# Literature Report 9

# Ugi Multicomponent Polymerization

**Reporter： Xiao-Yong Zhai**

**Checker： Zi-Biao Zhao**

**Date： 2019-05-20**

Wang, X. *et al. ACS Macro Lett.* **2016**, *5*, 1049.
Debuigne, A. *et al. ACS Macro Lett.* **2019**, *8*, 427.

# Contents

# CV of Antoine Debuigne

Antoine Debuigne

## Education:

- **1995–1999** B.S., University of Namur
- **1999–2004** Ph.D., University of Liege (Prof. R. Jérôme)
- **2004–2006** Postdoc., University of Toronto (Prof. M.K. Georges)
- **2006–2010** Postdoc., University of Liege (Prof. R. Jérôme)
- **2010–Present** Research Associate, University of Liege

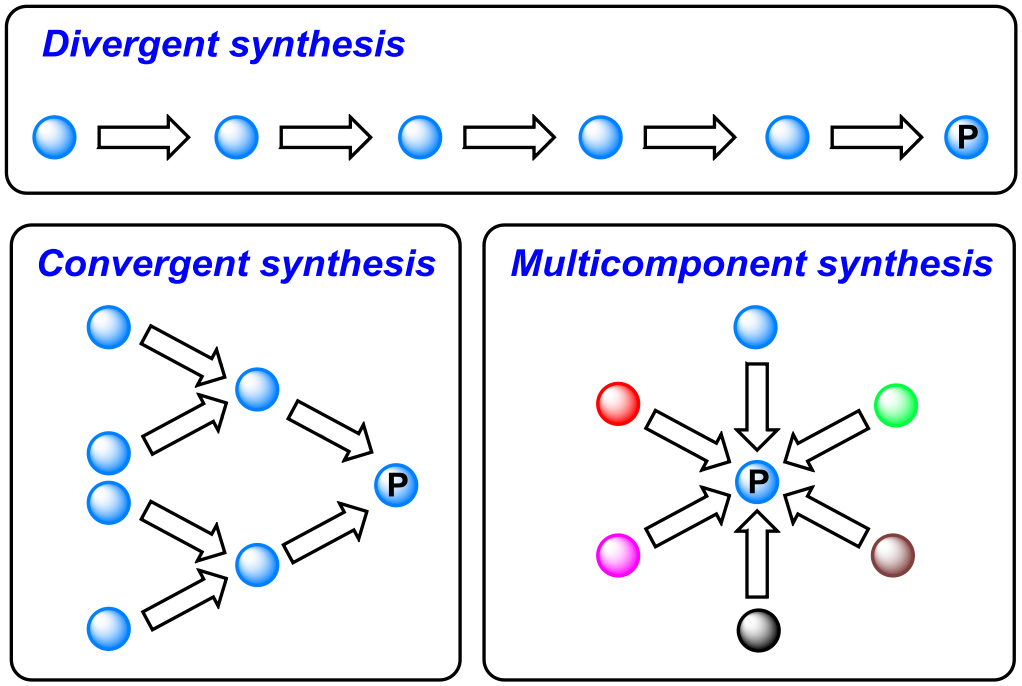
## Research:

★ Controlled radical polymerisation;

★ Emulsion polymerisation.

# Multicomponent Reactions

***Multicomponent reactions (MCRs) are one-pot reactions employing more than two starting materials.***



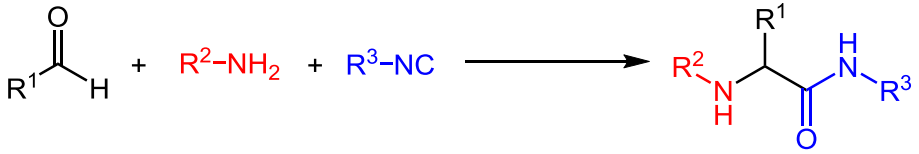

- Atom economic, Efficient, Convergent , High bond-forming-index
- Ugi, Passerini, van Leusen, Strecker, Hantzsch, Biginelli, *etc*.

Wang, K. *et al. Chem. Rev.* **2012**, *112*, 3083.

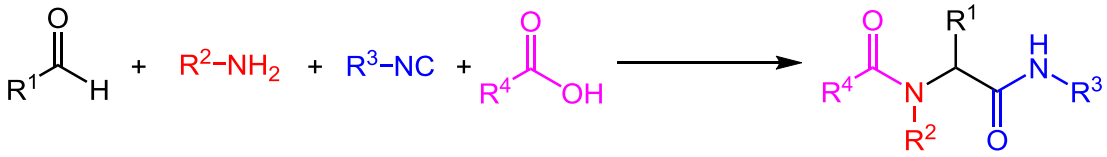
# Ugi Reaction

The Ugi four-component condensation between an aldehyde, an amine, a carboxylic acid and an isocyanide allows the rapid preparation of α-aminoacyl amide derivatives.

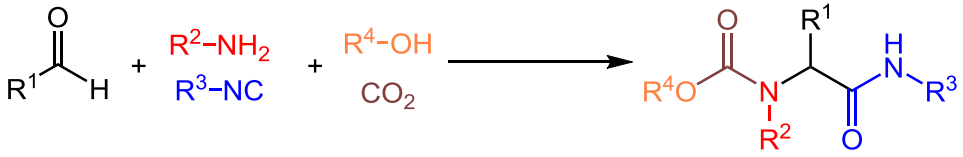
***Ugi three-component reaction (Ugi-3CR)***




***Ugi four-component reaction (Ugi-4CR)***



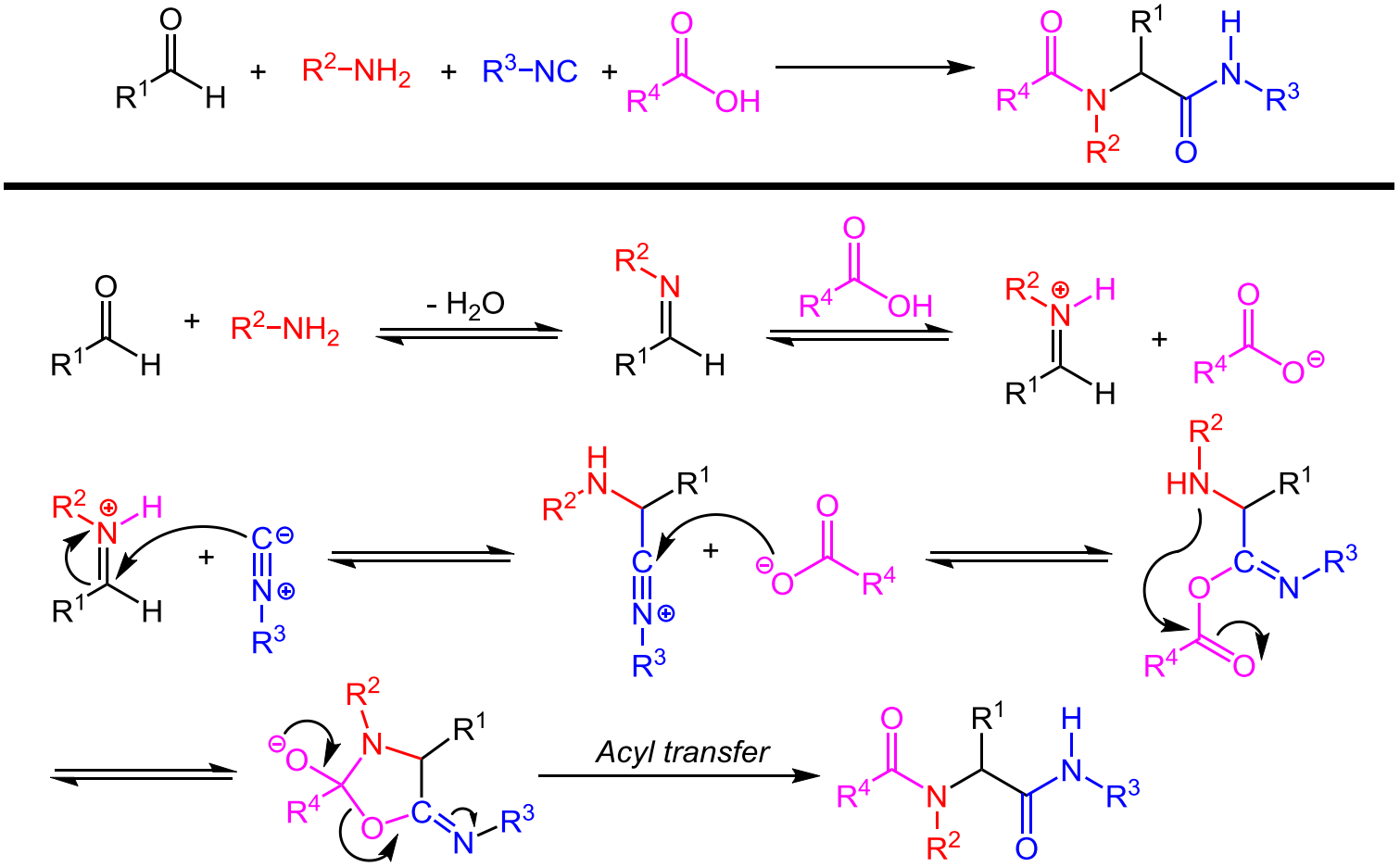

***Ugi five-component reaction (Ugi-5CR)***





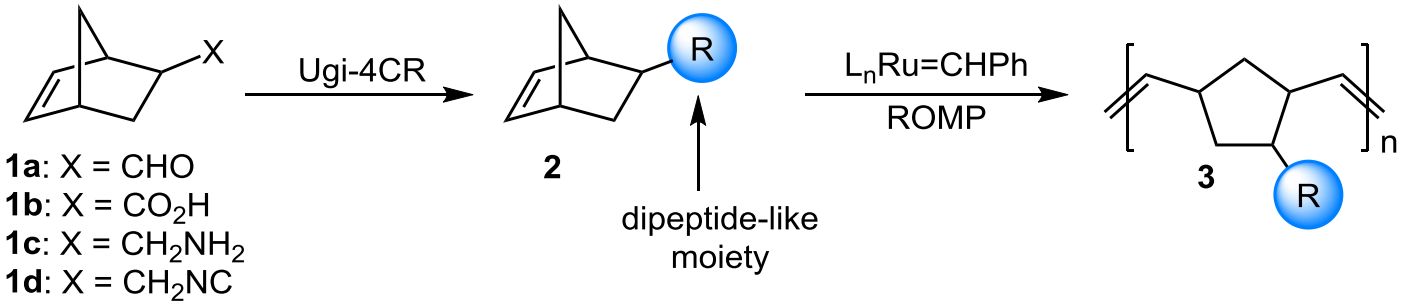
Ugi, I. *et al. Angew. Chem.* **1959**, *71*, 386.
Armstrong, R. W. *et al. J. Org. Chem.* **1998,** *63,* 867.
Wulff, W. D. *et al. Angew. Chem. Int. Ed.* **2014**, *53*, 3436.

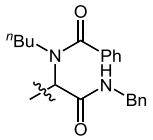
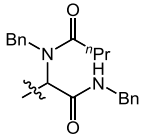
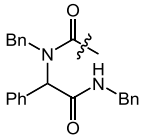
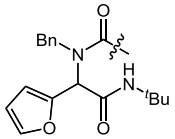
# Mechanism of Ugi 4-CR



# Introduction

## *Ugi-4CR*

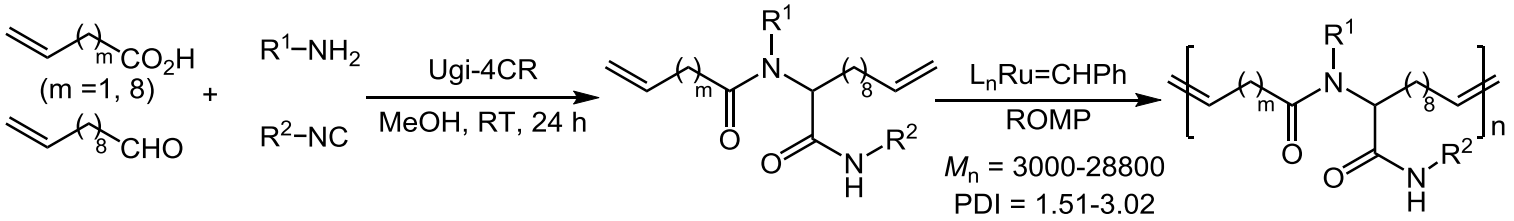



| Entry | R | $M_w$ | PDI | yield (%) | $T_g$ (°C) |
|---|---|---|---|---|---|
| 1 |  | 47600 | 2.03 | 84 | 137 |
| 2 |  | 49400 | 1.29 | 64 | 143 |
| 3 |  | 36400 | 1.41 | 85 | 169 |
| 4 |  | 22300 | 1.37 | 72 | Decomp. |

Wright, D. L. *et al. Mol. Diversity.* **2003**, *6*, 237.

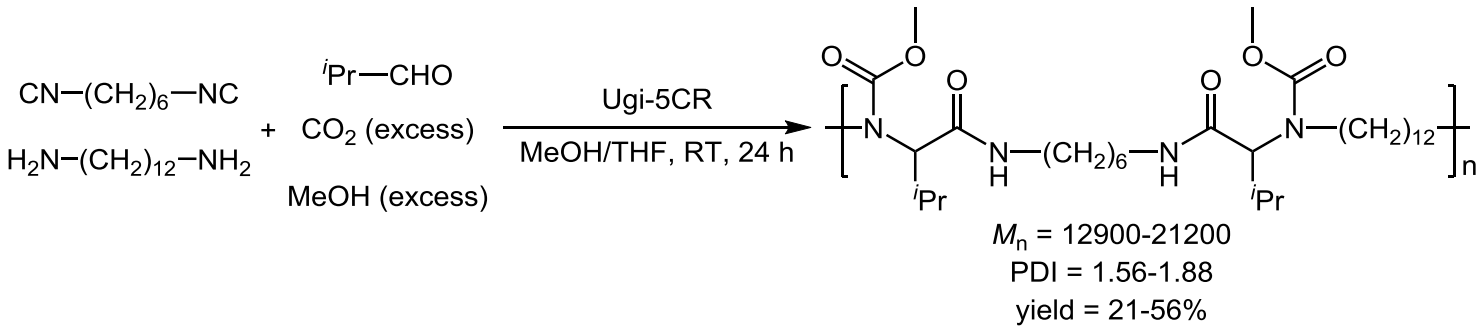
# Introduction

## *Ugi-4CR*




Meier, M. A. R. *et al. Chem. Eur. J.* **2012**, *18*, 5767.

## *Ugi-5CR*

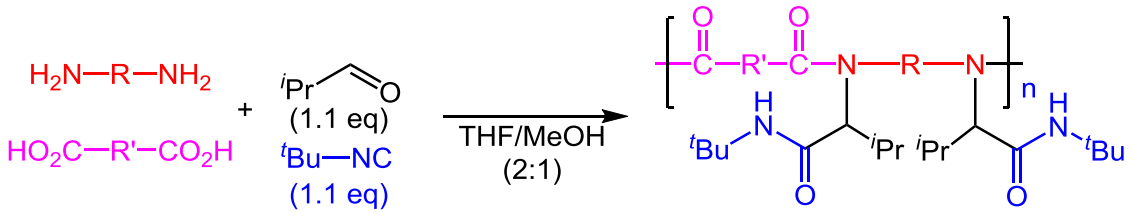



Meier, M. A. R. *et al. Macromol. Rapid Commun.* **2014**, *35,* 1866.

# Introduction

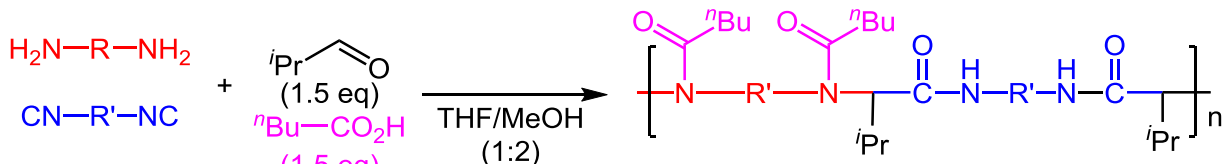
## *Ugi-4CR*

### *Type 1: Combination of Diamine and Dicarboxylic Acid*



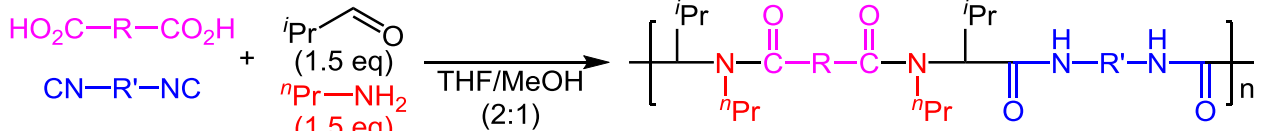

$M_n$ = 8500, PDI = 2.8

### *Type 2: Combination of Diamine and Diisocyanide*




$M_n$ = 12500-17800, PDI = 2.23-2.55

### *Type 3: Combination of Diisocyanide and Dicarboxylic Acid*

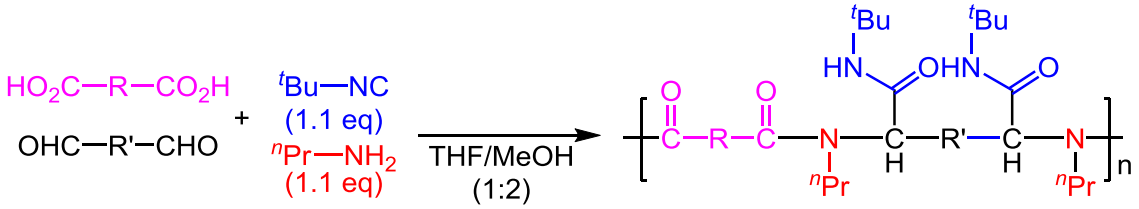



$M_n$ = 7200-7700, PDI = 2.24-2.38

Meier, M. A. R. *et al. Macromolecules* **2014**, *47*, 2774.

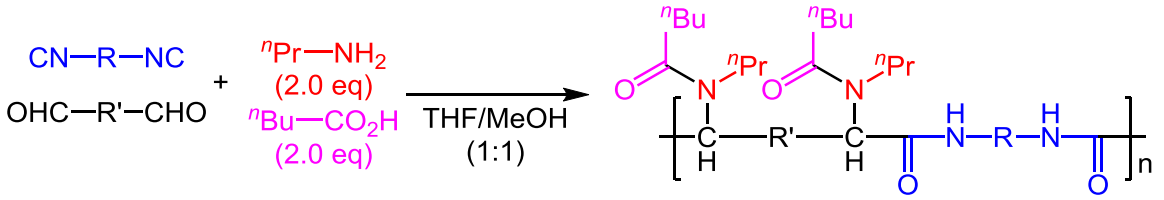
# Introduction

### *Type 4: Combination of Dialdehyde and Dicarboxylic Acid*



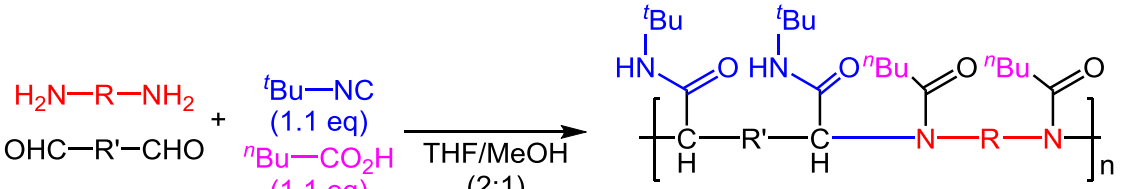

$M_n$ = 11800-14400, PDI = 1.93-1.95

### *Type 5: Combination of Diisocyanide and Dialdehyde*




$M_n$ = 10000-10800, PDI = 2.27-2.30

### *Type 6: Combination of Dialdehyde and Diamine*

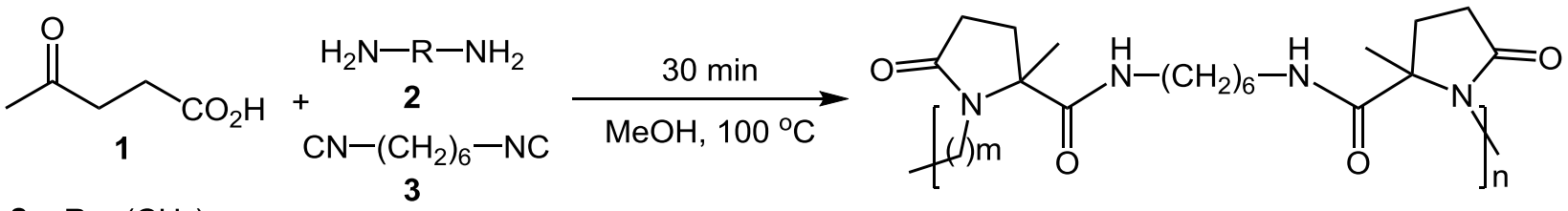



$M_n$ = 10700-12800, PDI = 2.08-2.22

Meier, M. A. R. *et al. Macromolecules* **2014**, *47*, 2774.

# Introduction

## *Ugi-4CR (AB-type monomer)*



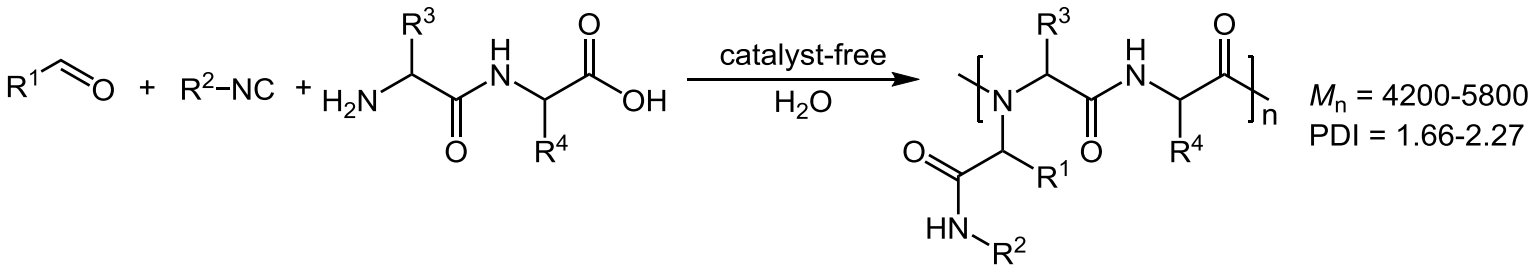

**2a**: R = $(CH_2)_2$
**2b**: R = $(CH_2)_6$
**2c**: R = $(CH_2)_{12}$
**2d**: R = $(CH_2)_2NH(CH_2)_6NH(CH_2)_2$

| Entry | **2** | $M_n$ | PDI | yield (%) | $T_g$ (°C) | $T_{d,\,max}$ (°C) |
|---|---|---|---|---|---|---|
| 1 | **2a** | 7530 | 1.42 | >99 | 120 | 449 |
| 2 | **2b** | 12320 | 2.66 | 93 | 86 | 462 |
| 3 | **2c** | 11760 | 1.63 | 95 | 63 | 462 |
| 4 | **2d** | 5230 | 1.36 | 96 | 52 | 377 |

Becer, C. R. *et al. Green Chem.* **2016**, *18*, 3272.

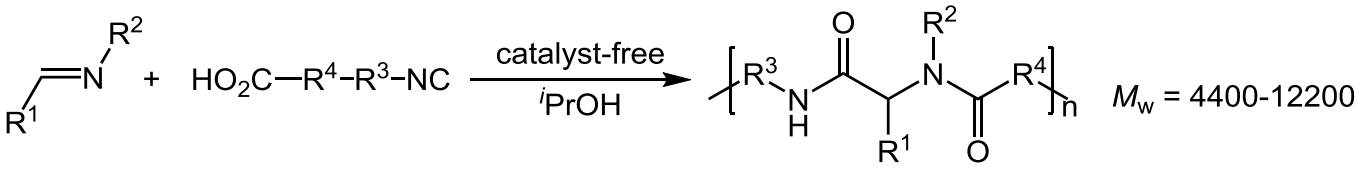
# Introduction

## *Ugi-4CR (AB-type monomer)*



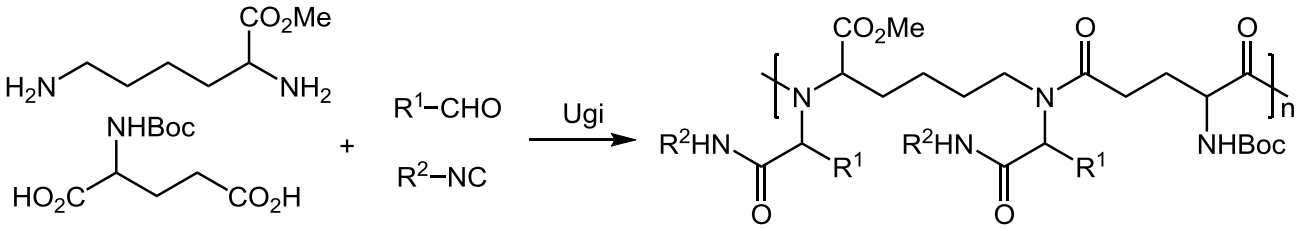

Debuigne, A. *et al. Chem. Commun.* **2017**, *53*, 12240.

## *Ugi-4CR (AB-type monomer)*



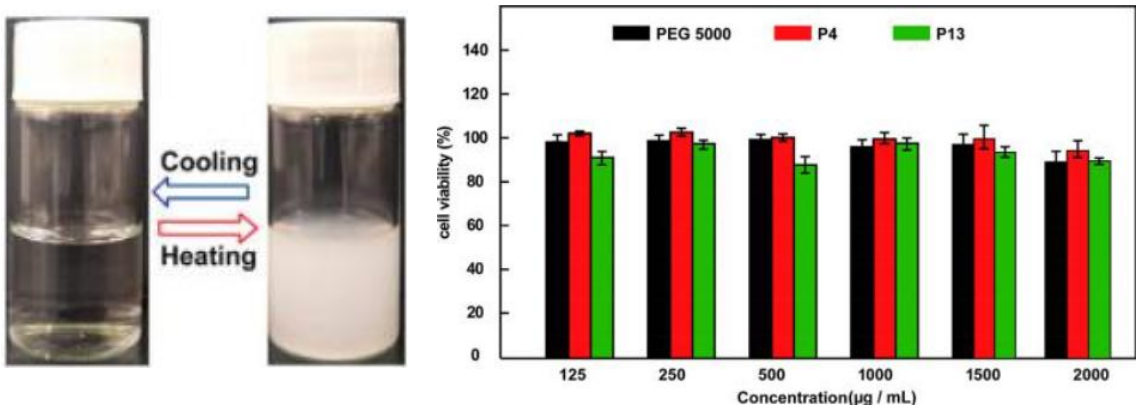

Gudeangadi, P. G. *et al. Chem. Commun.* **2017**, *53*, 3846.

# Introduction




*Natural Amino Acids* *Alternating Polypeptoids*

$M_n$ = 9000-15900, PDI = 1.7-2.4



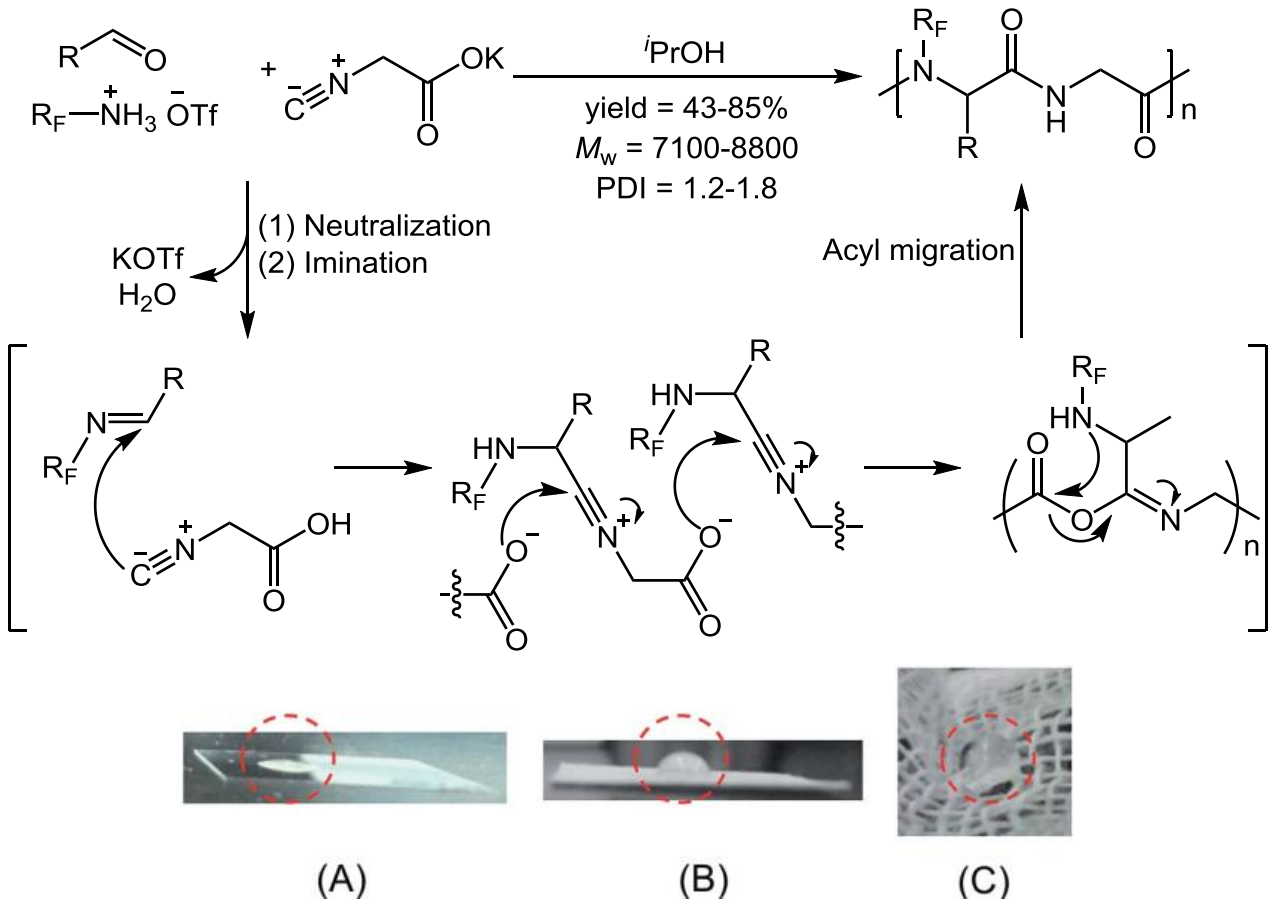

**(A)** **(B)**

(A) Visual turbidity change of P4 upon heating the aqueous solution;
(B) The cytotoxicity of P4 and P13 was assessed using HeLa cells and an MTT assay.

Tao, Y. *et al. Biomacromolecules* **2018**, *19*, 936.

# Introduction

## *Ugi-4CR (AB-type monomer)*

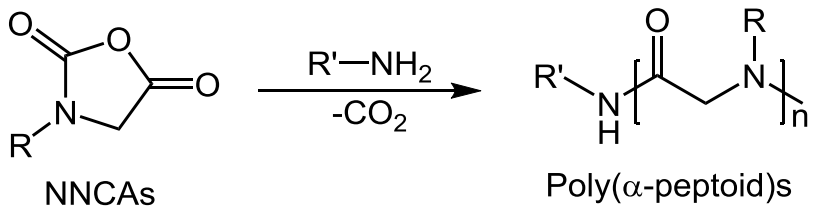



Photographs of water droplet on (A) glass plate, (B) filter paper, and (C) cotton gauze modified by P6.

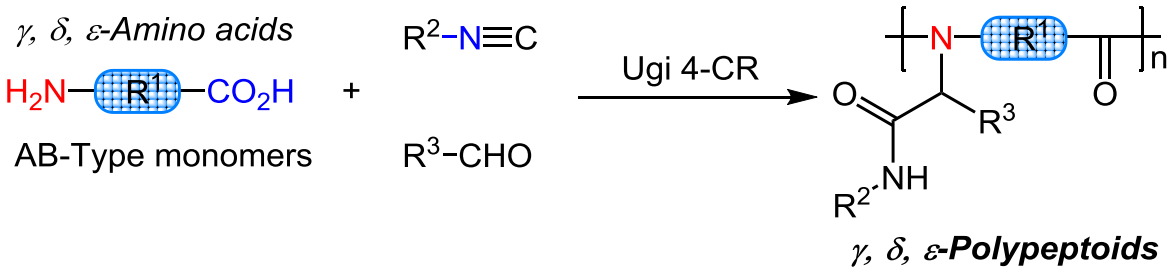
Imura, T. *et al. RSC Adv.* **2018**, *8*, 7509.

# Ugi Four-Component Polymerization

***Previous work: Ring opening polymerization of NNCAs***

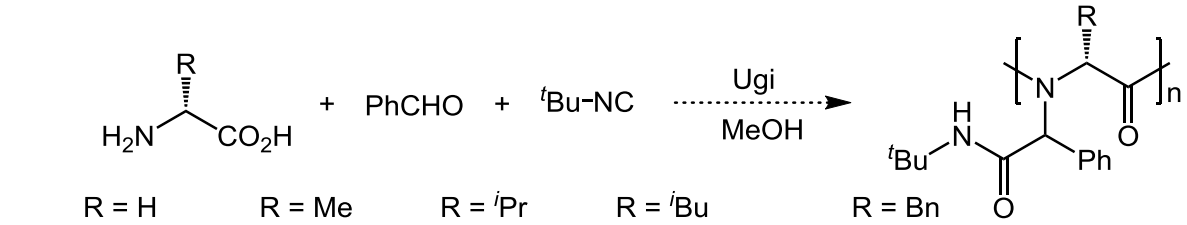



***Ugi four-component reaction***

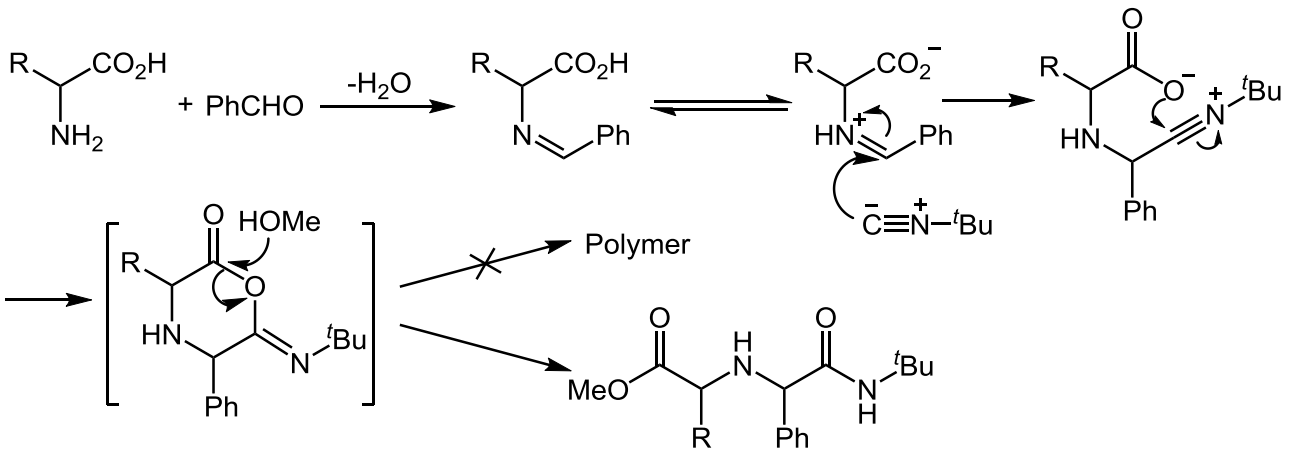



Wang, X. *et al. ACS Macro Lett.* **2016**, *5*, 1049 .

# Ugi Four-Component Polymerization



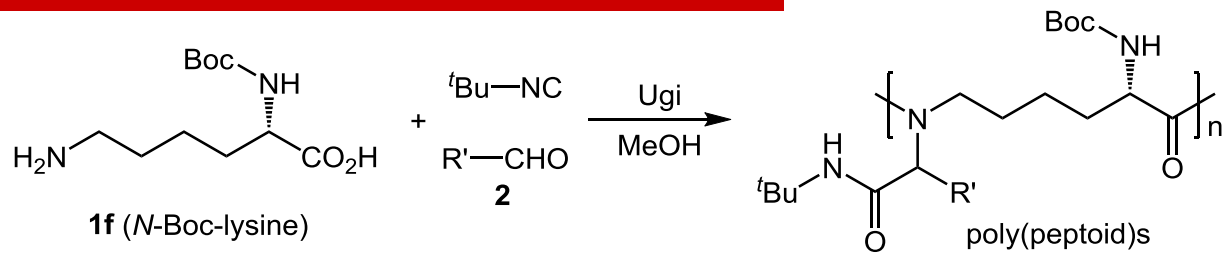

R = H **1a** (Glycine) R = Me **1b** (Alanine) R = $^{i}$Pr **1c** (Valine) R = $^{i}$Bu **1d** (Leucine) R = Bn **1e** (Phenylalanine)

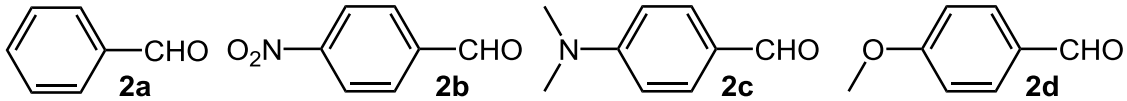


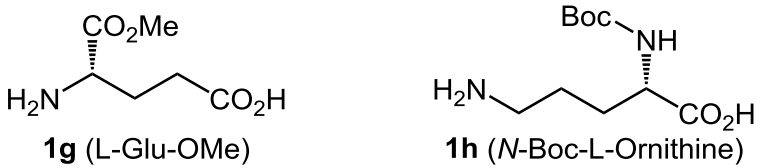

| Entry [a] | monomers | yield (%) [b] | $M_n$ [c] | PDI [c] |
|---|---|---|---|---|
| 1 | 1a+2a+3 | 46 | 3400 | 1.2 |
| 2 | 1b+2a+3 | 35 | 1600 | 1.1 |

[a] Reactions were carried out at room temperature for 96 h in MeOH. [1] = 0.5 M, [2] = 1.1 M, [3] = 1.1 M. [b] Calculated based on polymers recovered after precipitation in petroleum ether. [c] Determined by SEC in DMF.

# Ugi Four-Component Polymerization



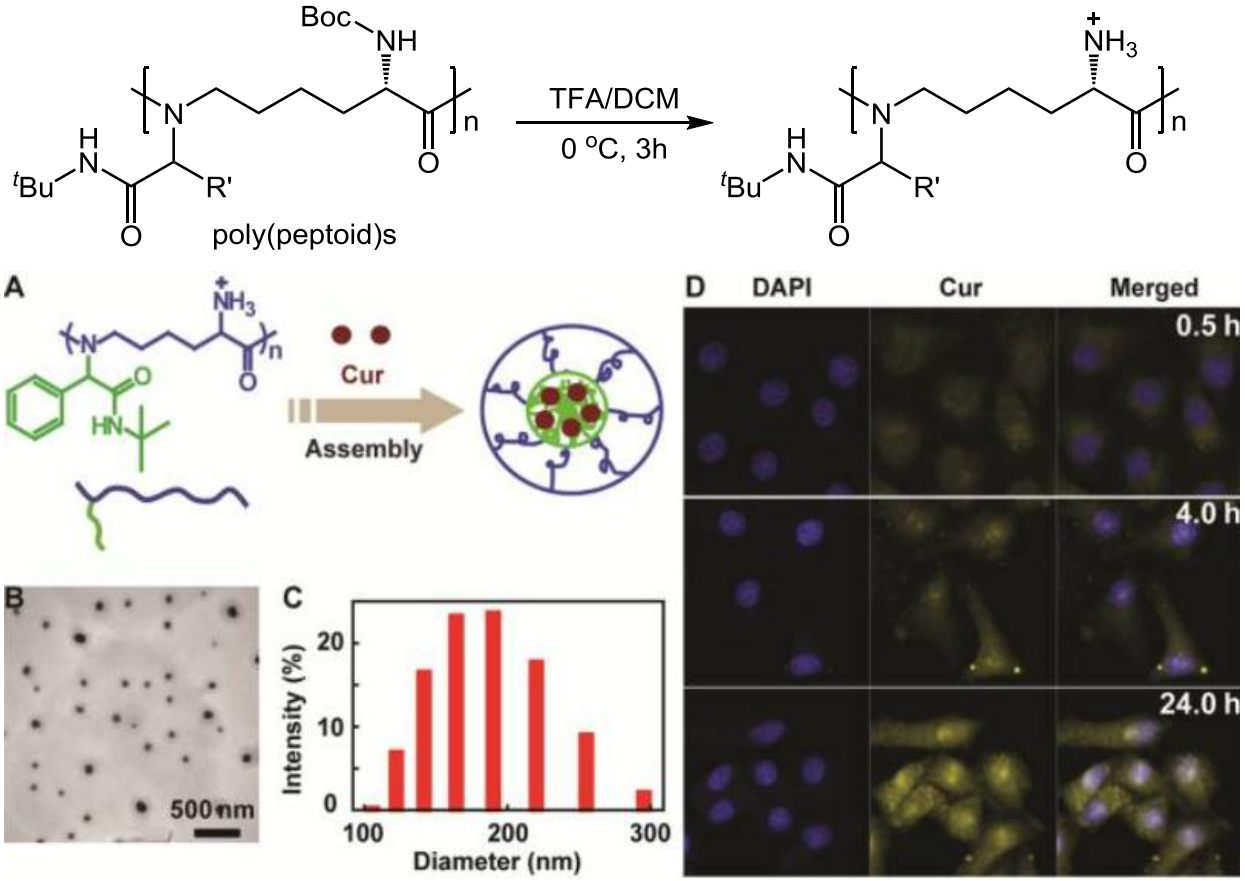




| Entry[a] | monomers | yield (%) [b] | $M_n$ [c] | PDI [c] |
|---|---|---|---|---|
| 1 | 1f+2a+3 | 81 | 11200 | 1.6 |
| 2 | 1f+2b+3 | 88 | 8000 | 1.3 |
| 3 | 1f+2c+3 | 87 | 9300 | 1.5 |
| 4 | 1f+2d+3 | 69 | 6700 | 1.8 |
| 5 | 1g+2a+3 | 74 | 4700 | 1.5 |
| 6 | 1h+2a+3 | 80 | 5100 | 1.6 |

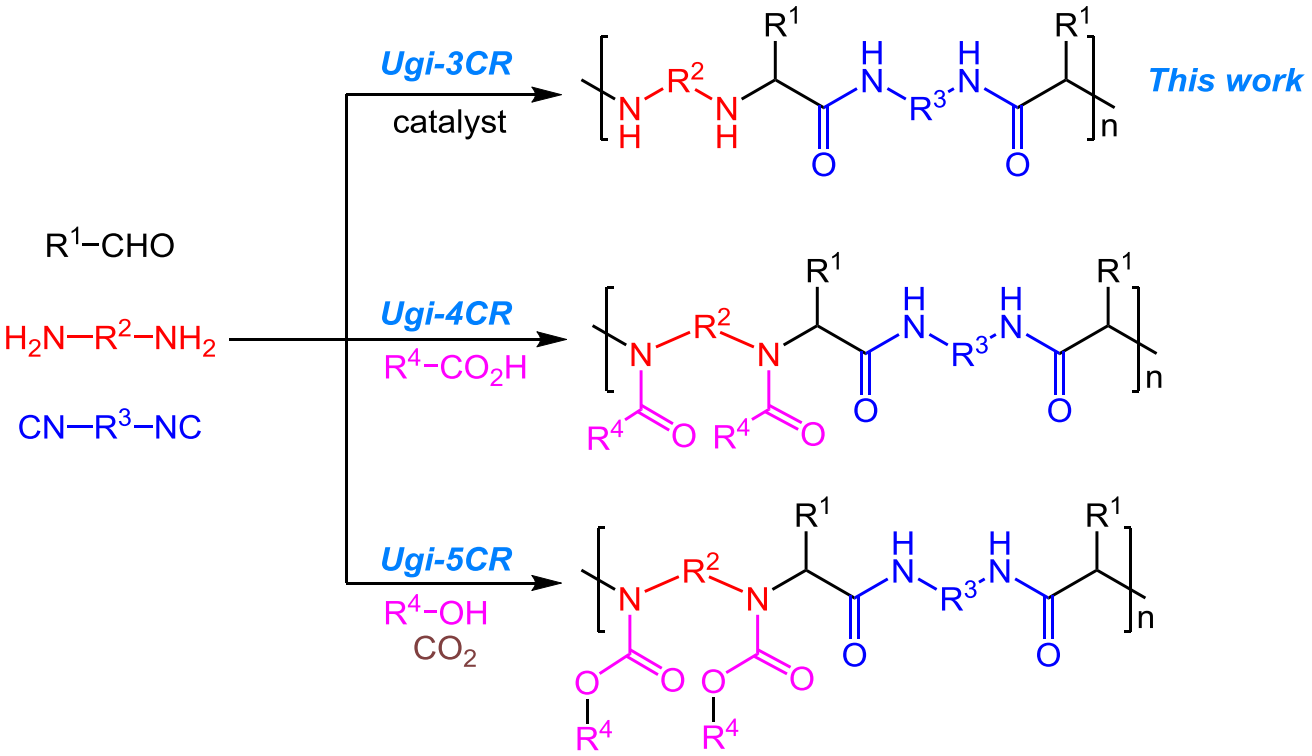
[a] Reactions were carried out at room temperature for 96 h in MeOH. [1] = 0.5 M, [2] = 1.1 M, [3] = 1.1 M. [b] Calculated based on polymers recovered after precipitation in petroleum ether. [c] Determined by SEC in DMF.

# Ugi Four-Component Polymerization



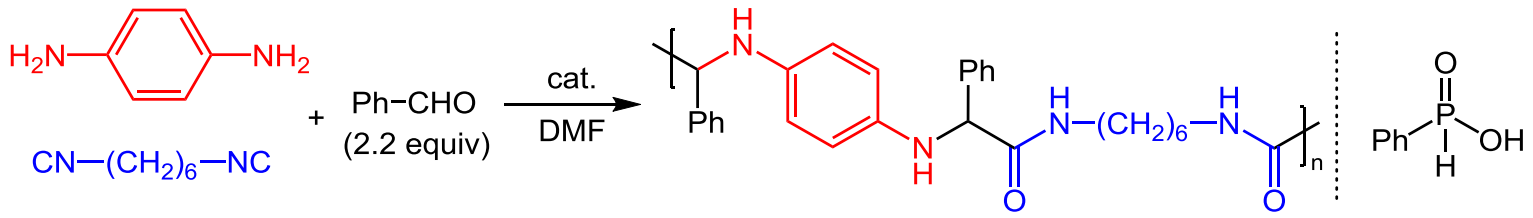

(A) Illustration on the self-assembly and preparation of Cur-loaded polypeptoid NPs.
(B) TEM image of Cur-loaded NPs.
(C) Size distribution of NPs measured by DLS.
(D) Confocal laser-scanning microscopy (CLSM) images on HeLa cells incubated with Cur-loaded polypeptoid NPs for 0.5, 4, and 24 h.

# Ugi Three-Component Polymerization




Debuigne, A. *et al. ACS Macro Lett.* **2019**, *8*, 427.

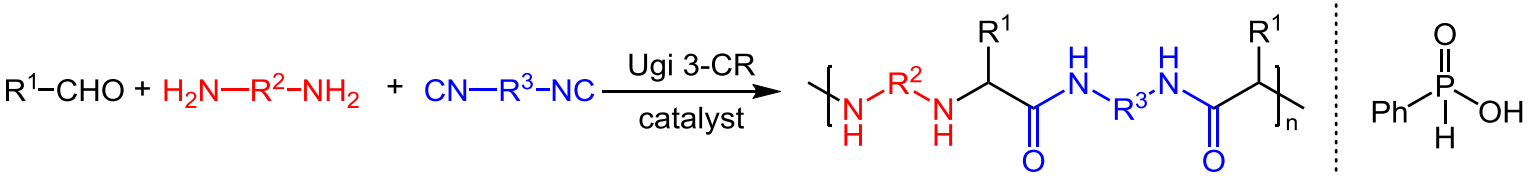
# Ugi Three-Component Polymerization

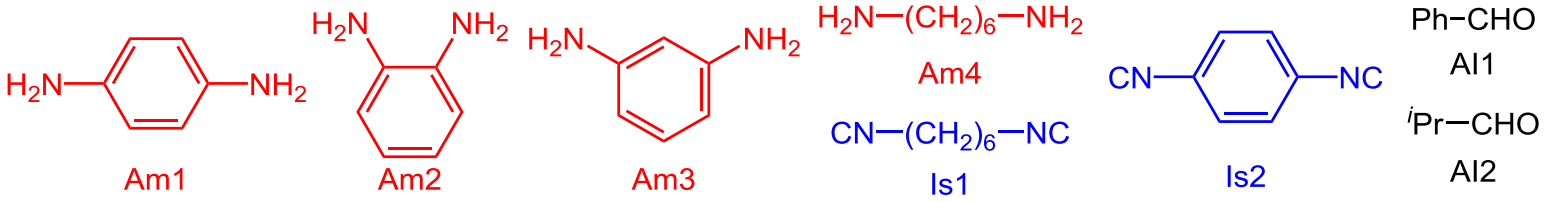



| Entry[a] | T (°C) | Cat. (mol%) | t (days) | DMF (mL) | $M_n$[b] | PDI[b] |
|---|---|---|---|---|---|---|
| 1 | 80 | 10 | 3 | 3 | 1400 | 1.6 |
| 2 | 50 | 10 | 3 | 3 | 5900 | 1.7 |
| 3 | 25 | 10 | 3 | 3 | 6300 | 2.4 |
| 4 | 6 | 10 | 3 | 3 | 1700 | 1.2 |
| 5 | 6 | 10 | 8 | 3 | 3100 | 1.7 |
| 6 | 50 | 10 | 1 | 3 | 4300 | 1.6 |
| 7 | 50 | 10 | 1 | 1.5 | 350 | 1.1 |
| 8 | 50 | 20 | 1 | 3 | 4300 | 1.9 |
| 9 | 50 | 50 | 1 | 3 | 3900 | 1.9 |

[a] Reaction conditions: PPA, p-phenylenediamine (1.5 mmol), benzaldehyde (3.3 mmol), and 1,6 diisocyanohexane (1.5 mmol) in DMF. [b] Determined by SEC in DMF.

# Ugi Three-Component Polymerization

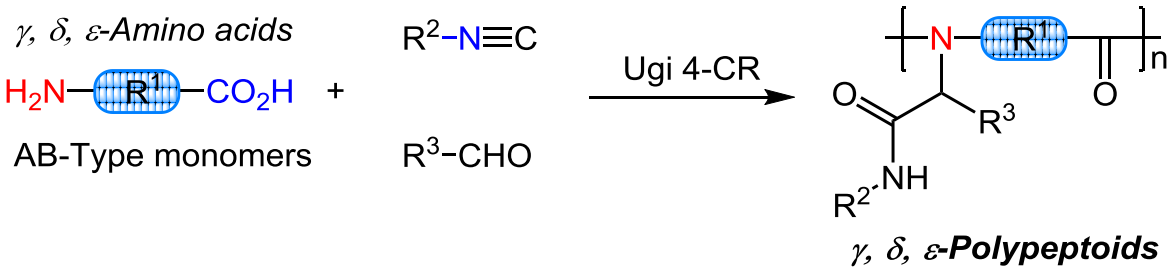



| Entry[a] | monomers | Cat. (mol%) | t (days) | $M_n$ | PDI |
|---|---|---|---|---|---|
| 1 | Am1+Is1+AI1 | 10 | 1 | 4300 | 1.6 |
| 2 | Am1+Is1+AI1 | 20 | 1 | 4300 | 1.9 |
| 3 | Am2+Is1+AI1 | 10 | 1 | 900 | 1.2 |
| 4 | Am3+Is1+AI1 | 10 | 1 | 7100 | 1.7 |
| 5 | Am3+Is1+AI2 | 10 | 1 | 1200 | 2.0 |
| 6 | Am3+Is2+AI1 | 10 | 3 | 7300 | 1.7 |
| 7 | Am3+Is2+AI2 | 10 | 1 | 3000 | 2.3 |
| 8 | Am3+Is2+AI2 | 20 | 1 | 12600 | 3.2 |
| 9 | Am4+Is2+AI2 | 10 | 1 | 1700 | 1.9 |
| 10 | Am4+Is2+AI2 | 20 | 1 | 2900 | 2.2 |

# Summary

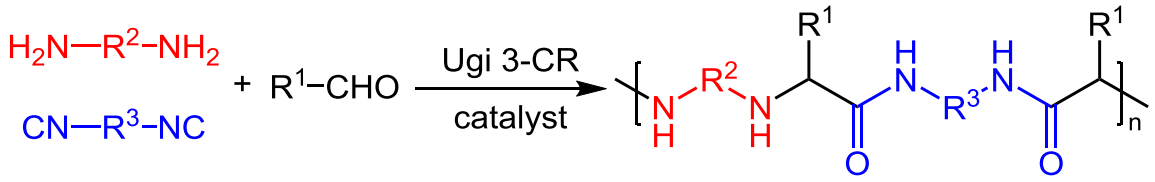
## *Ugi four-component reaction*




- ***Renewable sources***
- ***Atom-economy***
- ***Catalyst-free***
- ***Moderate condition***
- ***Functional diversity***
- ***Large scale***

Wang, X. *et al. ACS Macro Lett.* **2016**, *5*, 1049.

## *Ugi Three-component reaction*




- ***Straightforward method***
- ***High atom economy***
- ***$M_n$ = 3000-12000***

Debuigne, A. *et al. ACS Macro Lett.* **2019**, *8*, 427.

# The First Paragraph

The demand for diversely substituted multifunctional polymers able to sustain cutting-edge applications is steadily increasing these days. In this context, the development of simple and efficient macromolecular engineering tools becomes essential, and the emergence of multicomponent reactions (MCR) in polymer science takes on its full meaning. By definition, MCRs are highly efficient reactions involving more than two compounds that react and form one molecule containing essentially all atoms of the starting reagents. Such a straightforward and atom economic approach is highly valuable when considering the design of structurally complex macromolecules.

# The First Paragraph

MCRs have notably been used for monomer synthesis and polymer postmodification, in one-pot processes combining MCRs and radical polymerization, in strategies combining MCRs with click chemistry for the production of complex and functional macromolecular structures, but also as polymerization tools in step-growth processes. Only a few MCRs have been used in step-growth polymerization, which requires very high efficiency, including Biginelli, Hantzsch, Kabachnick-fields, Radziszewski, and the transition metal-catalyzed MCR, but the most popular ones consist in isocyanide-based MCRs, namely, the Passerini and the Ugi four-component (Ugi-4CR) reactions.

# The Last Paragraph

In conclusion, we investigated for the very first time the Ugi three component reaction in polymer synthesis. This straightforward and highly atom economic strategy paved the way to unprecedented poly(α-amino amide)s. In this work, diamines, diisocyanides, and aldehydes were combined in order to incorporate the amino and amido groups within the polymer backbone. Nevertheless, dialdehydes could also be associated with diamines or diisocyanides in the presence of the third monofunctional component giving access to macromolecules with lateral amino and amido groups. While further investigation is necessary to establish their full potential, we carried out preliminary studies of the thermal and solution properties of these poly(α-amino amide)s.

# The Last Paragraph

The aliphatic-rich derivative notably showed some pH-responsiveness in water via protonation-deprotonation of its amine functions. Overall, the present study represents a significant step forward in the design of poly(α-amino amide)s and adds a new string to the bow of the increasingly popular macromolecular engineering based on multicomponent reactions.

## Acknowledgement

***Thanks***

**for your attention**