOAc; (2) $HC(O)OC(O)CH_3$; (c) (1) $(NH_4)_2MoS_4$, MeCN/EtOH; (2) $HC(O)OC(O)CH_3$, EtOAc, 53%; (d) triphosgene, Et_3N, CH_2Cl_2, 0 °C to rt, 75–90%.

Further Elaboration of the *N*-Formyl Group



[a] Key: (a) NaOMe, MeOH, 0 °C; (b) $NaBH_4$, MeOH, 0 °C; (c) TFA, Et_3SiH, CH_2Cl_2; (d) TFA, allyltrimethylsilane, CH_2Cl_2; (e) $CHCl_3$, 150 °C (microwave), 30 min; (f) $LiN(TMS)_2$, THF; (g) TFA, CH_2Cl_2.

Summary

- Careful examination of reaction mechanisms could lead to novel discoveries from old chemical reactions.
- Common isonitriles do react with carboxylic acids under forcing conditions to give *N*-formyl amides. The formyl group could serve as a handle to construct various tertiary amides, which might otherwise be difficult to synthesize.