



Raising the Diversity of Ugi Reactions Through Selective Alkylations and Allylations of Ugi Adducts

Alaa Zidan, Abeer El-Naggar, Nour Abd El-Sattar, Ali Khalil Ali, Laurent El Kaim

► To cite this version:

Alaa Zidan, Abeer El-Naggar, Nour Abd El-Sattar, Ali Khalil Ali, Laurent El Kaim. Raising the Diversity of Ugi Reactions Through Selective Alkylations and Allylations of Ugi Adducts. *Frontiers in Chemistry*, 2019, 7 (20), 10.3389/fchem.2019.00020 . hal-02096847

HAL Id: hal-02096847

<https://polytechnique.hal.science/hal-02096847>

Submitted on 13 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Raising the diversity of Ugi reactions through selective alkylations and allylations of Ugi adducts

Alaa Zidan^{1,2}, Abeer M. El-Naggar², Nour E. A. Abd El-Sattar², Ali Khalil Ali^{2*}, Laurent El Kaïm^{1*}

¹Laboratoire de Synthèse Organique, CNRS, Ecole Polytechnique, ENSTA ParisTech, UMR 7652, Université Paris-Saclay, 828 Bd des Maréchaux, 91128 Palaiseau, France

² Chemistry Department, Faculty of Science, Ain Shams University, Abbasia, Cairo 11566, Egypt

* Correspondence:

Corresponding Authors

laurent.elkaim@ensta-paristech.fr; alikhilal@sci.asu.edu.eg

Keywords: Ugi reaction; allylation; palladium; Tsuji-Trost reaction; metathesis; piperidines.

Abstract: We report here selective Tsuji-Trost type allylation of Ugi adducts using a strategy based on the enhanced nucleophilicity of amide dianions. Ugi adducts derived from aromatic aldehydes were easily allylated at their peptidyl position with allyl acetate in the presence of palladium catalysts. These substitutions were compared to more classical transition metal free allylations using allyl bromides.

1 Introduction

Since its discovery and even more after the 1980's, the Ugi reaction has fascinated chemists with the high diversity brought by its four components nature together with its impressive functional tolerance (Dömling and Ugi, 2000; Hulme and Gore, 2003; Orru and de Greef, 2003; Zhu and Bienaymé, 2005; Dömling, 2006; Dömling et al., 2012; Zhu et al., 2014; Boyarskiy et al., 2015; Váradí et al., 2016; Lei et al., 2018). Besides important efforts devoted to the preparation of libraries of heterocycles through cyclization of properly functionalized Ugi adducts (Tempest, 2005; Sunderhaus and Martin, 2009; Ivachtchenko et al., 2010; Orru and Ruijter, 2010; 2010; Sadjadi and Heravi, 2011; Eckert, 2012; Sharma et al., 2015), a number of studies have focused on raising the diversity by letting Ugi adducts react in further intermolecular couplings (Elders et al., 2009; Brauch et al., 2010; Zarganes-Tzitzikas et al., 2015; Zarganes-Tzitzikas et al., 2015; Kaur et al., 2016). In contrast with the previous intramolecular couplings, these strategies (such as the combination of MCRs) are much more sensitive to steric hindrance and require more attention in selecting the functionalities required for further couplings. For this reason, most transformations involving the peptidyl position of Ugi adducts are limited to intramolecular reactions (Bossio et al., 1997; Trifilenkov et al., 2007; Salcedo et al., 2008; El Kaïm et al., 2011; Tyagi et al., 2013; Zhang et al., 2013; Ben Abdesslem et al., 2015; Ghandi et al., 2015; Vachhani et al., 2015; Li et al., 2016). We recently proposed a dianionic amide strategy to raise the nucleophilic behaviour of Ugi adducts derived from aromatic aldehydes and demonstrated the interest of this approach using bis-electrophilic derivatives prone to trap the

dianions and form heterocycles (scheme 1) (Zidan et al., 2017; Zidan et al., 2018). Following the high yielding cyclizations observed in these studies, we decided to explore more thoroughly the synthetic potential of these dianions (Thompson, 1994; Langer and Freiberg, 2004) towards more simple electrophiles. We now wish to report further applications of this chemistry in Tsuji-Trost reactions as well as metal-free alkylations with bromide derivatives (Scheme 1).

Scheme 1

2 Results and discussion

Following our interest in Tsuji-Trost reactions involving isocyanide based MCRs (Dos Santos and El Kaïm, 2014; Cordier et al., 2015; El Mamouni et al., 2016), we decided to explore the behaviour of Ugi adducts dianions towards allyl acetate. Besides the efficiency and regioselectivity issues of the reaction of these dianions with π -allyl palladium complexes, such study might bring interesting pathways for further enantioselective approaches. For this study, Ugi adduct **1a** was selected due to its good behaviour in our previous studies with propargyl bromide and diiodomethane. It was prepared in 89% yield from 4-chloro-benzaldehyde, propylamine, acetic acid and *tert*-butylisocyanide. (Table 1). When **1a** was heated with allyl acetate in THF using 2.5 equivalents of potassium *tert*-butoxide together with a Pd(dba)₂/PPh₃ catalytical couple, we were delighted to observe a selective C-allylation of **1a** giving **3a** in 65% isolated yield after 2 hours refluxing (entry 1, Table 1).

Table 1.

Different bases in various solvents were then evaluated using the same palladium/phosphine couple. The enhanced nucleophilicity of the 1,3-amide dianion towards the π -allyl palladium cationic complex was confirmed experimentally by comparing the use of 2.5 and 1.3 equiv of KHMDS (affording respectively 93% and 37% isolated yields : entries 4 and 5, Table 1). NaH in DMSO, gave the best conditions affording to our delight a nearly quantitative yield of **3a** in only one hour at room temperature (entry 9, Table 1). Further modifications of the catalyst using more complex phosphines led to longer reaction time and lower yields (entries 10-12, Table 1), while in absence of palladium source, no product was observed (entry 13, Table 1).

A set of Ugi adducts were then prepared in methanol and submitted to these optimized allylation conditions. The results are gathered in Scheme 2. As observed in our previous studies (Zidan et al., 2017; Zidan et al., 2018), an aryl group tethering the peptidyl position is required for efficient allylation. Indeed, Ugi adduct **1j** prepared from isovaleraldehyde failed to form the expected **3j** probably due to the inability to form the dianionic intermediate with this less acidic substrate. Surprisingly, we didn't observe much correlation between yields and the electronic nature of the aldehyde as shown by the similar yields obtained with both 4-nitro or 4-methoxy substituted derivatives **3b** and **3c**. A much stronger effect of the substitution partner of the aromatic moiety was observed with 2-chloro substituted Ugi adduct **1h** which failed to give any adduct under these conditions as observed with **1j**. The same behaviour was observed for the attempted synthesis of the fluoro analogue **3i**. This lack of reactivity can probably be explained by the steric hindrance brought by substituents at the ortho position preventing to reach the planar geometry required for benzylic anion stabilization. Initial trials on enantioselective allylations were rather deceiving. When triphenylphosphine was replaced by BINAP (5mol %) for the reaction of **1a** with **2a**, **3a** could be formed rapidly in good yield (89%) but poor enantioselectivity (5%) whereas the use of Trost ligand (DACH-phenyl) failed to give any allylation reaction. A wider scope of chiral ligands as well as

alternative solvents allowing lower temperatures will have to be evaluated to reach an enantioselective version. The reaction could not be extended to more substituted allylic acetate derivatives such as cinnamyl acetate. The latter failed to react with Ugi adduct **1a** even under prolonged heating, leading only to saponification of the ester and isolation of cinnamyl alcohol.

Scheme 2.

Submitting propargylamine-derived Ugi adduct **1s** to the same reaction conditions didn't afford any allylated product but resulted in the clean formation of 2,3-dihydropyrrole **4** (Scheme 3), a reaction already reported by Miranda *et al.* in 2012 (Polindara-García and Miranda, 2012). They could isolate the same dihydropyrrole **4** in 36% yield treating **1s** with *t*-BuOK (2.5 equiv) in THF, while we could obtain 79% yield with our conditions. This selectivity was not very surprising when considering the respective intra and intermolecular properties of the two pathways. However, the ability to form enyne derivatives from Ugi adducts together with the interest of reversing a preferred selectivity were challenging enough to explore different set of conditions. Indeed, the dihydropyrrole formation probably involves a first isomerization into allene followed by further 5-endo-trig cyclization. This could leave some space for a previous intermolecular allylation if the lifetime of the dianion could be reduced by increasing the kinetic of the allylation step. Introducing the allyl acetate together with the palladium catalyst and the Ugi adduct in DMSO followed by the addition of the base resulted in a lower 54% yield of **4** together with a complex mixture of allylated products. We next explored the use of allyl bromide as a potential electrophilic species in the absence of palladium. When adding the latter to Ugi adduct **1s** followed by NaH, we were delighted to observe the expected enyne **3s** obtained in 58% isolated yield without any trace of dihydropyrrole (Scheme 3). This interesting control of the selectivity offers an attractive access to enyne derivatives for further cyclization studies.

Scheme 3.

These conditions settled with allyl bromide proved useful as well for the reaction of other alkyl bromides and iodides as shown in Scheme 4. The lowest 30% yield of **6c** obtained using 3-bromocyclohex-1-ene may be explained by the use of secondary halides together with the high steric hindrance around the peptidyl position of the Ugi adduct. In order to confirm further the importance of forming dianionic intermediates, the formation of **3a** was attempted using allyl bromide in excess (1.5 equiv) but reducing the amount of sodium hydride to 0.9 equiv. In this case, only traces of allylated compound could be identified after 2h at rt whereas the reaction was completed after the same time when using 2.5 equiv of sodium hydride. Interestingly, whereas under Tsuji-Trost type conditions we couldn't observe any allylation of both 2-chloro and 2-fluoro substituted derivatives **1h** and **1i**, the latter gave us a moderate 40% isolated yields of **3i** when using just sodium hydride with allyl bromide.

Scheme 4.

A further interest of the use of palladium free conditions may be found in the ability to carry the reaction starting directly from the four Ugi components. Indeed remaining isocyanides after the Ugi reaction are potentially inhibitor for most classical palladium catalyzed processes making thus one-pot processes difficult to achieve (El Kaim *et al.*, 2008).¹ After completion of the Ugi adduct, the

¹ However, one-pot processes may be envisioned if the remaining isocyanide is destroyed by an acidic hydrolysis prior palladium addition.

methanol was evaporated under reduced pressure. The solvent was then replaced by DMSO. Addition of sodium hydride followed by allyl bromide afforded the final allylated Ugi adducts in good overall yields (Scheme 5).

Scheme 5.

With this easy allylation of Ugi adducts in hand, we decided to take advantage of the diversity offered by the latter coupling to explore Ugi/allylation/Ring Closure Methathesis (RCM) strategies towards various nitrogen based heterocycles. The use of RCM as Ugi post-condensation has already demonstrated its power for the formation of 5, 6-membered heterocycles as well as macrocyclic derivatives (Banfi et al., 2003; Beck et al., 2003; Hebach and Kazmaier, 2003; Ribelin et al., 2007; Ku et al., 2011). However the synthetic potential of these strategies is in a way limited by the need of introducing the two allylated moieties at an early stage which reduces the diversity offered by the two-step process. The late stage allylation we propose is highly versatile allowing to settle the strategy with a single alkenyl moiety in the starting components. Thus using allyl amine, we could easily prepare a library of piperidines with five points of diversity (Scheme 6).

Scheme 6.

This access to 3,4-dehydropiperidine derivatives **7** could be further enriched by a potential isomerisation into cyclic enamines as demonstrated by the ruthenium hydride catalysed conversion of **7a** into **8** (Scheme 6). The versatility of the method can be pictured by the alternative choice of the alkenyl moiety on the acidic component such as in cinnamic acid offering now a very simple access to 3,4-dehydropiperidine-2-one **9** (Scheme 7).

Scheme 7.

3 Conclusion

In summary, we have extended the potential of the Ugi reaction using 1,3-amide dianionic species as intermediates for efficient allylations at the peptidyl moiety of Ugi adducts. The procedure raises the diversity of Ugi adducts and offers unique opportunities for the preparation of nitrogen based heterocycles through association with ring closure metathesis. The power of the latter strategy has been demonstrated by the preparation of various piperidines which are important scaffolds for medicinal applications.

Scheme 1. Reaction of Ugi amide dianion with mono and biselectrophiles.

Scheme 2. Scope of the Ugi/Tsuji-Trost cascade

Scheme 3. Allylation of Ugi propargyl adduct.

Scheme 4. Scope of alkylating agents

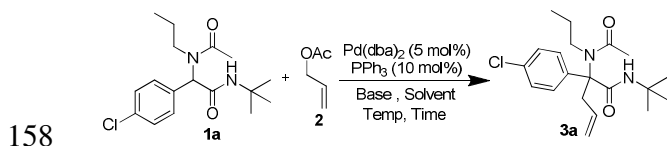
Scheme 5. Cascade one pot reaction

Scheme 6. Ugi/allylation/RCM strategy

Scheme 7. Ugi/allylation/MCR towards piperidones

3.1 Tables

Table 1. Screening of various conditions^a



Entry	Base (equiv)	Solvent	Temp (°C)	Time (h)	Yield (%)
1	<i>t</i> -BuOK(2.5)	THF	reflux	2	65
2	<i>t</i> -BuOK(2.5)	DMF	70	12	70
3	KHMDS (2.5)	THF	reflux	1	95
4	KHMDS (2.5)	THF	50	1	93
5	KHMDS (1.3)	THF	50	1	37
6	KHMDS (2.5)	THF	rt	1	88
7	NaH (2.5)	THF	reflux	12	45
8	NaH (2.5)	DMF	70	12	50
9	NaH (2.5)	DMSO	rt	1	96
10 ^b	NaH (2.5)	DMSO	rt	12	Traces
11 ^c	NaH (2.5)	DMSO	rt	12	80
12 ^d	NaH (2.5)	DMSO	rt	1	94
13 ^e	KHMDS (2.5)	THF	rt	12	-

159 ^aReaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), Pd(dba)₂ (0.025 mmol) and PPh₃ (0.05 mmol)
 160 in solvent (0.5 M). ^bUsing Xantphos (5 mol%) instead of PPh₃. ^cUsing Johnphos (10 mol%) instead of
 161 PPh₃. ^dUsing Pd(PPh₃)₄ (5 mol%) instead of Pd(dba)₂/PPh₃. ^eReaction without Pd(dba)₂ and PPh₃.

162

4 Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

5 Author Contributions

AZ was responsible for designing and performing the experiments. AZ, AMLN, NEAAES, AKA and LEK discussed the evolution of the project and revised the manuscript together, LEK and AKA directed the project and wrote the publication.

6 Acknowledgment and dedication

We dedicate this work to our colleague Mohamed Ali Hassan who passed away few months before the end of this study. We gratefully acknowledge a Scholarship from the Egyptian Government, which was awarded to A. Zidan.

7 References

- Banfi, L., Basso, A., Guanti, G., and Riva, R. (2003). Application of tandem Ugi reaction/ring-closing metathesis in multicomponent synthesis of unsaturated nine-membered lactams. *Tetrahedron Lett.* 44, 7655-7658. doi: [10.1016/j.tetlet.2003.08.027](https://doi.org/10.1016/j.tetlet.2003.08.027).
- Beck, B., Larbig, G., Mejat, B., Magnin-Lachaux, M., Picard, A., Herdtweck, E., and Dömling, A. (2003). Short and Diverse Route Toward Complex Natural Product-Like Macrocycles. *Org. Lett.* 5, 1047-1050. doi: [10.1021/ol034077e](https://doi.org/10.1021/ol034077e).
- Ben Abdesslem, A., Abderrahim, R., Agrebie, A., Dos Santos, A., El Kaïm, L., and Komesky, A. (2015). Formal [3+2] cycloaddition of Ugi adducts towards pyrrolines. *Chem. Commun.* 51, 1116-1119. doi: [10.1039/C4CC08282F](https://doi.org/10.1039/C4CC08282F).
- Bossio, R., Marcos, C.F., Marcaccini, S., and Pepino, R. (1997). Studies on Isocyanides and Related Compounds. An Unusual Synthesis of Functionalized Succinimides. *Synthesis*, 1389-1390. doi: [10.1055/s-1997-1367](https://doi.org/10.1055/s-1997-1367).
- Boyarskiy, V., Bokach, N., Luzyanin, K.V., and Kukushkin, V. (2015). Metal-mediated and Metal-catalyzed reactions of isocyanides. *Chem. Rev.* 115, 2698-2779. doi: [10.1021/cr500380d](https://doi.org/10.1021/cr500380d).
- Brauch, S., Gabriel, L., and Westermann, B. (2010). Seven-component reactions by sequential chemoselective Ugi–Mumm/Ugi–Smiles reactions. *Chem. Commun.* 46, 3387-3389. doi: [10.1039/B927388C](https://doi.org/10.1039/B927388C).
- Cordier, M., Dos Santos, A., El Kaïm, L., and Narboni, N. (2015). Passerini/Tsuji–Trost strategies towards achieving lactams and cyclopentane derivatives. *Chem. Commun.* 51, 6411-6414. doi: [10.1039/C5CC00584A](https://doi.org/10.1039/C5CC00584A).
- Dömling, A. (2006). Recent developments in isocyanide based multicomponent reactions in applied chemistry. *Chem. Rev.* 106, 17-89. doi: [10.1021/cr0505728](https://doi.org/10.1021/cr0505728).
- Dömling, A., and Ugi, I. (2000). Multicomponent reactions with isocyanides. *Angew. Chem. Int. Ed.* 39, 3168-3210. doi: [10.1002/1521-3773\(20000915\)39:18<3168::AID-ANIE3168>3.0.CO;2-U](https://doi.org/10.1002/1521-3773(20000915)39:18<3168::AID-ANIE3168>3.0.CO;2-U).
- Dömling, A., Wang, K., and Wang, W. (2012). Chemistry and Biology of multicomponent reactions. *Chem. Rev.* 112, 3083-3135. doi: [10.1021/cr100233r](https://doi.org/10.1021/cr100233r).

- 202 Dos Santos, A., and El Kaïm, L. (2014). Reductive Passerini/Tsuji–Trost Strategy towards β,γ -
203 Unsaturated Amides. *Synlett* 25, 1901-1903. doi: 10.1055/s-0033-1340187.
- 204 Eckert, H. (2012). Diversity Oriented Syntheses of Conventional Heterocycles by Smart Multi
205 Component Reactions (MCRs) of the Last Decade. *Molecules* 17, 1074. doi:
206 10.3390/molecules17011074.
- 207 El Kaïm, L., Gizzi, M., and Grimaud, L. (2008). New MCR–Heck–Isomerization Cascade toward
208 Indoles. *Org. Lett.* 10, 3417-3419. doi: 10.1021/ol801217a.
- 209 El Kaïm, L., Grimaud, L., Le Goff, X.-F., Menes-Arzate, M., and Miranda, L.D. (2011).
210 Straightforward four-component access to spiroindolines. *Chem. Commun.* 47, 8145-8147.
211 doi: 10.1039/C1CC12236C.
- 212 El Mamouni, E.H., Cattoen, M., Cordier, M., Cossy, J., Arseniyadis, S., Ilitki, H., and El Kaïm, L.
213 (2016). Selective Tsuji–Trost type C-allylation of hydrazones: a straightforward entry into
214 4,5-dihydropyrazoles. *Chem. Commun.* 52, 14490-14493. doi: 10.1039/C6CC08171A.
- 215 Elders, N., Van Der Born, D., Hendrickx, L.J.D., Timmer, B.J.J., Krause, A., Janssen, E., De Kanter,
216 F.J.J., Ruijter, E., and Orru, R.V.A. (2009). The efficient One-Pot reaction of up to eight
217 components by the union of Multicomponent reactions. *Angew. Chem. Int. Ed.* 48, 5856-
218 5859. doi: 10.1002/anie.200902683.
- 219 Ghandi, M., Zarezadeh, N., and Abbasi, A. (2015). One-pot synthesis of spiropyrrloquinoline-
220 isoindolinone and their aza-analogs via the Ugi-4CR/metal-free intramolecular bis-annulation
221 process. *Org. Biomol. Chem.* 13, 8211-8220. doi: 10.1039/C5OB01095K.
- 222 Hebach, C., and Kazmaier, U. (2003). Via Ugi reactions to conformationally fixed cyclic peptides.
223 *Chem. Commun.* 0, 596-597. doi: 10.1039/B210952B.
- 224 Hulme, C., and Gore, V. (2003). Multi-component reactions: emerging chemistry in drug discovery
225 from xylocain to crixivan. *Curr. Med. Chem.* 10, 51-80. doi: 10.2174/0929867033368600.
- 226 Ivachtchenko, A.V., Ivanenkov, Y.A., Kysil, V.M., Krasavin, M.Y., and Ilyin, A.P. (2010).
227 Multicomponent reactions of isocyanides in the synthesis of heterocycles. *Russ. Chem. Rev.*
228 79, 787-817. doi: 10.1070/RC2010v079n09ABEH004086.
- 229 Kaur, T., Gautam, R.N., and Sharma, A. (2016). Assembly of New Heterocycles through an Effective
230 Use of Bisaldehydes by Using a Sequential GBB/Ugi Reaction. *Chem. Asian J.* 11, 2938-
231 2945. doi: 10.1002/asia.201601009.
- 232 Ku, I.W., Kang, S.B., Keum, G., and Kim, Y. (2011). Synthesis of α,β -Unsaturated 2-
233 Oxopyrrolidinyl Acetamide derivatives by Application of the Ugi/RCM Reaction Sequence.
234 *Bull. Kor. Chem. Soc.* 32, 3167-3170. doi: 10.5012/bkcs.2011.32.8.3167.
- 235 Langer, P., and Freiberg, W. (2004). Cyclization Reactions of Dianions in Organic Synthesis. *Chem.*
236 *Rev.* 104, 4125-4150. doi: 10.1021/cr010203l.
- 237 Lei, J., Meng, J.P., Tang, D.Y., Frett, B., Chen, Z.Z., and Xu, Z.G. (2018). Recent advances in the
238 development of polycyclic skeletons via Ugi reaction cascades. *Mol. Divers.* 22, 503-516.
239 doi: 10.1007/s11030-017-9811-2.
- 240 Li, Z., Kumar, A., Peshkov, A., and Van Der Eycken, E.V. (2016). A domino Ugi/Michael approach
241 for the synthesis of α,β -unsaturated γ -lactams. *Tetrahedron Lett.* 57, 754-756. doi:
242 [10.1016/j.tetlet.2016.01.014](https://doi.org/10.1016/j.tetlet.2016.01.014).

- Orru, R., and De Greef, M. (2003). Recent advances in Solution-Phase multicomponent methodology for the synthesis of heterocyclic compounds. *Synthesis* 10, 1471-1499. doi: 10.1055/s-2003-40507.
- Orru, R.V.A., and Ruijter, E. (2010). *Synthesis of Heterocycles via Multicomponent Reactions I*. Berlin, Heidelberg: Springer Verlag.
- Orru, R.V.A., and Ruijter, E. (2010). *Synthesis of Heterocycles via Multicomponent Reactions II*. Berlin Heidelberg: Springer Verlag.
- Polindara-García, L.A., and Miranda, L.D. (2012). Two-Step Synthesis of 2,3-Dihydropyrroles via a Formal 5-endo Cycloisomerization of Ugi 4-CR/Propargyl Adducts. *Org. Lett.* 14, 5408-5411. doi: 10.1021/ol3024727.
- Ribelin, T.P., Judd, A.S., Akritopoulou-Zanze, I., Henry, R.F., Cross, J.L., Whittern, D.N., and Djuric, S.W. (2007). Concise Construction of Novel Bridged Bicyclic Lactams by Sequenced Ugi/RCM/Heck Reactions. *Org. Lett.* 9, 5119-5122. doi: 10.1021/ol7023373.
- Sadjadi, S., and Heravi, M.M. (2011). Recent application of isocyanides in synthesis of heterocycles. *Tetrahedron* 67, 2707-2752. doi: 10.1016/j.tet.2011.01.086.
- Salcedo, A., Neuville, L., and Zhu, J. (2008). Palladium-Catalyzed Intramolecular C-Arylation of Benzylic Carbon: Synthesis of 3-Benzoxazolyloindolinones by a Sequence of Ugi-4CR/Postfunctionalization. *J. Org. Chem.* 73, 3600-3603. doi: 10.1021/jo800266y.
- Sharma, U.K., Sharma, N., Vachhani, D.D., and Van Der Eycken, E.V. (2015). Metal-mediated post-Ugi transformations for the construction of diverse heterocyclic scaffolds. *Chem. Soc. Rev.* 44, 1836-1860. doi: 10.1039/C4CS00253A.
- Sunderhaus, J.D., and Martin, S.F. (2009). Applications of multicomponent reactions to the synthesis of diverse heterocyclic scaffolds. *Chem. Eur. J.* 15, 1300-1308. doi: 10.1002/chem.200802140.
- Tempest, P.A. (2005). Recent advances in heterocycle generation using the efficient Ugi multiple-component condensation reaction. *Curr. Opin. Drug Discov. Devel.* 8, 776-788. doi: 10.1080/17518253.2012.691183.
- Thompson, C.M. (1994). *Dianion Chemistry in Organic Synthesis*. Boca Raton: CRC press.
- Trifilenkov, A.S., Ilyin, A.P., Kysil, V.M., Sandulenko, Y.B., and Ivachtchenko, A.V. (2007). One-pot tandem complexity-generating reaction based on Ugi four component condensation and intramolecular cyclization. *Tetrahedron Lett.* 48, 2563-2567. doi: 10.1016/j.tetlet.2007.02.015.
- Tyagi, V., Khan, S., and Chauhan, P.M.S. (2013). Facile synthesis of diverse isoindolinone derivatives via Ugi-4CR followed by Cu-catalyzed deamidative C(sp²)-C(sp³) coupling. *Tetrahedron Lett.* 54, 1279-1284. doi: 10.1016/j.tetlet.2012.12.091.
- Vachhani, D.D., Butani, H.H., Sharma, N., Bhoya, U.C., Shah, A.K., and Van Der Eycken, E.V. (2015). Domino Heck/borylation sequence towards indolinone-3-methyl boronic esters: trapping of the σ -alkylpalladium intermediate with boron. *Chem. Commun.* 51, 14862-14865. doi: 10.1039/C5CC05193B.
- Váradi, A., Palmer, T., Dardashti, R., and Majumdar, S. (2016). Isocyanide-based multicomponent reactions for the synthesis of heterocycles. *Molecules* 19. doi: 10.3390/molecules21010019.

- 284 Zarganes-Tzitzikas, T., Patil, P., Khoury, K., Herdtweck, E., and Dömling, A. (2015). Concise
285 Synthesis of Tetrazole-keto-piperazines by Two Consecutive Ugi Reactions. *Eur. J. Org.*
286 *Chem.* 1, 51-55. doi: 10.1002/ejoc.201403401.
- 287 Zarganes-Tzitzikas, T., Chandgude, A.L., and Dömling, A. (2015). Multicomponent reactions, union
288 of MCRs and beyond. *Chem. Rec.* 15, 981-996. doi: 10.1002/tcr.201500201.
- 289 Zhang, L., Zhao, F., Zheng, M., Zhai, Y., and Liu, H. (2013). Rapid and selective access to three
290 distinct sets of indole-based heterocycles from a single set of Ugi-adducts under microwave
291 heating. *Chem. Commun.* 49, 2894-2896. doi: 10.1039/C3CC00111C.
- 292 Zhu, J., and Bienaymé, H. (2005). *Multicomponent reactions*. Weinheim: Wiley-VCH.
- 293 Zhu, J., Wang, Q., and Wang, M.-X. (2014). *Multicomponent reactions in organic synthesis*.
294 Weinheim: Wiley-VCH.
- 295 Zidan, A., Cordier, M., El-Naggar, A.M., Abd El-Sattar, N.E.A., Hassan, M.A., Ali, A.K., and El
296 Kaïm, L. (2018). Propargylation of Ugi Amide Dianion: An Entry into Pyrrolidinone and
297 Benzoindolizidine Alkaloid Analogues. *Org. Lett.* 20, 2568-2571. doi:
298 10.1021/acs.orglett.8b00687.
- 299 Zidan, A., Garrec, J., Cordier, M., El-Naggar, A.M., Abd El-Sattar, N.E.A., Ali, A.K., Hassan, M.A.,
300 and El Kaim, L. (2017). β -Lactam Synthesis through Diodomethane Addition to Amide
301 Dianions. *Angew. Chem. Int. Ed.* 56, 12179-12183. doi: 10.1002/anie.201706315.

302