

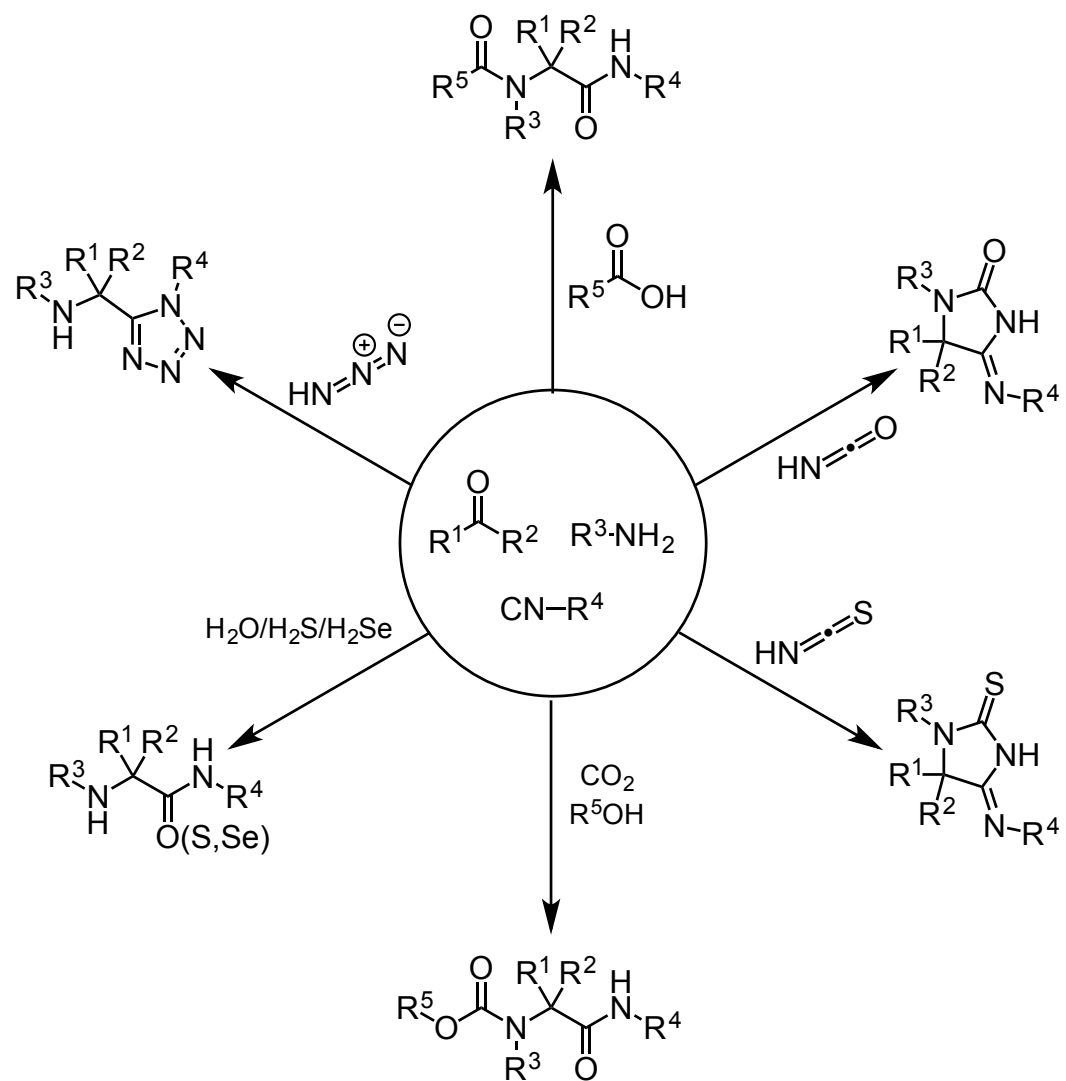
Named Reaction of the Day

Jen Crawford

Synthesis Club

27 March 2017

Ugi Multicomponent Reaction (U-4CR)



Uses:

- *Peptide coupling*
- *α -amino acid synthesis*
- *Combinatorial chemistry*

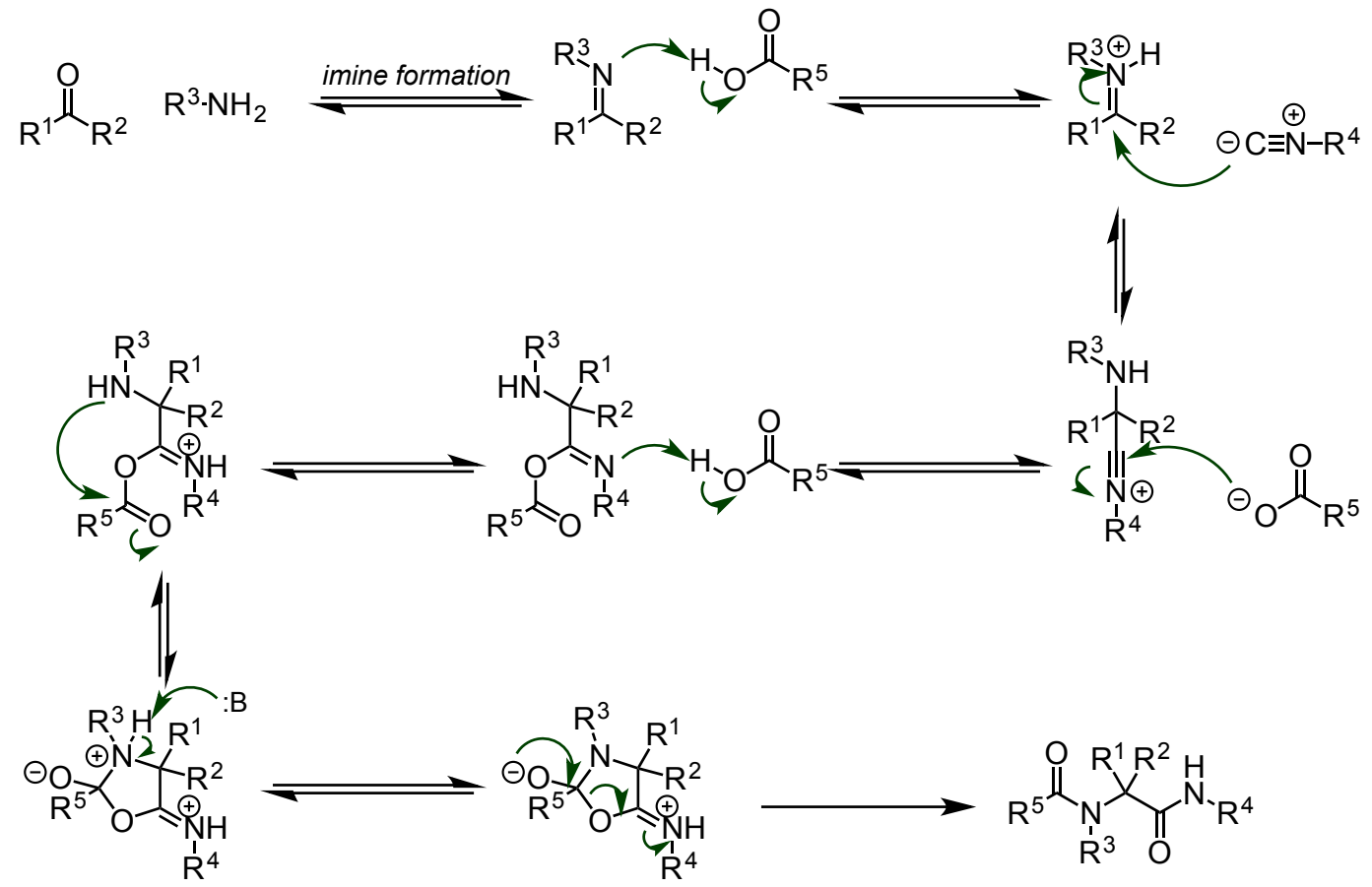
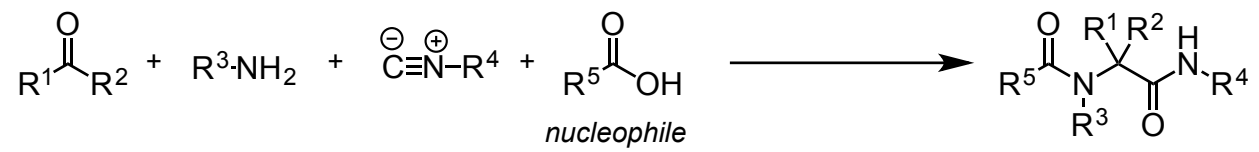
Limitations:

- *Stereoselectivity from chiral amine auxiliaries only*
- *Limited commercial availability of isocyanates*
- *Possible 3-CR side reactions (e.g. Passerini reaction)*

Modifications:

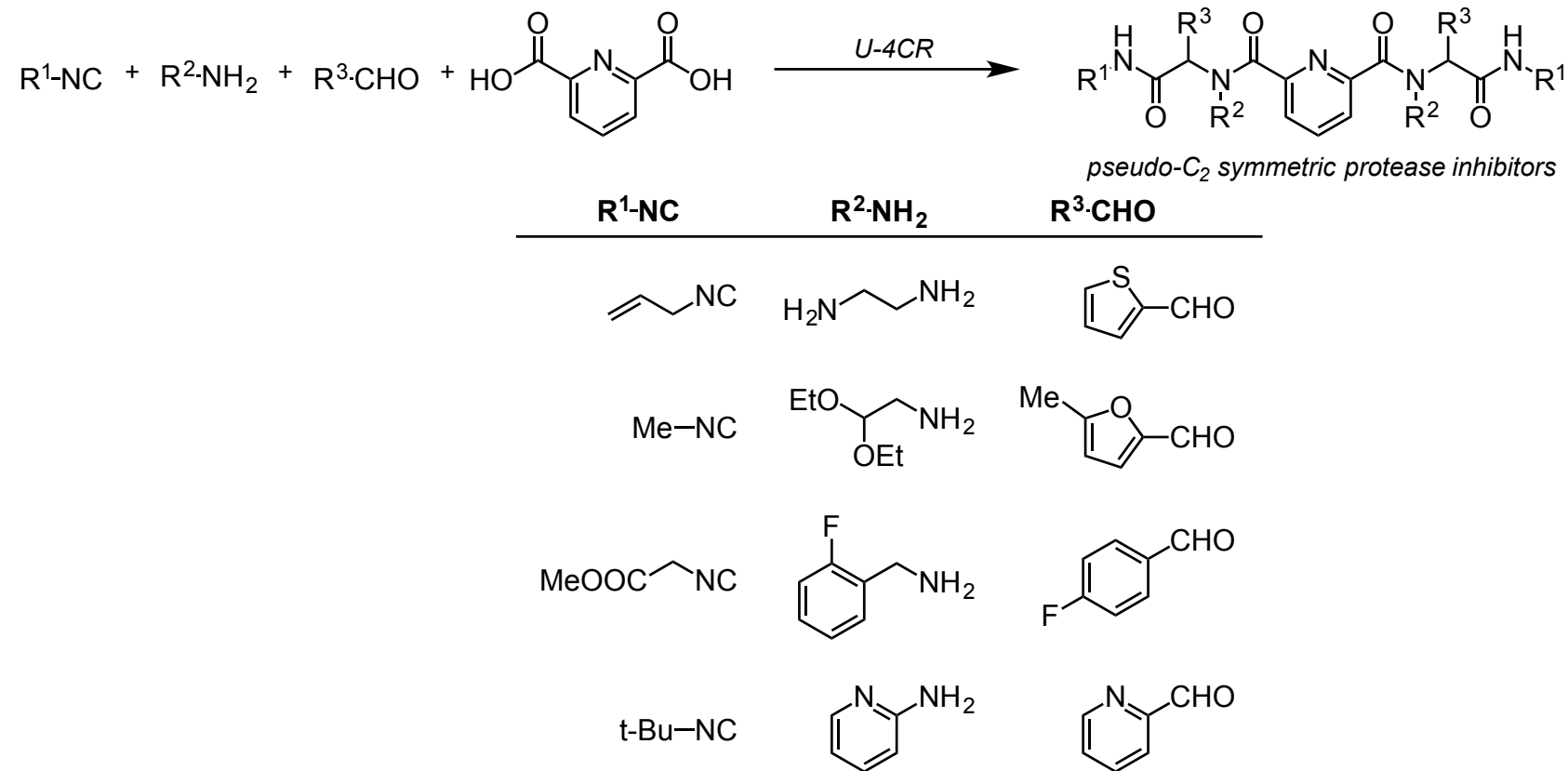
- *Heterocycle synthesis*
- *Post-condensation cyclizations*
 - *Increase product diversity (e.g. Ugi-Heck, Ugi-Diels Alder)*

Proposed mechanism



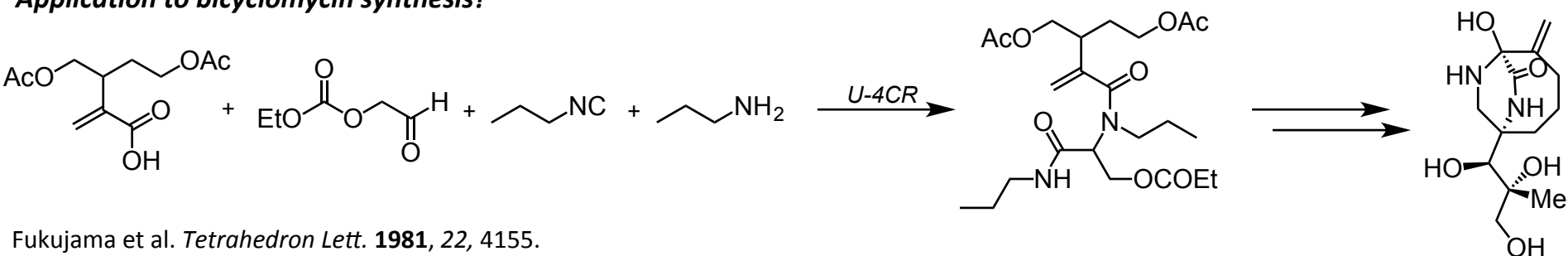
Combinatorial chemistry

13 reagents → 8256 products



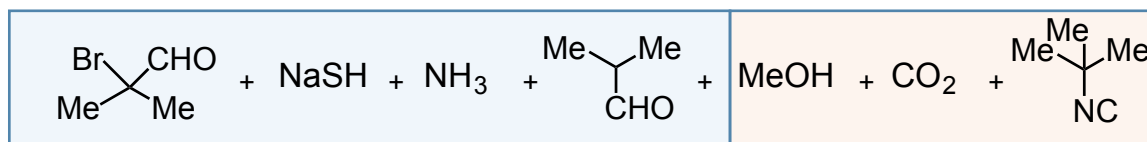
Domling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, 39, 3168.

Application to bicyclomycin synthesis?

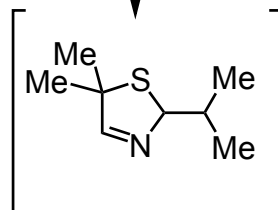


Fukujama et al. *Tetrahedron Lett.* **1981**, 22, 4155.

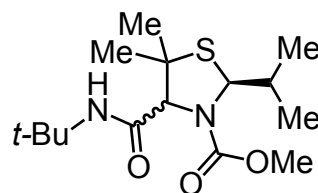
Limit to the number of components?



A-4CR



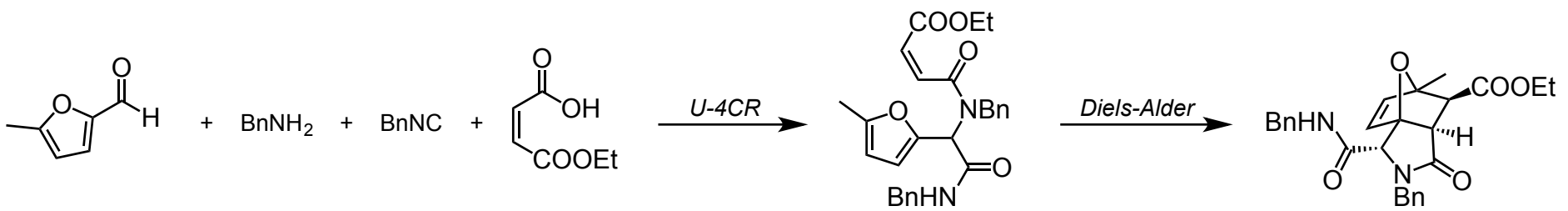
U-4CR



43%

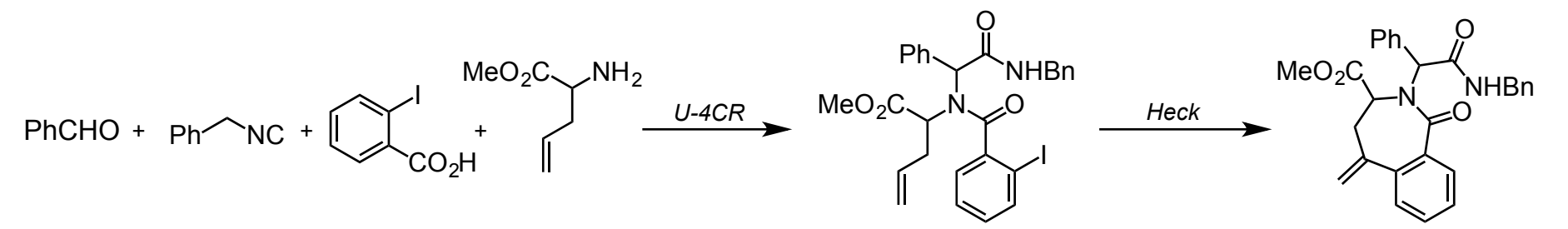
Post Condensation Cyclization → Functionalized Heterocyclic Scaffolds

Ugi-Diels Alder



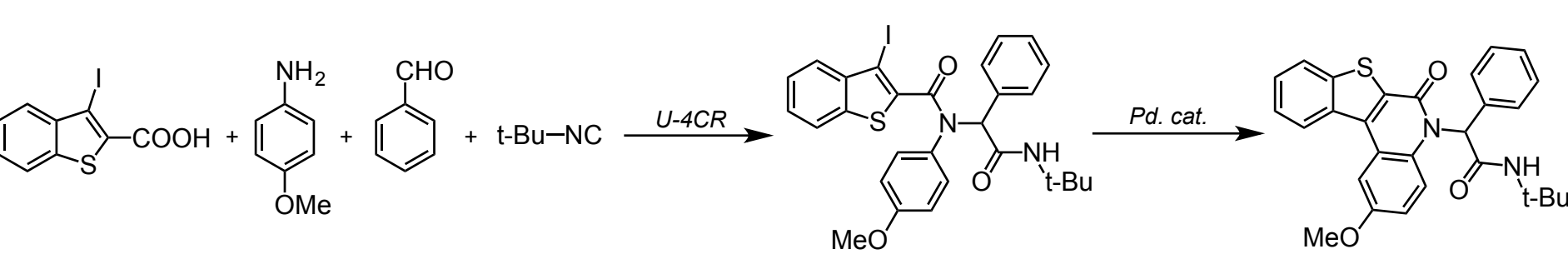
Paulvannan, K. *Tetrahedron Lett.* **1999**, 40, 1851.

Ugi-Heck



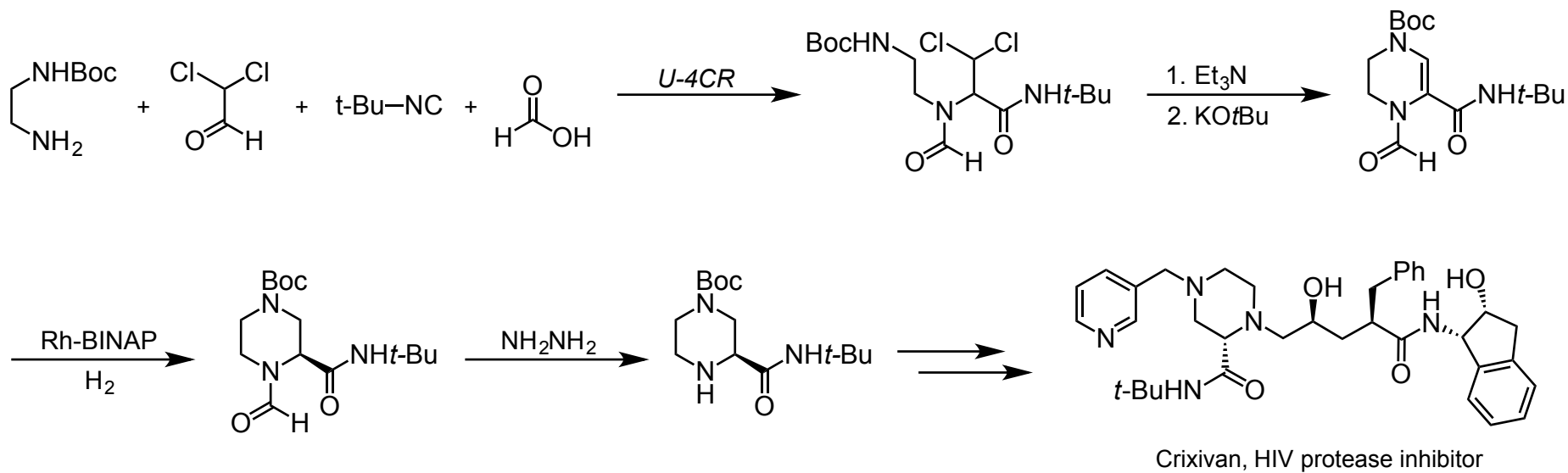
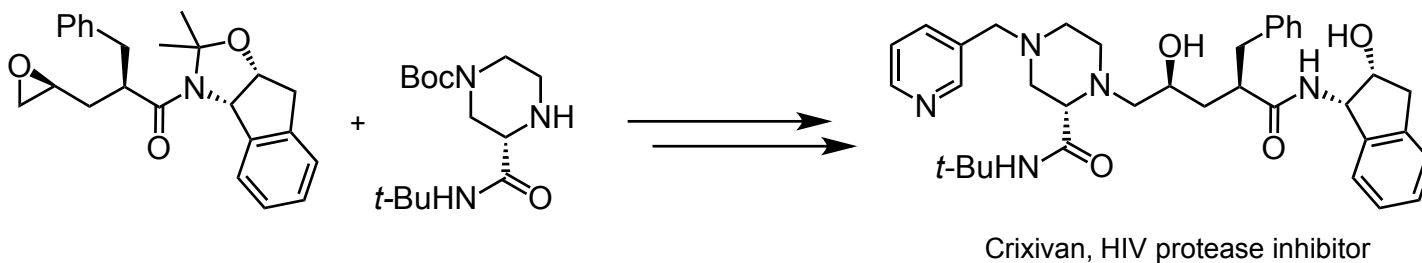
Gracias, V.; Djuric, S.W. *Tetrahedron Lett.* **2004**, 45, 417.

Ugi-Arylation

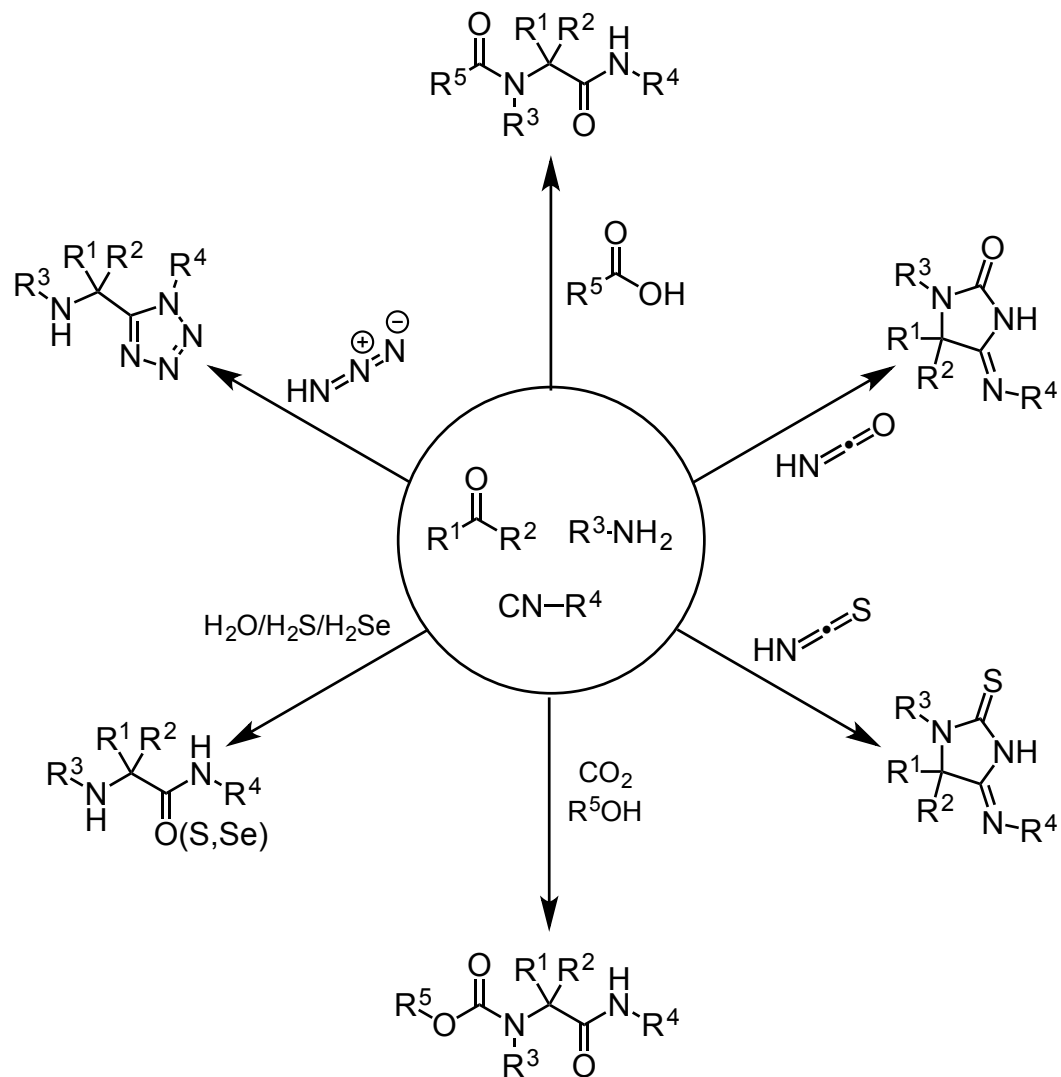


Ma et al. *J. Comb. Chem.* **2006**, 8, 696.

Crixivan synthesis



Summary



- **Useful for combinatorial chemistry in drug discovery**
- **Post-condensation cyclizations for heterocycle synthesis**
- **Mild conditions**
- **Wide functional group tolerance**