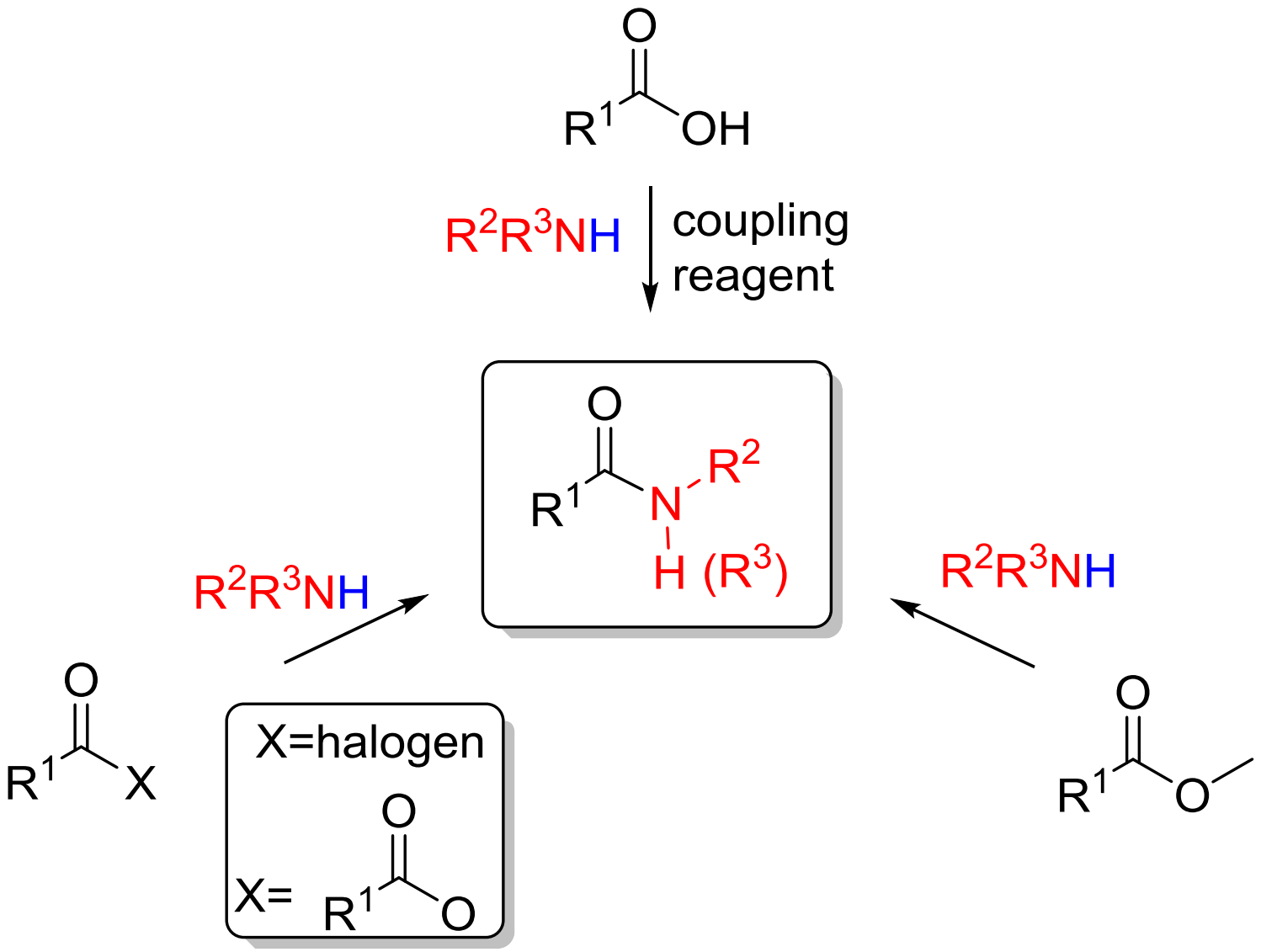
# NH активиране на органични съединения – обхват и приложение

Д-р Ивайло Славчев

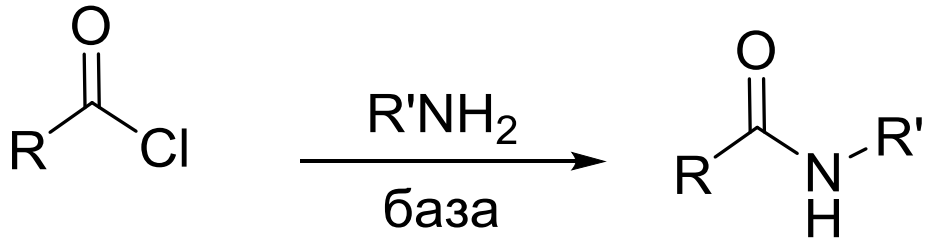
ИОХЦФ-БАН

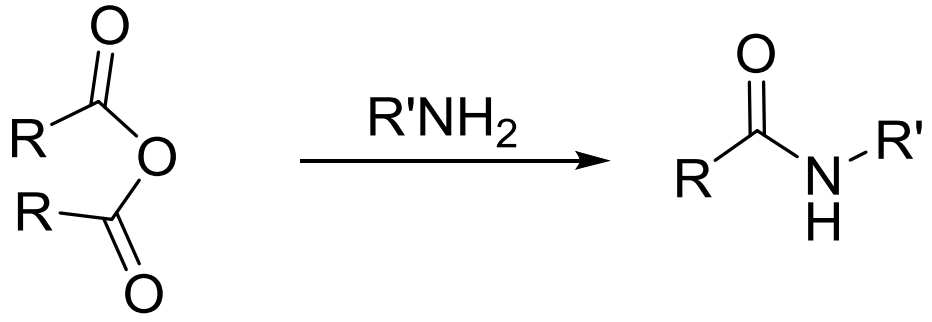
Лаб. „Органичен синтез и стереохимия“


O
R1
OH
R2R3NH
coupling
reagent
O
R1
N
R2
H (R3)
R2R3NH
R2R3NH
O
R1
X
X=halogen
X=
O
R1
O
O
R1
O

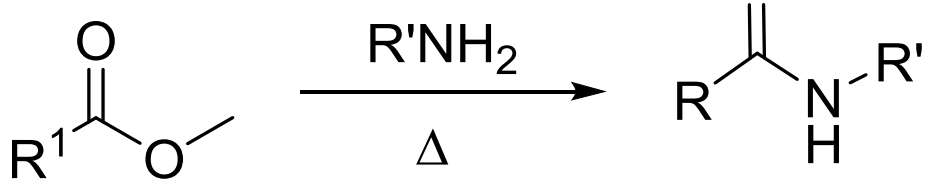
# Класически методи на амиден синтез

**1.**

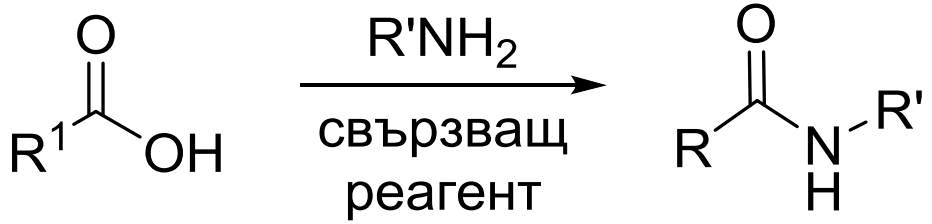



**2.**




**3.**

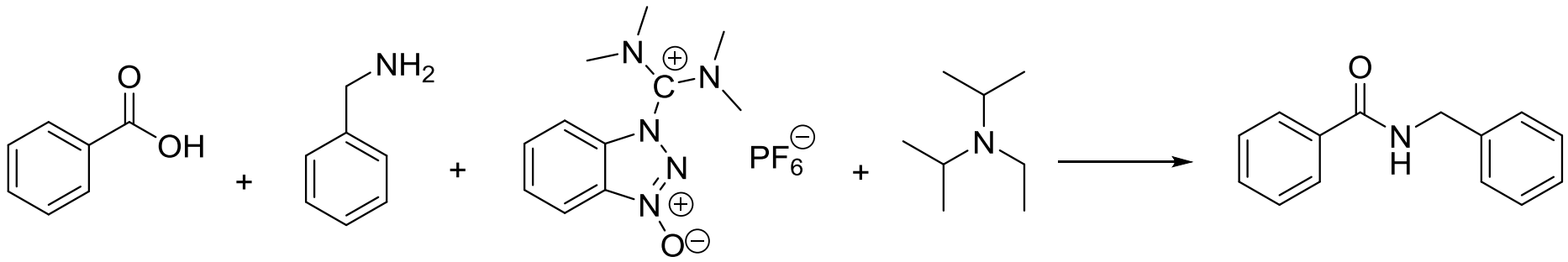


## Недостатъци на класическите методи на амиден синтез

- Ограничена достъпност
- Проблеми с рецемизация, хидролиза и т.н.
- Твърди условия
- Лоша атомна икономия

# Атомна икономия (ефикасност)

$$\text{Атомна икономия} = \frac{\text{M (целеви продукт)}}{\text{M (всички реагенти)}}$$



$$\text{Атомна икономия} = \frac{211.26}{737.77} = 28\%$$

REVIEW

doi:10.1038/nature10702

# Rethinking amide bond synthesis

Vijaya R. Pattabiraman[1] & Jeffrey W. Bode[1]

One of the most important reactions in organic chemistry—amide bond formation—is often overlooked as a contemporary challenge because of the widespread occurrence of amides in modern pharmaceuticals and biologically active compounds. But existing methods are reaching their inherent limits, and concerns about their waste and expense are becoming sharper. Novel chemical approaches to amide formation are therefore being developed. Here we review and summarize a new generation of amide-forming reactions that may contribute to solving these problems. We also consider their potential application to current synthetic challenges, including the development of catalytic amide formation, the synthesis of therapeutic peptides and the preparation of modified peptides and proteins.

Amide linkages[1] are not only the key chemical connections of proteins but they are also the basis for some of the most versatile and widely used synthetic polymers. Chemical reactions for their formation are among the most executed transformations in organic chemistry (Fig. 1). The prevalence of amide functionality, particularly in peptides and proteins[2], sometimes gives the incorrect impression that there are no remaining synthetic challenges. This is surprising, as it is often the case that even simple amides resist formation, forcing practitioners to resort to ever more exotic and expensive reagents for their synthesis. Furthermore, the favourable properties of amides, such as high polarity, stability and conformational diversity, make it one of the most popular and reliable functional groups in all branches of organic chemistry. Improved methods for the synthesis of amide functionality, whether catalytic and waste-free or chemoselective and suitable for fragment coupling, are in great



In living systems, most amide bonds are formed by the complex factories that are ribosomes. Long, complex proteins are assembled amino acid by amino acid, using a templated amidation of amines and the active esters of amino acid monomers and RNA (Fig. 2a)[3]. Synthetic chemists, by contrast, do not have the luxury of working on this single-molecule scale, and instead deal with trillions of molecules that must be coaxed into precise reaction trajectories. This strategy necessitates that nearly every functional group be protected by a bulky hydrophobic appendage, leading to a reliable, but rather wasteful approach to peptide synthesis, in which dozens of molecules are sacrificed to form just one amide bond[4].

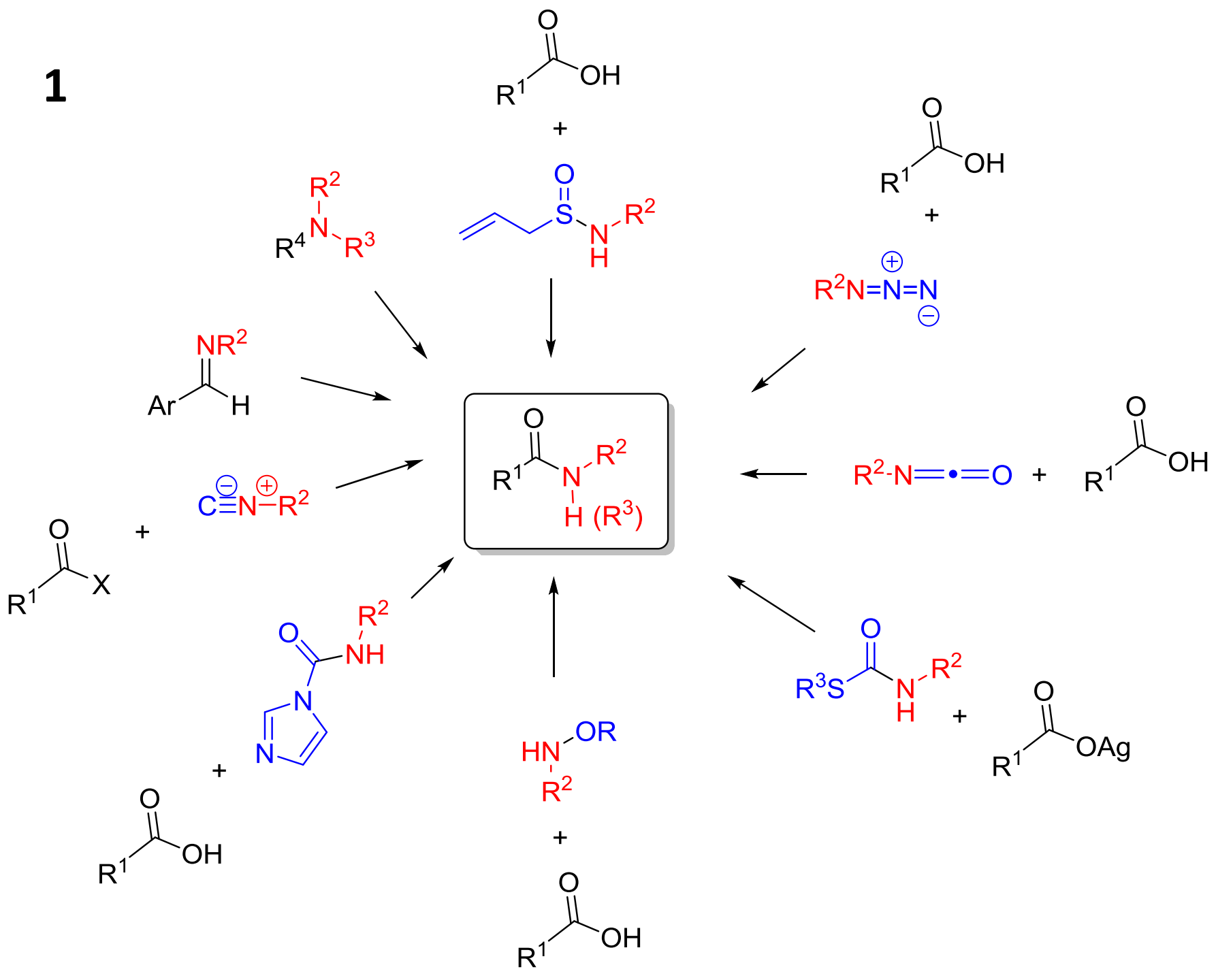
The current methods for amide formation are remarkably general but at the same time widely regarded as expensive and inelegant. Not surprisingly, in 2007 the American Chemical Society Green Chemistry Institute (comprising members from major pharmaceutical industries

1. Класически ацилиращ агент с аминен сурогат.

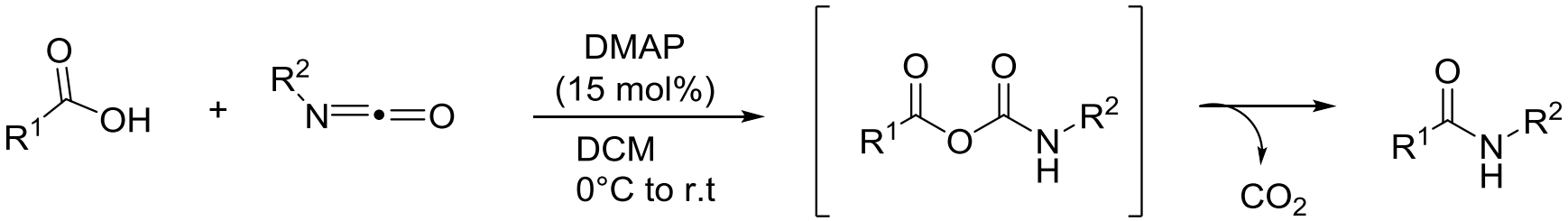
2. Класически амин агент със сурогат на ацилиращ агент

3. Аминен сурогат със сурогат на ацилиращ агент

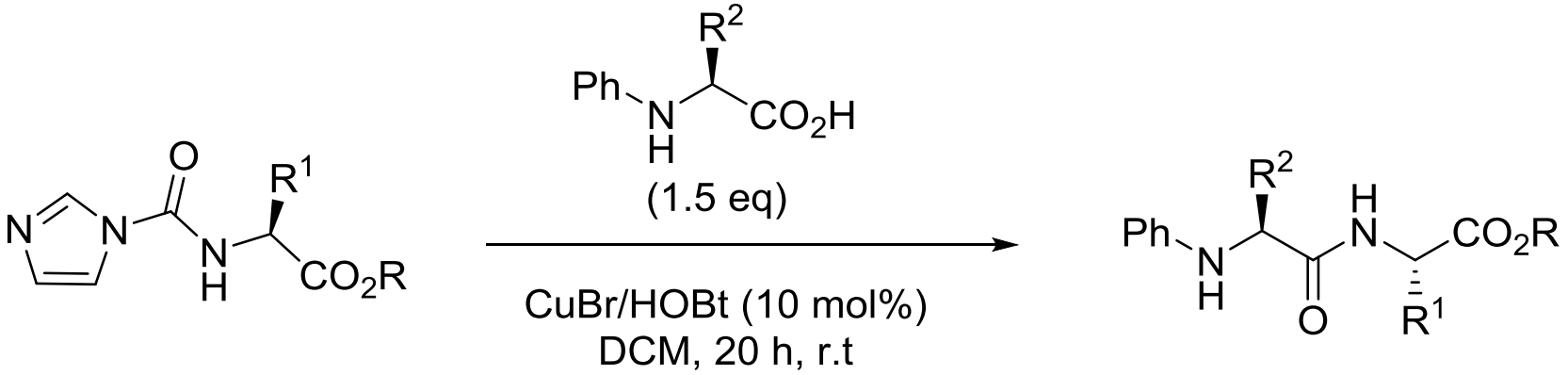
4. Класически ацилиращ агент с класически амин в иновативни реакционни условия


1
O
R1
OH
+
R2
R4
N
R3
O
S
N
H
R2
R2N=N=N
NR2
Ar
H
C≡N−R2
O
R1
X
+
O
R1
N
R2
H (R3)
R2-N=•=O
+
O
R1
OH
O
NH
N
N
R2
+
HN
OR
R2
+
O
R1
OH
O
R1
OH
+
O
R3S
N
R2
H
+
O
R1
OAg

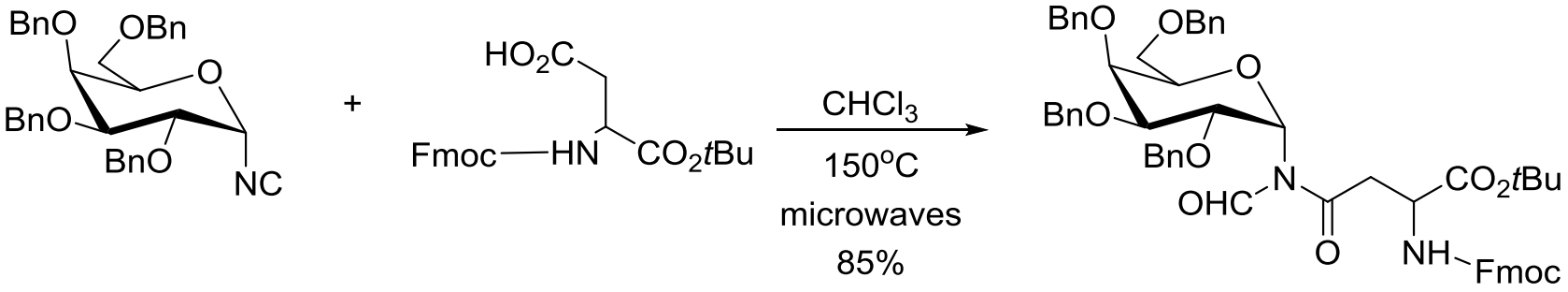
## Амидиране на изоцианати



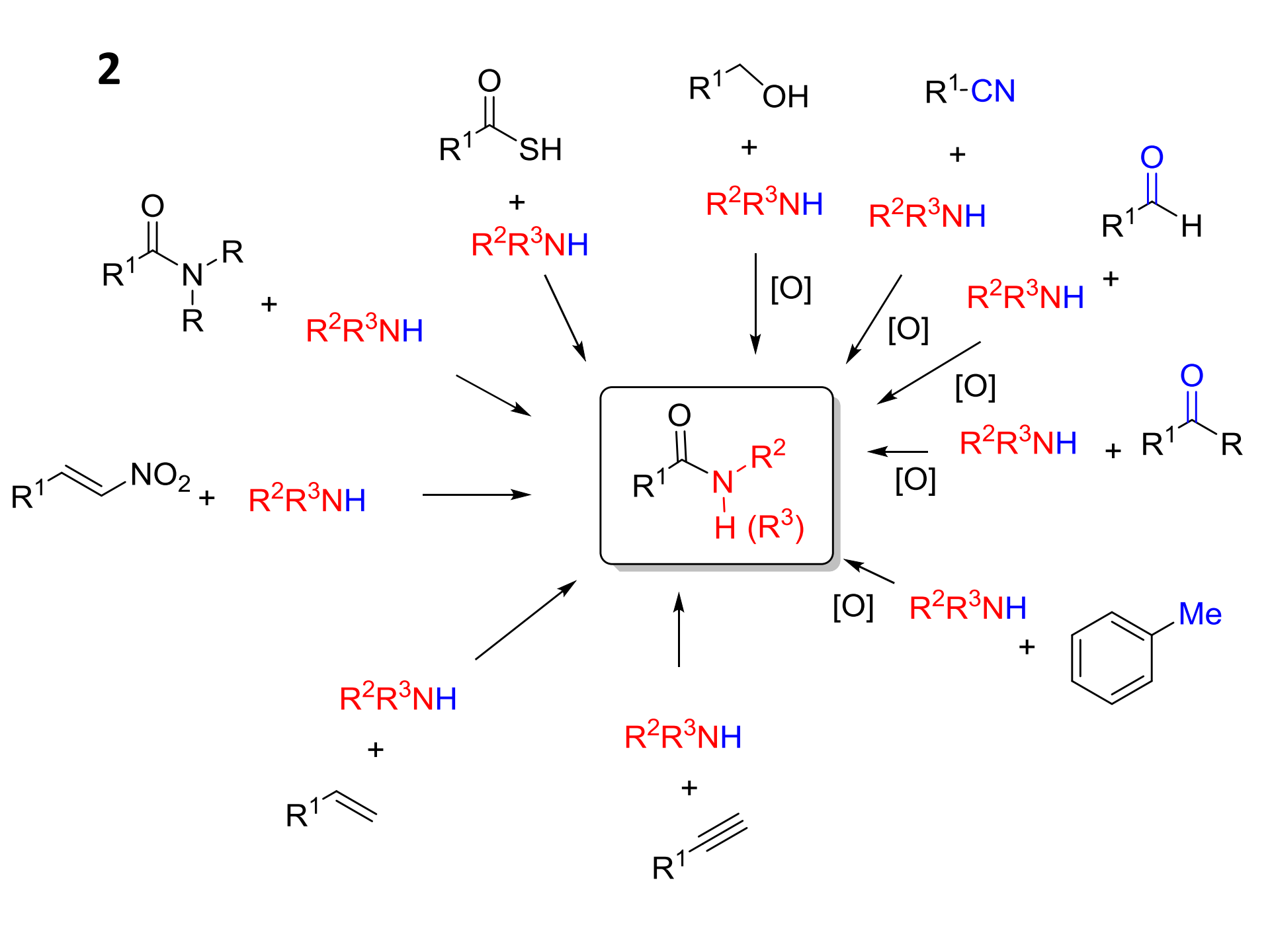

## CDI активирани естери



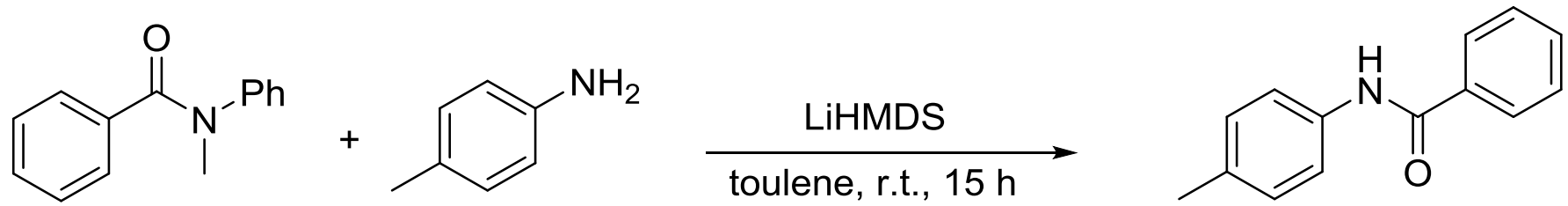

## Амидиране на изонитрили



**2**


R1 SH
+
R2R3NH
R1 OH
+
R2R3NH
[O]
R1-CN
+
R2R3NH
[O]
R1 H
+
R2R3NH
[O]
R1 N R R
+
R2R3NH
R1 NO2
+
R2R3NH
R1 N R2 H (R3)
[O]
R2R3NH
+
R1 R
[O]
R2R3NH
+
Me
R2R3NH
+
R1
R2R3NH
+
R1

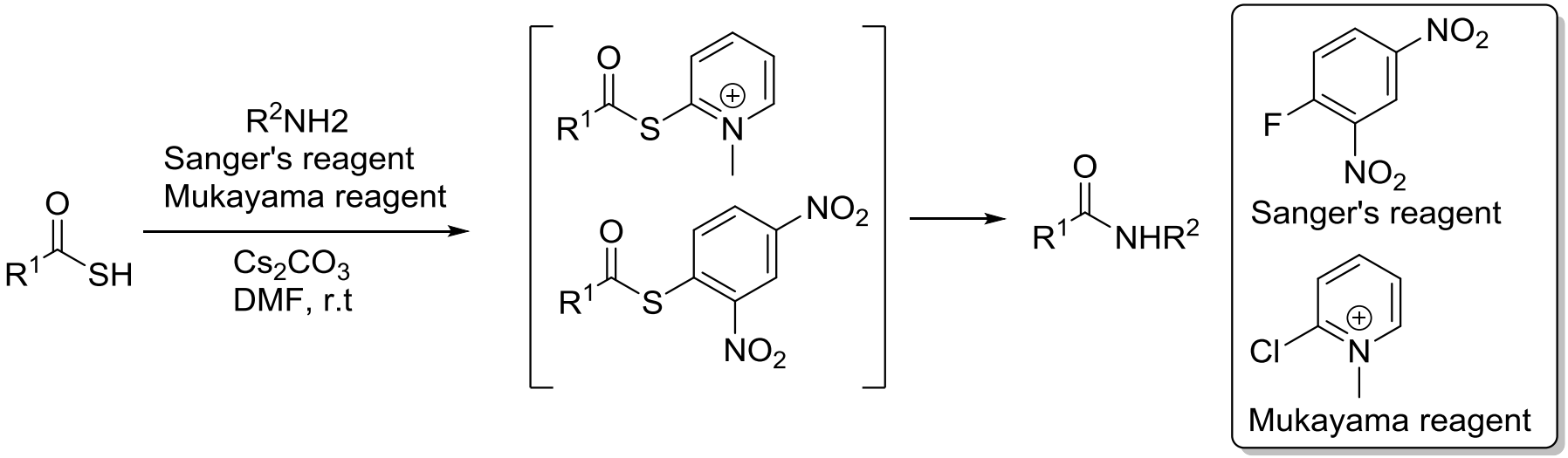
## Трансамидиране

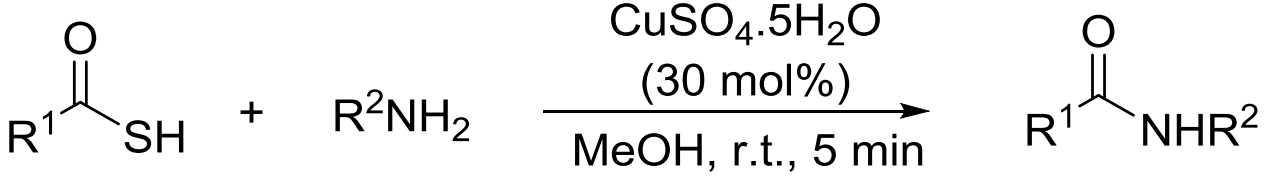



*J. Am. Chem. Soc.* ***2019****, 141, 11161-11172*

97%

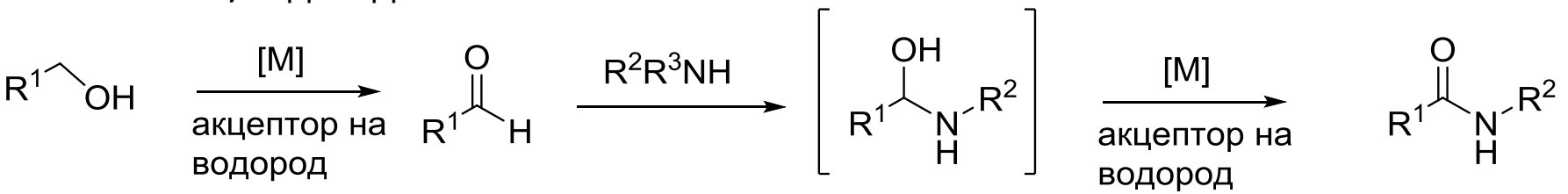
## Тиокиселини



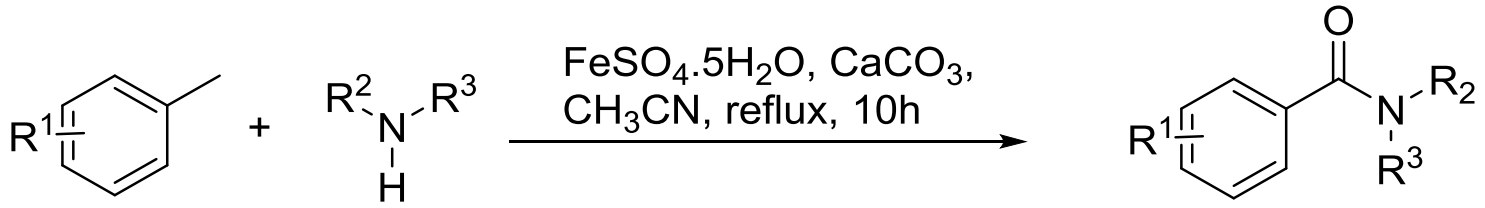



# Окислително редукционни трансформации

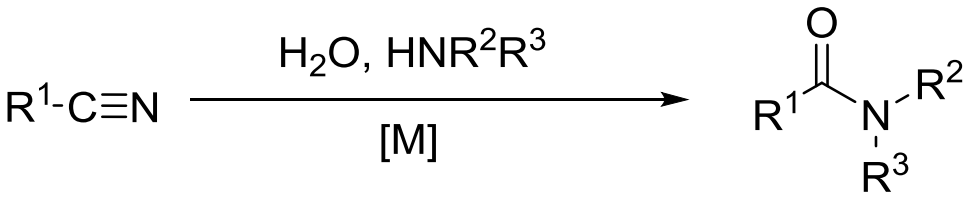
С алкохоли/алдехиди



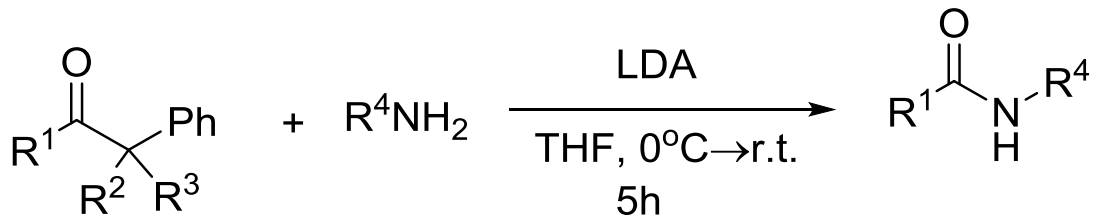

С ароматни съединения



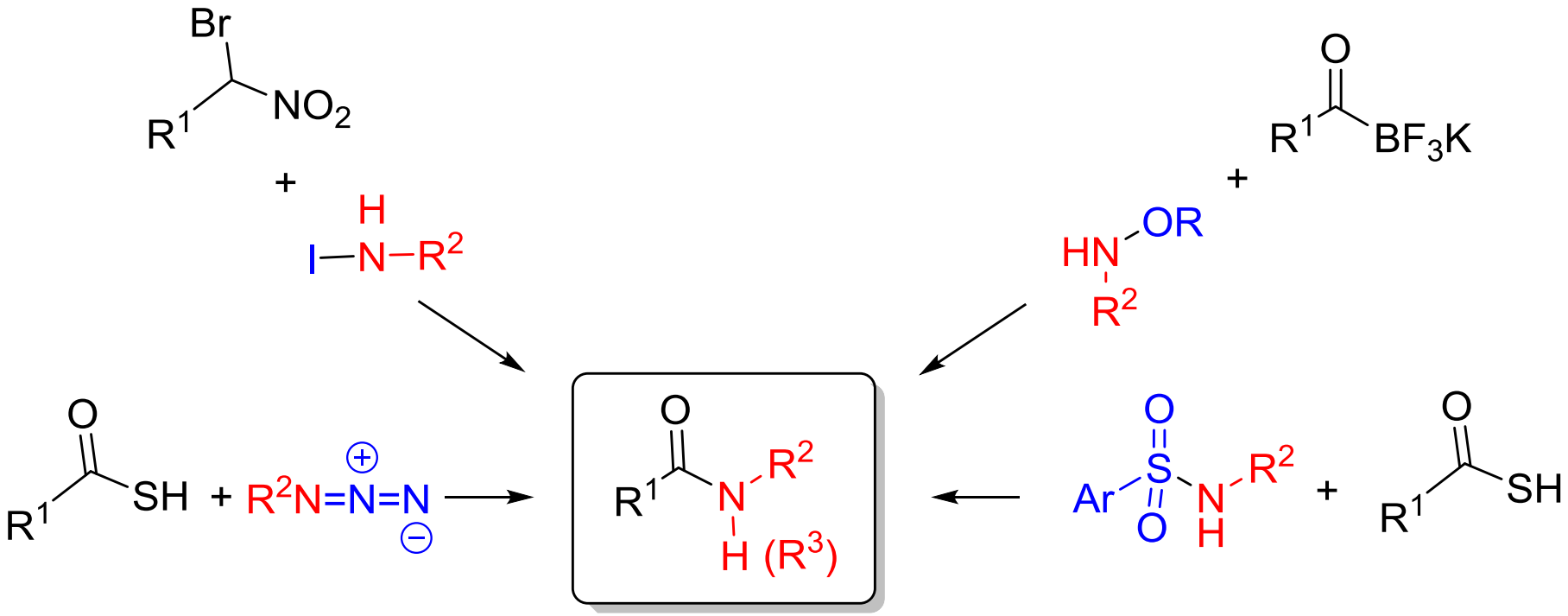

С нитрили



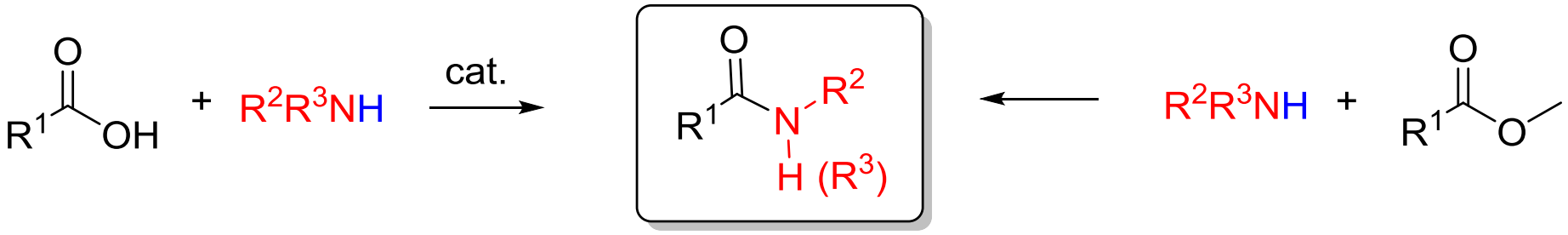

С кетони



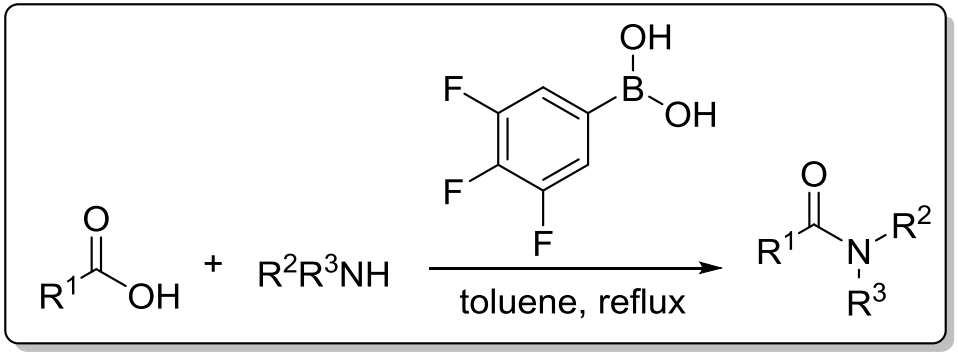
**3**

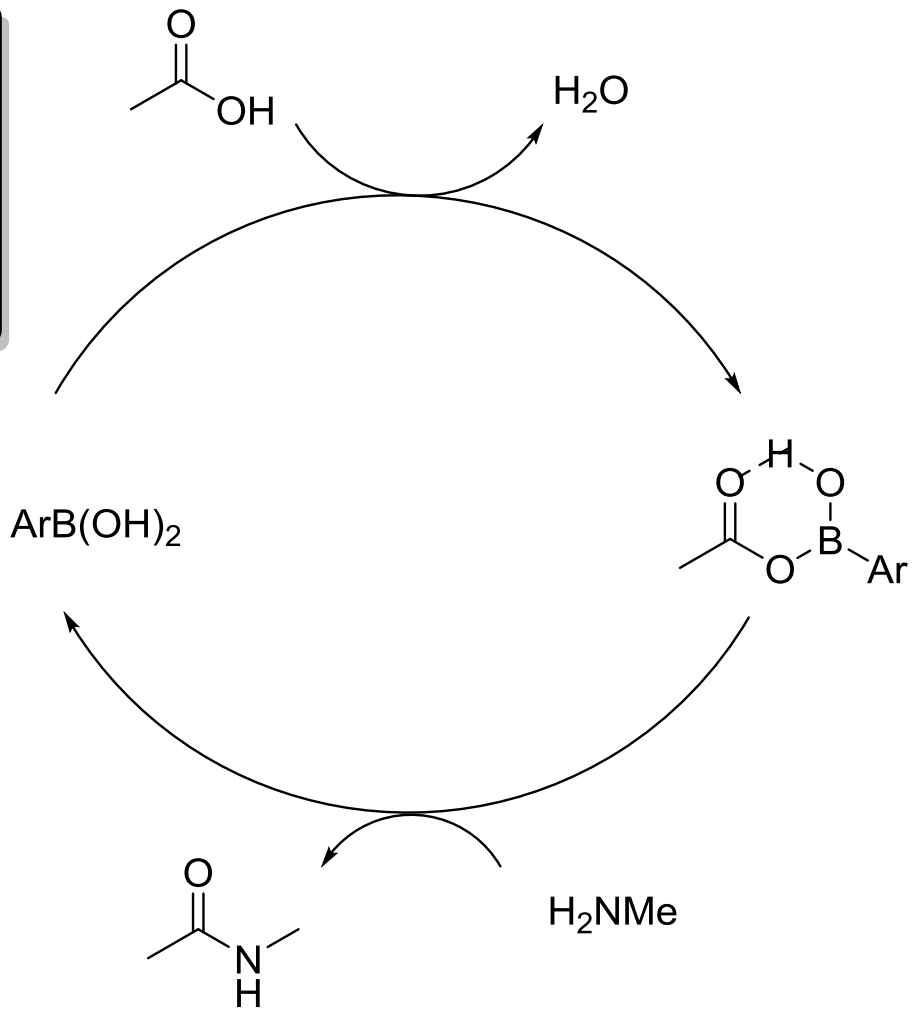

Br
R1
NO2
+
H
I—N—R2
O
R1
BF3K
+
HN
OR
R2
O
R1
SH
+ R2N=N=N
O
R1
N
R2
H (R3)
O
Ar
S
O
N
H
R2
+
O
R1
SH

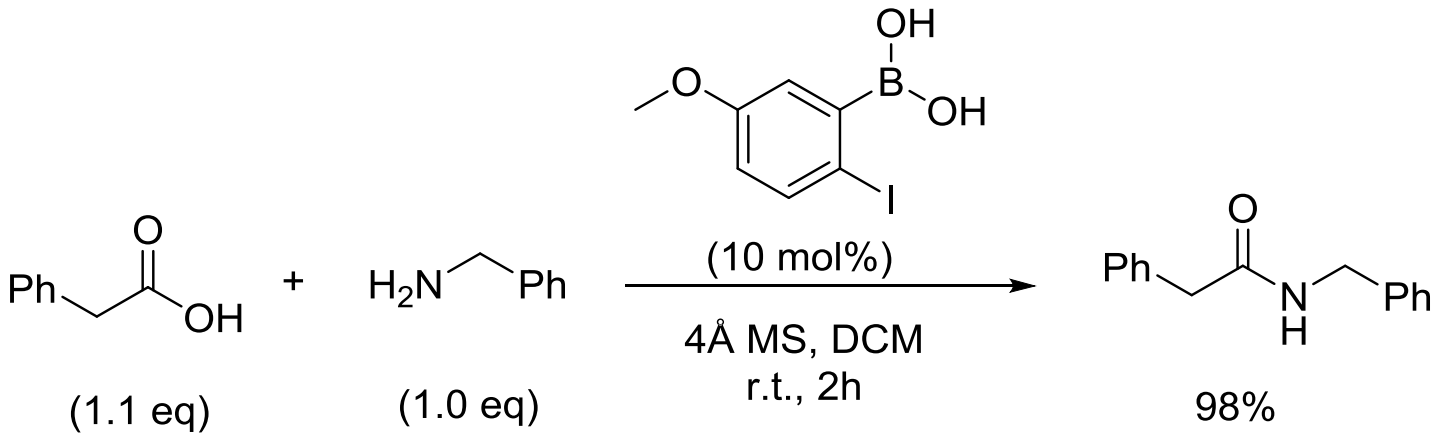
**4**



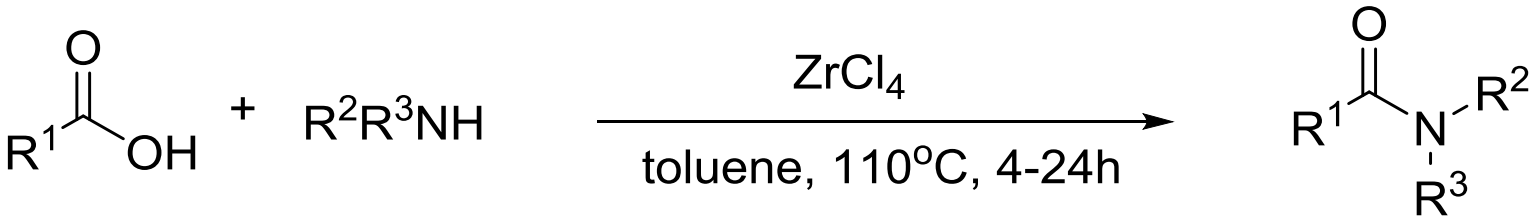
# Карбоксилни киселини с органоборни катализатори



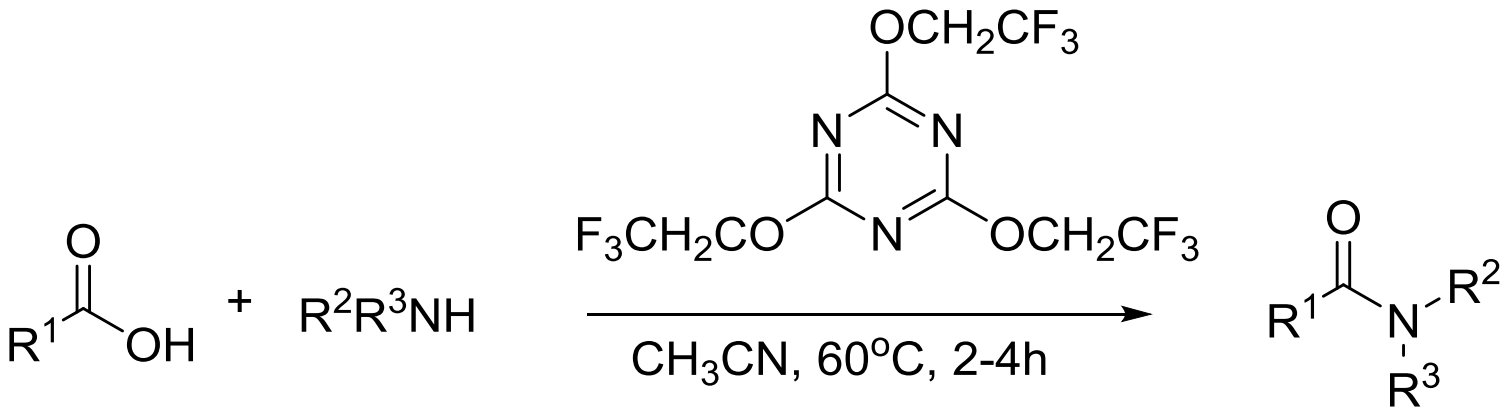





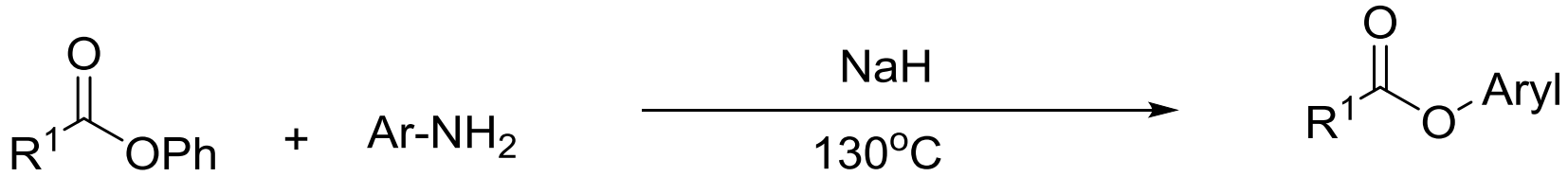

**Метал-катализирано амидиране на карбоксилни киселини**



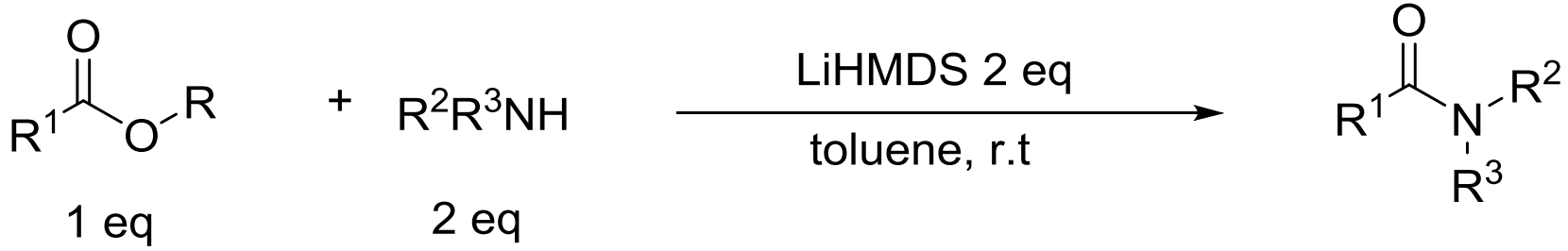
## Създаване на амидна връзка чрез органокатализ



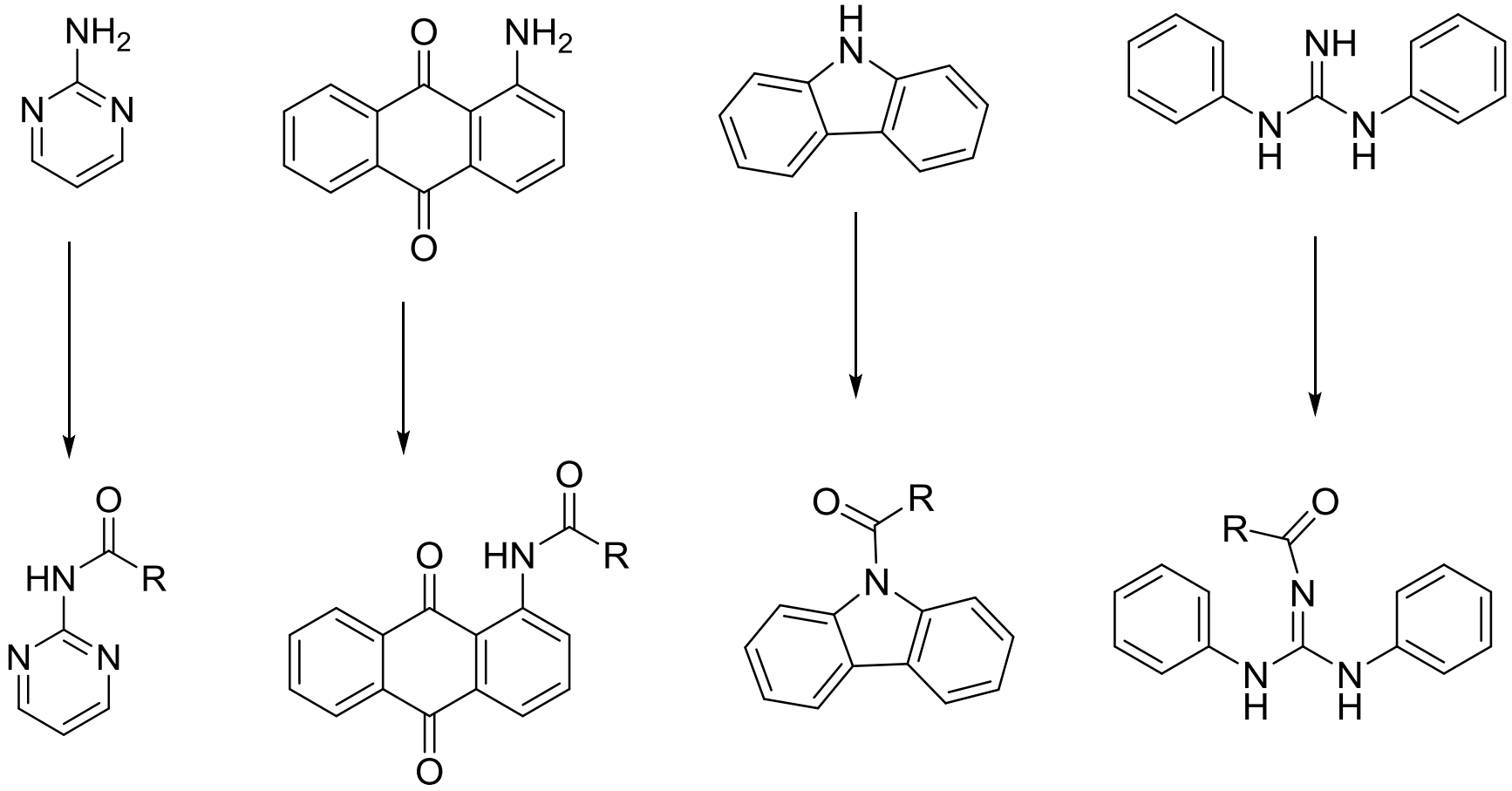

## Амидиране на естери без наличие на катализатор




*RSC Adv., **2019**, 9, 1536–1540*




*J. Am. Chem. Soc. **2019**, 141, 11161−11172*


NH2
N
N
O
HN
R
O
NH2
O
O
O
HN
R
O
H
N
O
R
N
NH
N
H
N
H
R
O
N
N
H
N
H

**Благодаря**
за вниманието