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RECENT ADVANCES IN THE DEVELOPMENT AND APPLICATIONS OF POST-UGI TRANSFORMATIONS

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Abstract – The Ugi reaction is one of the most prominent multiple component coupling reactions (MCRs) due to the large number of applications it has found in organic synthesis. In this review we summarize recent advances in the field of Ugi-post condensation reactions covering the literature for the past two years.

The Ugi multicomponent reaction was discovered about half a century ago by Ivar Ugi[1] and has become, along with its numerous variations, one of the most prominent reactions in organic synthesis. In its original version it consists of the reaction of four components (U-4CR): an aldehyde, an amine, an acid and an isocyanide typically in a protic solvent such as MeOH (Figure 1).

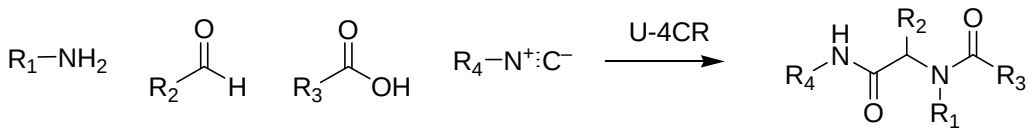


Figure 1

Later on, a five-center-four-component coupling variation was discovered (U-5C-4CR) as shown in Figure 2. In this case aminoacid and alcohol inputs result in a different molecular backbone.[2]

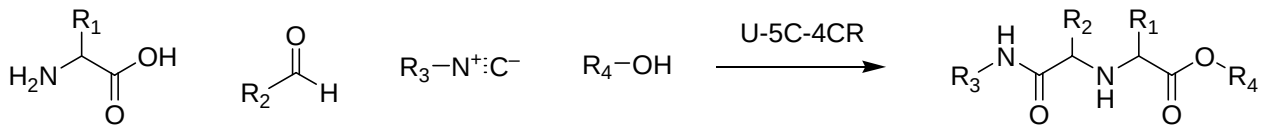


Figure 2

The reaction is very attractive because it is robust, tolerates a variety of substituents and also because it provides access to a variety of different molecular frameworks that would otherwise require numerous synthetic steps.

During the past 50 years numerous variations of the reactants have provided access to additional structural diversity. One approach has been the substitution of some of the components with other reactive groups that assume the same role in the reaction.[3] For e.g. the use of hydrazoic acid instead of carboxylic acids resulted in the formation of tetrazoles. Another approach has been the use of components containing two of the functional groups participating in the Ugi reaction allowing for the formation of heterocyclic compounds.

Some recent developments include the use of the Smiles rearrangement in the Ugi reaction where the carboxylic component was replaced by a phenolic component.[4] Another interesting variation of the Ugi reaction is the use of bis-secondary diamines instead of a primary amine to provide new structural diversity.[5] Pirrung et al. introduced fragrant convertible isocyanides[6] while the Sung group reported the use of 2-nitrobenzylamine as ammonia equivalent in the Ugi reaction.[7] One of the first examples of an asymmetric Ugi reaction without chiral amines to prepare chiral pyrroloketopiperazines in moderate diastereoselectivities is described.[8] Also a new Ugi reaction employing organometallic reagents and nitriles has been reported.[9]

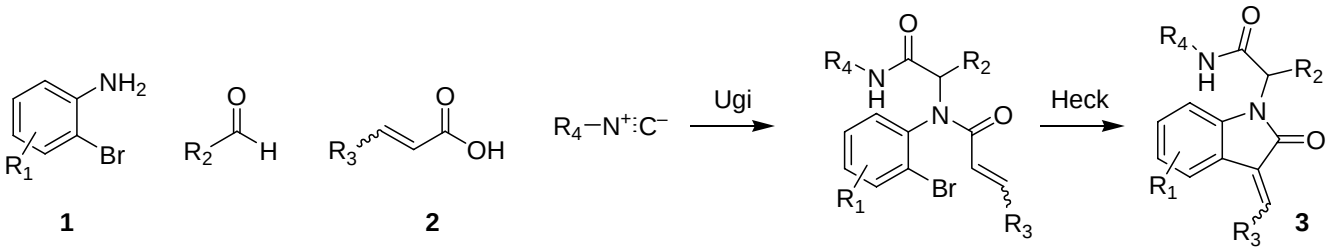
As an alternative approach the four components of the Ugi reaction provide a variety of opportunities to introduce additional functional groups that upon assembly of the Ugi framework either spontaneously or after treatment with additional reagents/conditions further react yielding even more complex molecules. This field of research i.e. the combination of a multicomponent reaction with a subsequent transformation has flourished over the past two decades. The first examples appear with the early work of Armstrong and co-workers (Ugi/1,3-dipolar cycloaddition and Ugi/intramolecular cyclization)[10] and later with the work of Paulvannan (Ugi/Diels Alder),[11] Marcaccini (Ugi/Knoevenagel),[12] Bienaymé (Ugi/Intramolecular 1,4-addition/elimination)[13] and Hulme (Ugi/de-Boc/cyclization).[14] Since then the Ugi reaction has been combined with a plethora of other transformations nicely summarized most recently by Dömling[15] and by Marcaccini and Torroba.[16] Excellent reviews cover the literature of isocyanide based multicomponent reactions, including the Ugi reaction until the end of 2005.[17]

In this review we will focus on recent Ugi/post-condensation reactions that have appeared in the literature in 2006 and the first half of 2007.

Ugi/Heck

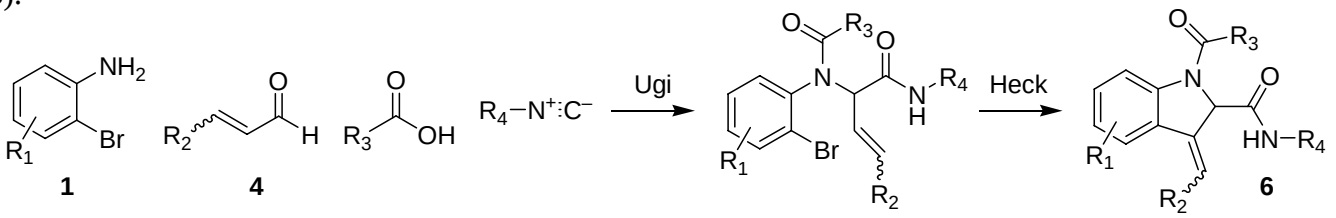
The combination of the Ugi reaction with a sequential Heck intramolecular reaction has been already described in the work of Gracias *et al.*[18] and Yang *et al.*[19] Recently researchers at Priaton have illustrated the utility of this approach for the synthesis of indole scaffolds. Thus a one-pot two-step synthetic procedure was developed for the synthesis of indol-2-ones **3** with four potential points of diversity starting from 2-bromoanilines **1** and substituted acrylic acids **2** (Scheme 1).[20] The Ugi reaction proceeded for 24h

at 50 ºC in trifluoroethanol and upon completion the solvent was changed to acetonitrile. Addition of 10% $Pd(OAc)_2$ and PPh_3 and heating for another 24 h at 80 ºC provided the corresponding indol-2-ones in 35-63 % overall yields.



Scheme 1

When the double bond moiety was part of the aldehyde component **4** (Scheme 2), following the same synthetic procedure as above, a different indole framework **6** was obtained in 19-48% yields.[21] The use of formic acid resulted in partial cleavage of the formyl group and subsequent isomerization generated 1*H*-indoles **7** in moderate yields (15-38%) (Figure 3). Convertible isocyanides[10] were also compatible with the reaction conditions and enabled the synthesis of 1*H*-indole-2-carboxylic acids such as **8** (Figure 3).



Scheme 2

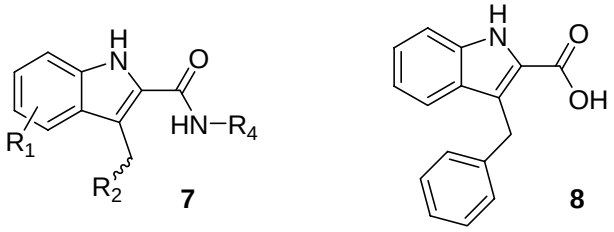
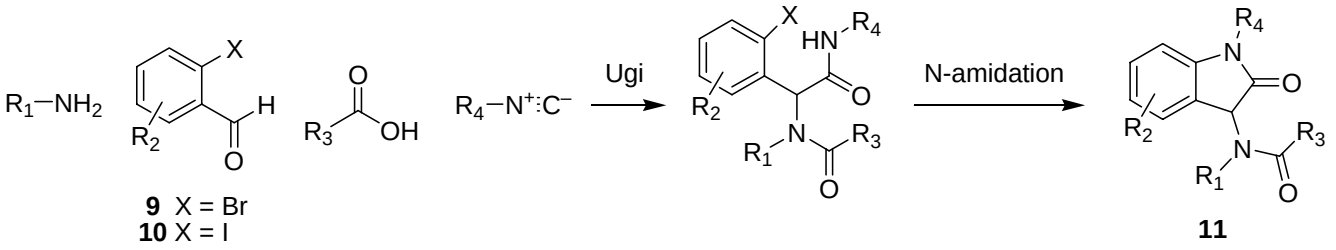


Figure 3

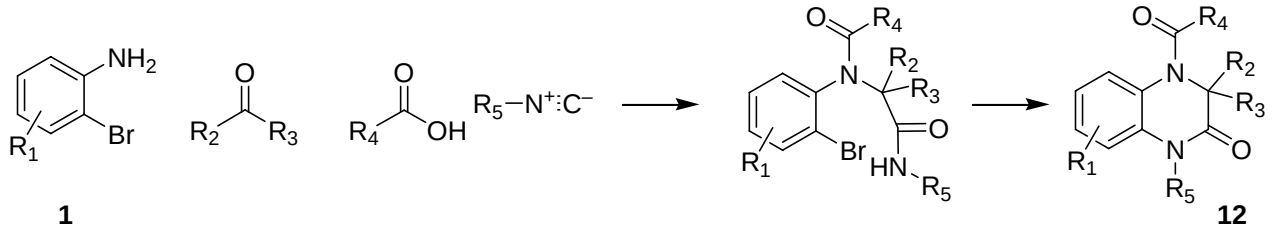
Ugi/Buchwald-Hartwig

Indol-2-ones **11** (Scheme 3) can also be accessed by the Ugi reaction followed by an intramolecular *N*-aryl amidation. The reaction was first reported utilizing 2-bromobenzaldehydes **9**[22] and performing the amidation step at 100 ºC, using 5% $Pd_2(dba)_3$, tri-*o*-tolylphosphine and base (Cs_2CO_3 for aliphatic isocyanides or K_2CO_3 for benzylic isocyanides) in toluene. The yields for the cyclization step were low to moderate (4-45 %). Subsequently, Zhu and co-workers reported on the use of 2-iodobenzaldehydes **10**, Me-Phos as the ligand and microwave heating to obtain much higher yields for the cyclization step (60-99%).[23]

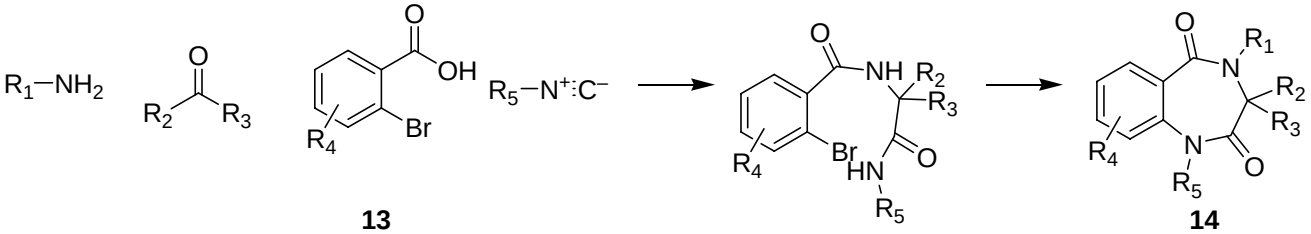


Scheme 3

If 2-bromoanilines **1** were used in the Ugi step the resulting intramolecular amidation provided quinoxalin-2-ones **12** in 25-50% yields (Scheme 4) while the use of 2-bromobenzoic acids **13** resulted in benzodiazepine-2,5-diones **14** in 28-51% yields (Scheme 5).



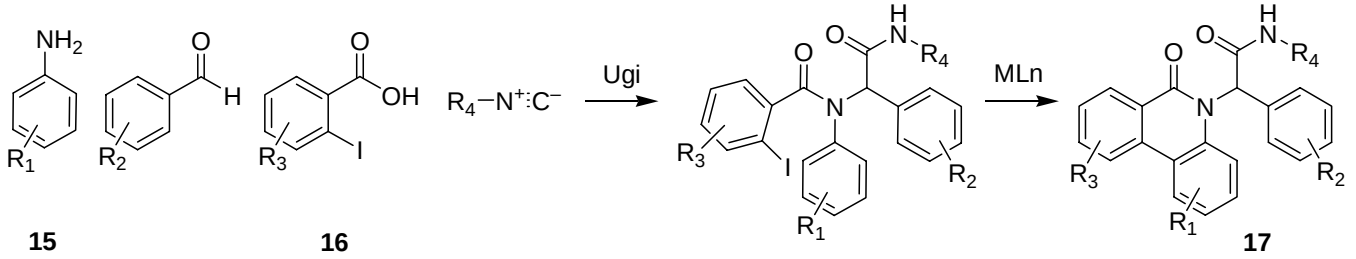
Scheme 4



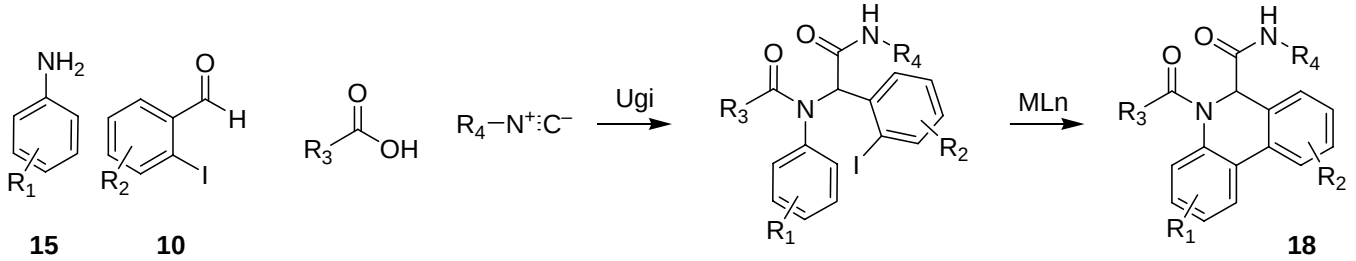
Scheme 5

Ugi/C-H activation

Utilizing similar intermediates as above the Yang group was able to obtain products deriving from a Pd catalysed intramolecular arylation[24] instead of an *N*-aryl amidation. In this report anilines **15** (Scheme 6) were paired with 2-iodobenzoic acids **16**. The utilization in the second step of 5% $Pd(OAc)_2$, dppf, *n*-Bu_4NBr and K_2CO_3 in DMF at 80 ºC resulted in direct C-C bond formation of quinolines **17** in excellent yields (79-98%). When 2-iodoaldehydes **10** (Scheme 7) were used as an input and PCy_3 as the ligand in the C-H activation step excellent yields of quinolines **18** were obtained (78-95%). Following similar strategies and employing 2-iodo-carboxylilc acid derivatives of indoles, benzo[*b*]thiophenes and benzo[*b*]furans tetracyclic heterocycles were also obtained in excellent yields.



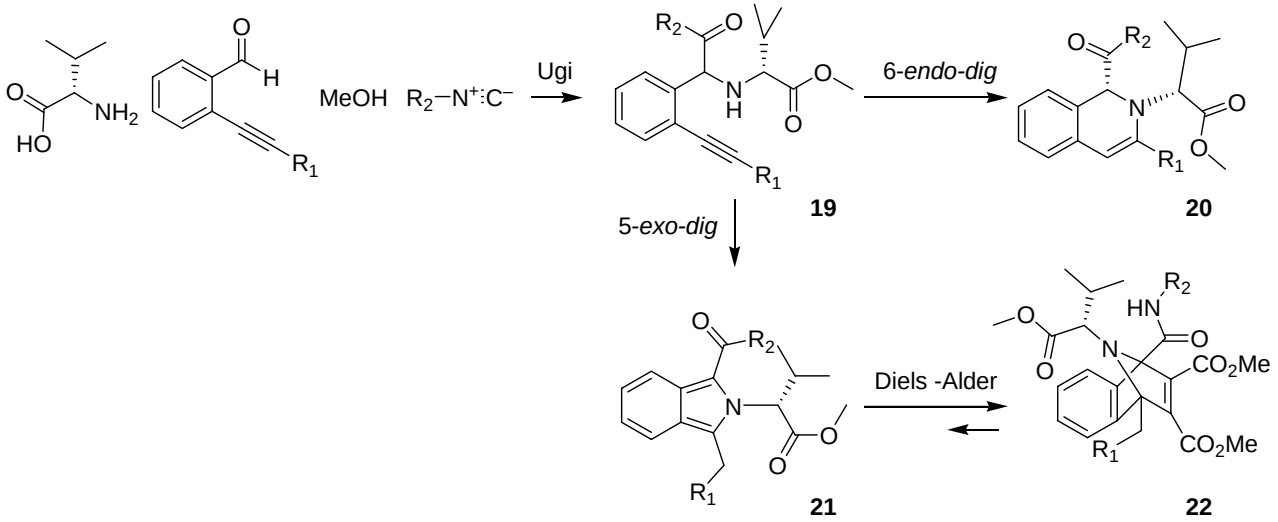
Scheme 6



Scheme 7

Ugi/Gold catalysed hydroamination

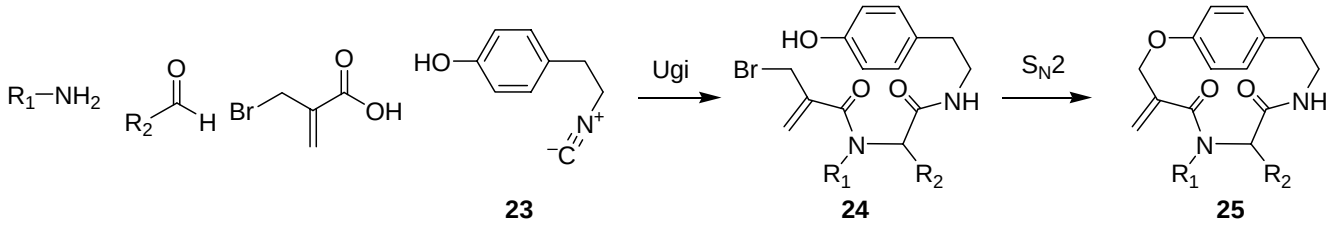
Dyker *et al*. reported on the combination of the Ugi 5-center-4-component reaction with hydroamination of the resulting secondary amine **19** (Scheme 8) to yield isoindoles **20** and dihydroisoquinolines **21**.[25] The hydroamination reaction proceeded efficiently with 3 mol % of AuCl in acetonitrile at 80 ºC to provide a mixture of products derived from 6-*endo*-dig and 5-*exo*-dig cyclizations in good overall yields (>70%). The 5-*exo*-dig products were further isomerized under the reaction conditions to the corresponding isoindoles **21**. Diels-Alder reaction of isoindoles furnished a 3:1 mixture of diastereomers **22** which could partially be converted back to starting isoindoles **21**.



Scheme 8

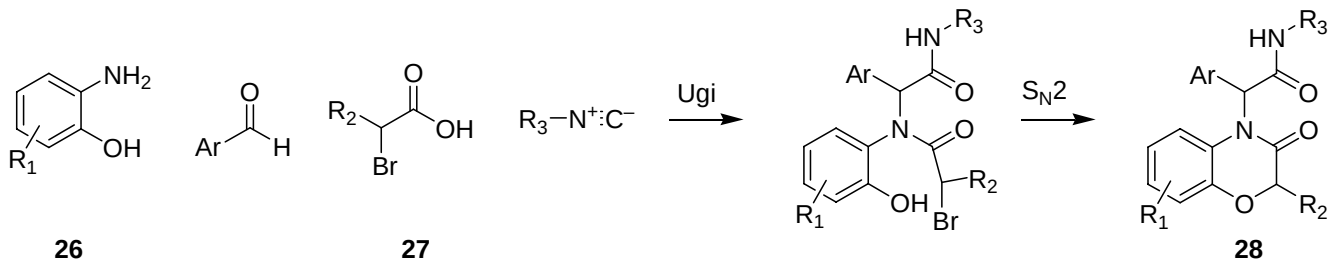
Ugi/Intramolecular Ether formation

A novel macroetherification reaction was coupled with Ugi adducts from isocyanide **23**[26] to provide 14-membered ansa-cyclopeptide alkaloid mimics **25** (Scheme 9) that could be further functionalized. Initial formation of the imine intermediate in the Ugi step proved to be crucial for efficient synthesis of the Ugi adducts **24**. The etherification reaction proceeded under carefully controlled conditions using K_2CO_3 and 18-crown-6 in acetone to provide macrocyles **25** in 19-95% yields.



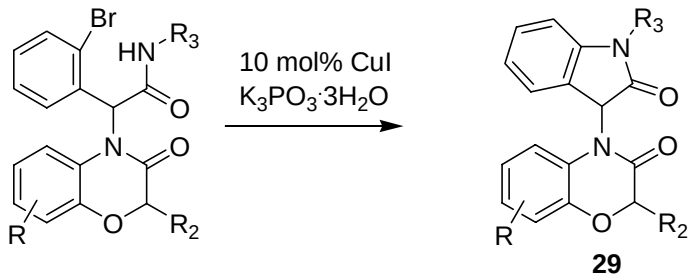
Scheme 9

A microwave assisted one-pot Ugi/intramolecular *O*-alkylation has also been reported.[27] The reactions proceed in good yields (64-85%) by first performing the Ugi reaction in the microwave at 80-100 ºC in MeOH and followed by addition of aq. K_2CO_3 and further heating in the microwave at 120-150 ºC for 15 min (Scheme 10). Highly functionalized 3-oxo-1,4-benzoxazines **28** were obtained in this manner from 2-hydroxy anilines **26** and α-bromo acetic acids **27**.



Scheme 10

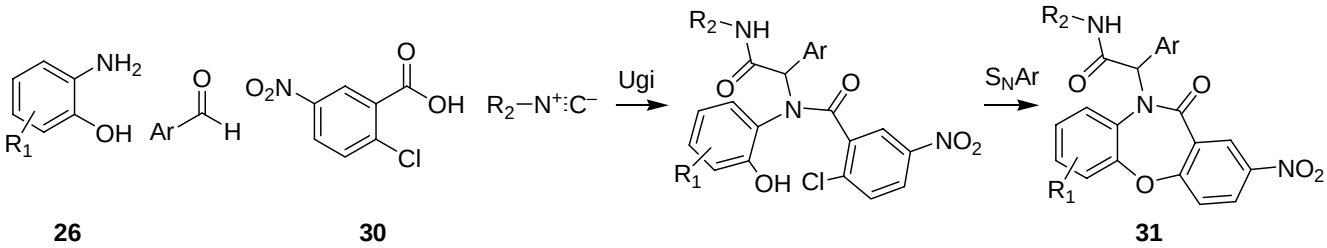
If the Ar group of **28** is appropriately functionalized further copper mediated amidations were possible and found to provide novel 3-oxo-1,4-benzoxazines substituted with 2-oxindoles **29** (Scheme 11).



Scheme 11

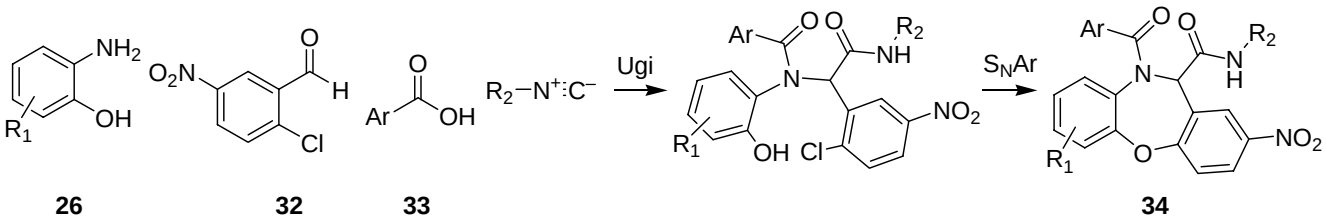
Ugi/S_NAr

When the methodology employed in Scheme 10 was applied using 2-chloro-5-nitro benzoic acid **30** instead of α-bromo acetic acids **27** as one of the inputs in the Ugi reaction (Scheme 12), dibenzo-oxazepinones **31** were obtained in excellent yields (81-87%).[28] The high yields obtained were due to a slight modification of the original protocol using a 2:1 mixture of MeOH/H_2O as the solvent and heating after addition of the base only at 100 ºC for 10 min. Several of these adducts were further transformed to 2-oxindole derivatives similar to the ones described in Scheme 12.



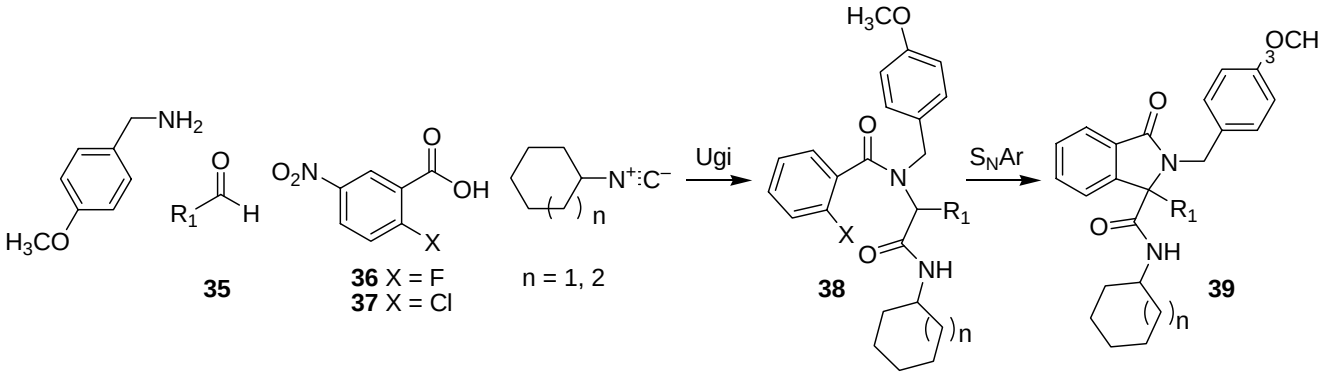
Scheme 12

2-Chloro-5-nitro benzaldehydes **32** (Scheme 13) proved to be more challenging and the sequence was found to work better by increasing the acidity of the carboxylic acid **33** (17-49% yields). In this case a different oxazepine skeleton **34** was obtained.



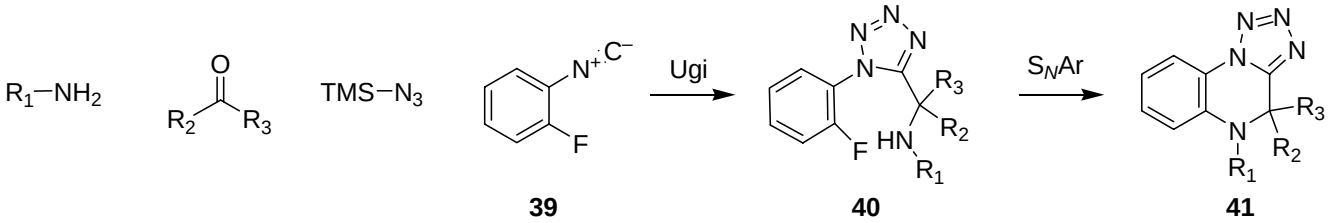
Scheme 13

An interesting C-C bond forming nucleophilic aromatic substitution has also been reported.[29] In this instance 2-fluoro and 2-chloro 5-nitro benzoic acids, **36** and **37** respectively, participated in the Ugi reaction to provide Ugi adducts **38**. If aldehyde **35** was aromatic with electron withdrawing substituents or electron-deficient heteroaromatic, the acidity of the C-H bond attached to R_1 in intermediate **38** was increased and favored nucleophilic aromatic substitution. Treatment of **38** with a base such as Et_3N in DMF at 120 ºC resulted in the generation of novel 3-oxoisoindolines **39** in 45-85% yields.



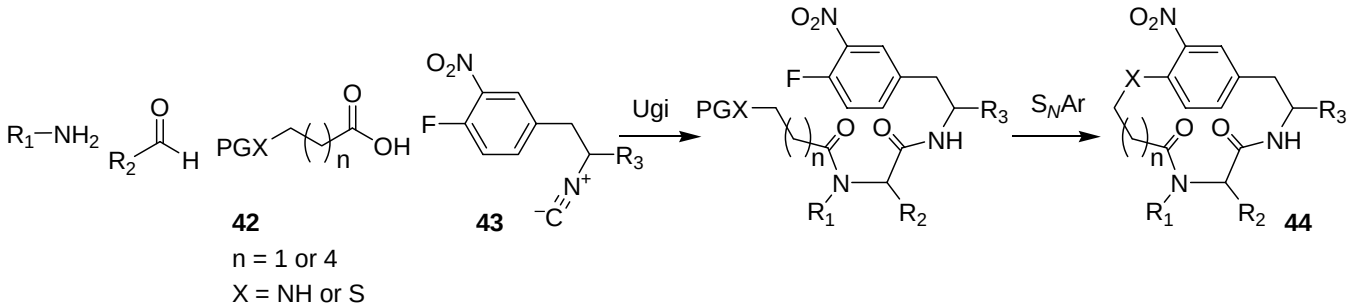
Scheme 14

The first example of the Ugi/tetrazole variation in combination with S_NAr was also reported.[30] The Ugi step was performed utilizing 2-fluorophenylisocyanide **39** (Scheme 15) and proceeded in moderate yields (17-65 %). The resulting secondary amines **40** were subjected to high yielding nucleophilic aromatic substitution reactions (57-96%) by exposure to Cs_2CO_3 in DMF at 100 ºC to afford fused tetrazolo-dihydroquinoxalines **41**.



Scheme 15

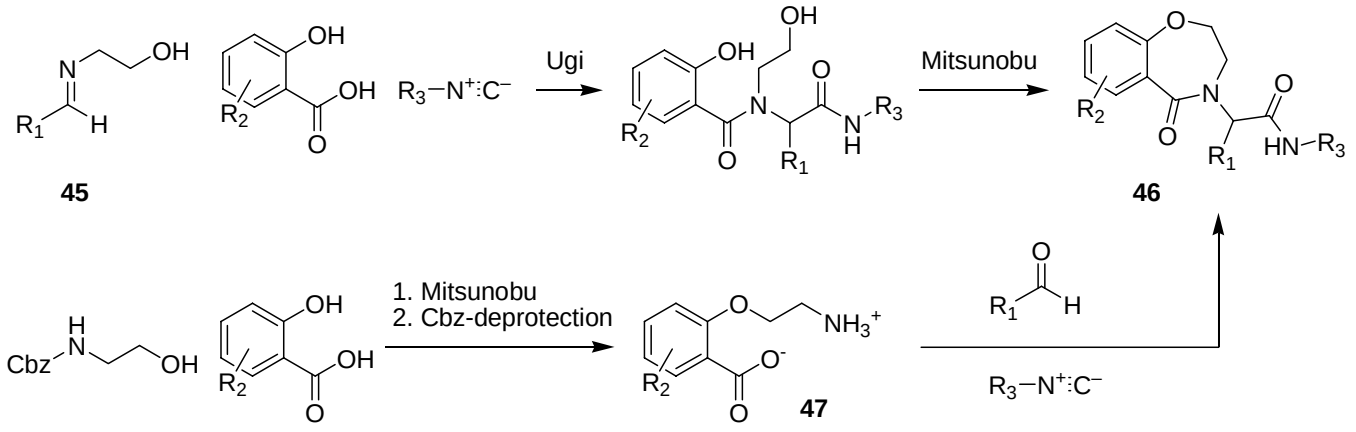
Using a carboxylic acid tethered to a potential nucleophile (compounds **42)** and 4-fluoro-3-nitro phenethyl isocyanides **43** (Scheme 16) the combination of the Ugi reaction with the S_NAr reaction provided para-cyclophanes **44**.[31] The nucleophilic aromatic substitution proceeded efficiently upon deprotection of the nucleophiles with TFA and subsequent treatment with K_2CO_3 in DMF at rt in 23-98% yields.



Scheme 16

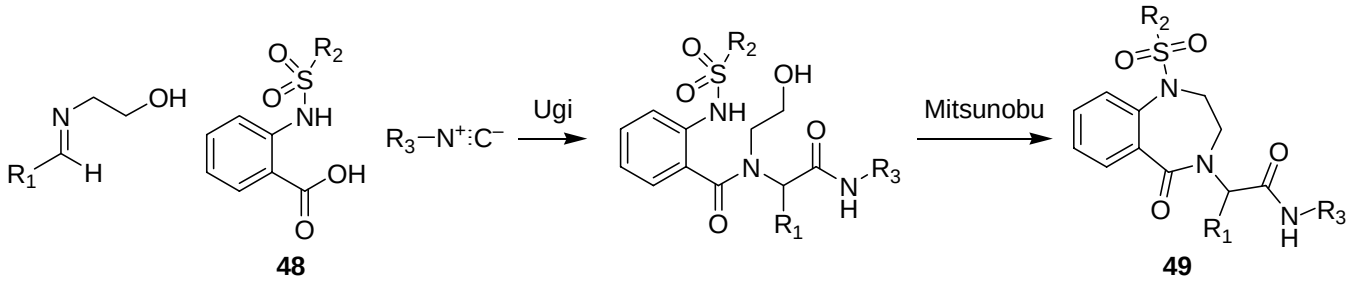
Ugi/Mitsunobu

Banfi, Riva and co-workers reported on the combination of the Ugi reaction with the Mitsunobu transformation to access dihydrobenzoxazepinones **46** (Scheme 17).[32] The Ugi reaction proceeded in good yields (51-81%) by pre-forming imine **45**. Mitsunobu reactions were carried out using DEAD/ PPh_3/ Et_3N in 34-88% yields. An alternative route was also explored reversing the sequence of reactions by performing aminoacid **47**. Although this sequence required one more synthetic step for the deprotection of the amine, it introduced aldehyde and isocyanide diversity elements in the last step and provided, in some cases, better overall yields.



Scheme 17

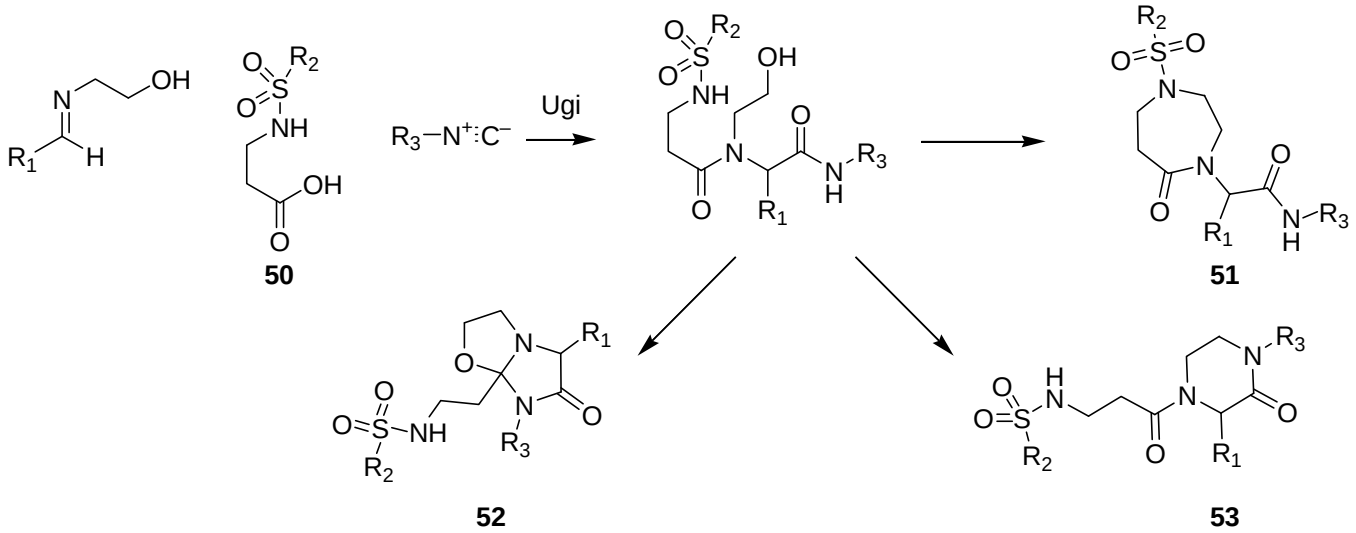
The same group has also reported on the use of sulfonamides and hydroxamates instead of phenols in the Mitsunobu step.[33] By employing similar conditions to the ones described for Scheme 17, clean products **49** (Scheme 18) were obtained in excellent yields (51-98%) in the case of aromatic sulfonamides **48**.



Scheme 18

However, in initial experiments, aliphatic sulfonamides **50** (Scheme 19) gave mixtures of desired product **51** with compounds **52** and **53**. Synthesis of **52**, which was inseparable from **51**, was suppressed by using N,N'-sulfuryl diimidazole and NaH or NaHMDS in DMF. These conditions provided the desired product **51** in 27-68% yields along with byproduct **53** in 10-50% yields. Hydroxamate moieties only

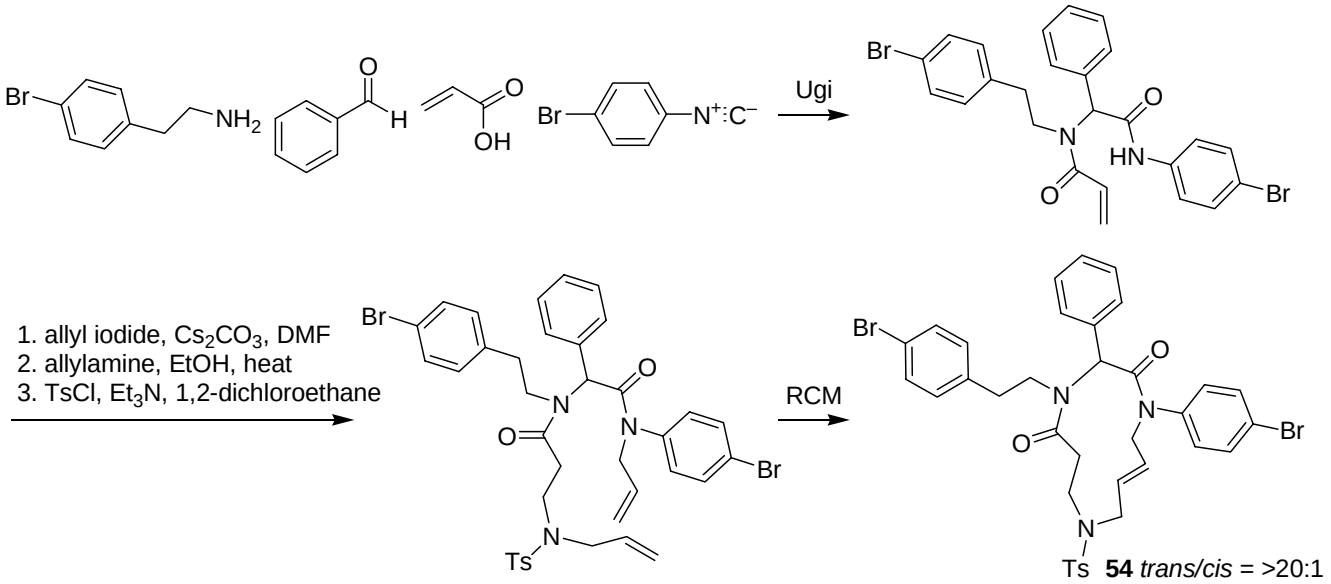
afforded *O*-cyclized adducts or other side products.



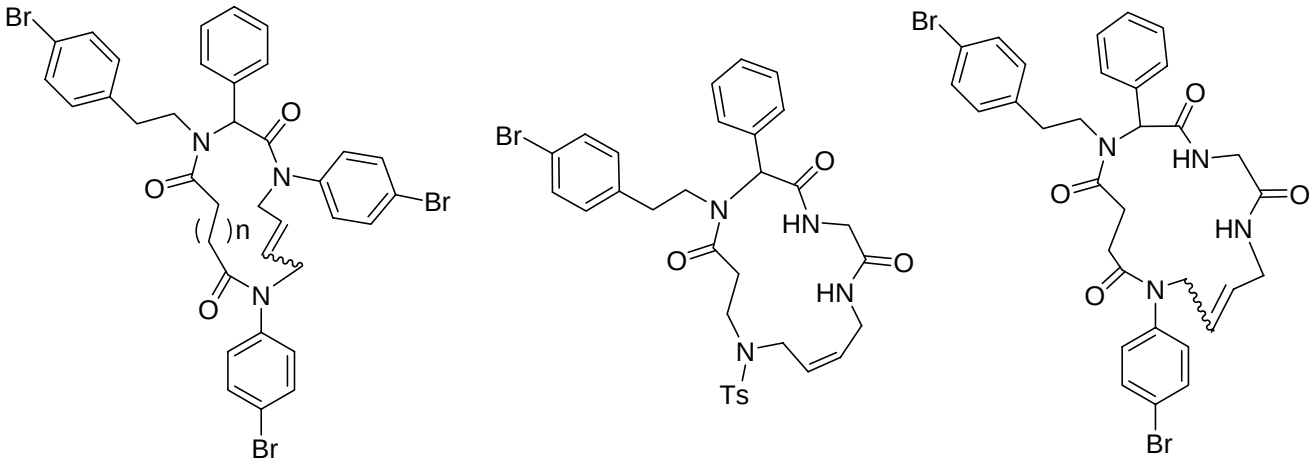
Scheme 19

Ugi/RCM

A diversity oriented synthesis of various macrocyclic peptidomimetics was reported.[34] The double bonds required for the RCM were introduced into the Ugi skeleton by alkylation and Michael addition reactions. RCM was carried out using 20 mol % second generation Hoveyda-Glubbs catalyst at 80 ºC in 1,2-dichloroethane to yield a 12-membered lactam **54** (Scheme 20). Following similar strategies additional 13-16 membered rings, compounds **55-59** (Figure 4), were obtained in very good overall yields. The stereochemistry of the double bond was in most cases well defined, its outcome depending on the thermodynamic stability of the newly formed ring.



Scheme 20



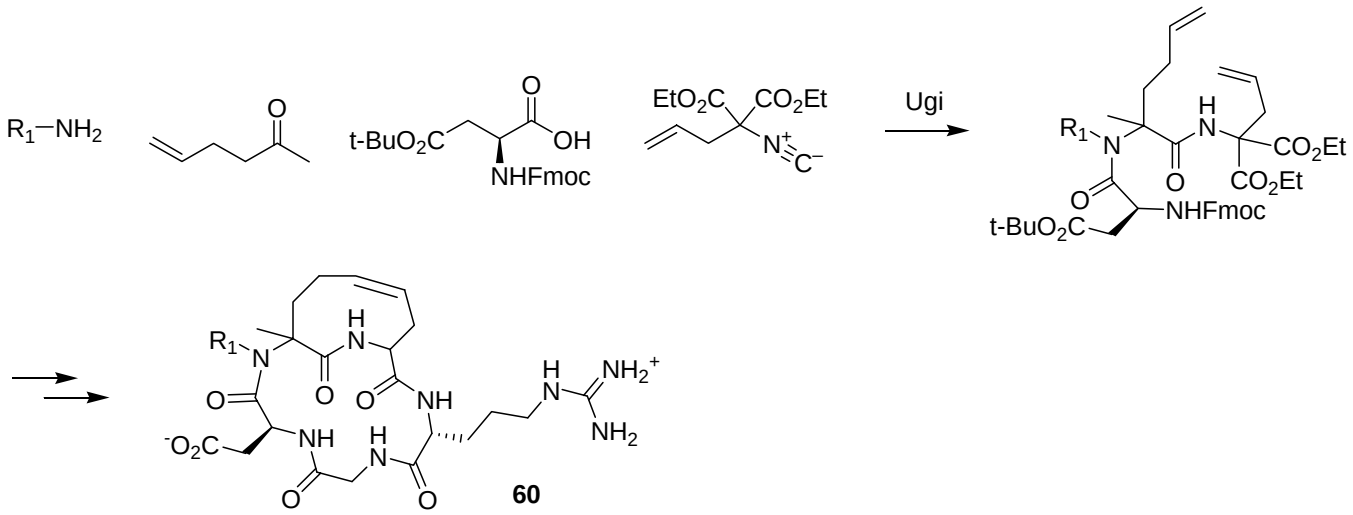
55 n=1 *trans/cis* = 1:>20
56 n=2 *trans/cis* = 1:>20
57 n=3 *trans/cis* = >20:1

58 *trans/cis* = 1:>20

59 *trans/cis* = 5:1

Figure 4

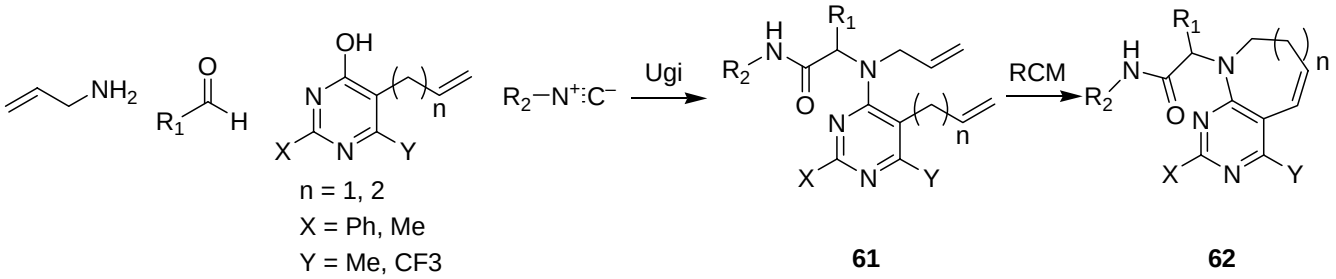
By applying the same strategy, the initial cores of several conformationally biased integrin ligands **60** (Scheme 21) have been prepared.[35] The compounds reported exhibited nanomolar activity against integrin αvβ3 and they were remarkably selective over integrin αvβ5.



60

Scheme 21

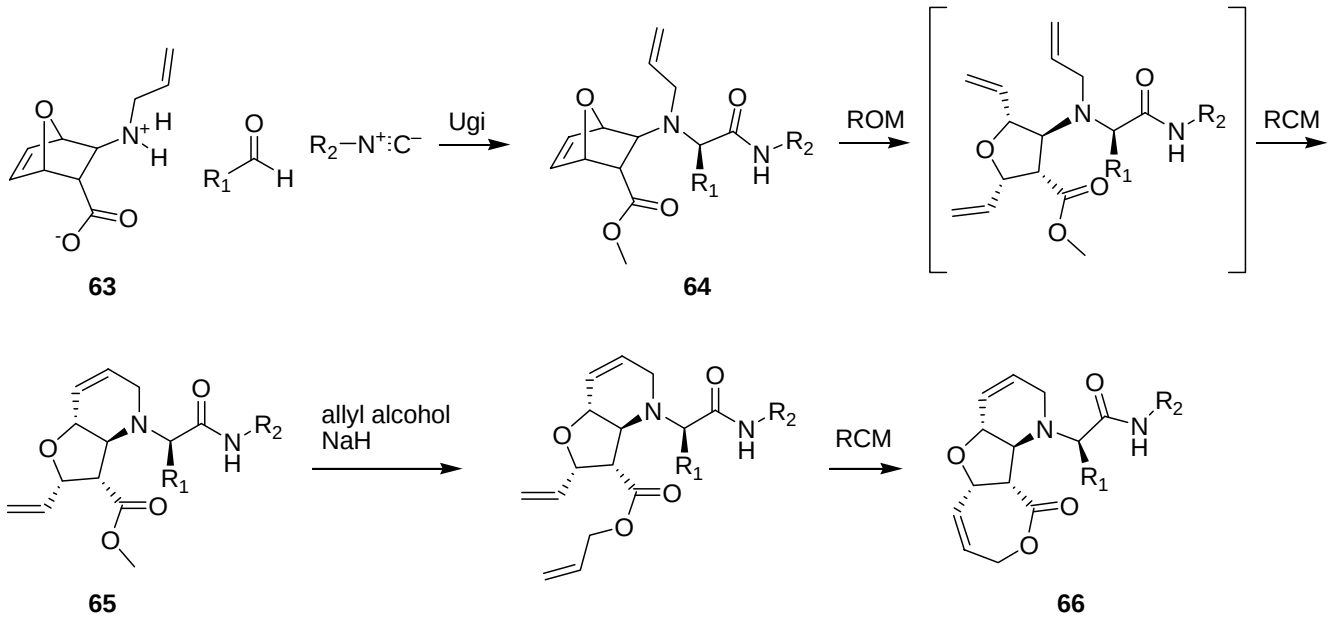
The combination of a newly discovered variation of the Ugi/Smiles reaction[4] followed by RCM has also been reported.[36] Compounds **61** (Scheme 22) were obtained in 52-70% yields by heating the Ugi components in toluene at 100 ºC. The ring closing metathesis was performed using 10 mol % second generation Hoveyda-Glubbs catalyst at 110 ºC in toluene to yield the pyrimido fused compounds **62** in 47-89% yields. While some RCM reactions proceed at rt providing the expected RCM product, heating resulted in isomerization of the initially formed double bond so as to conjugate with the pyrimidine ring.



Scheme 22

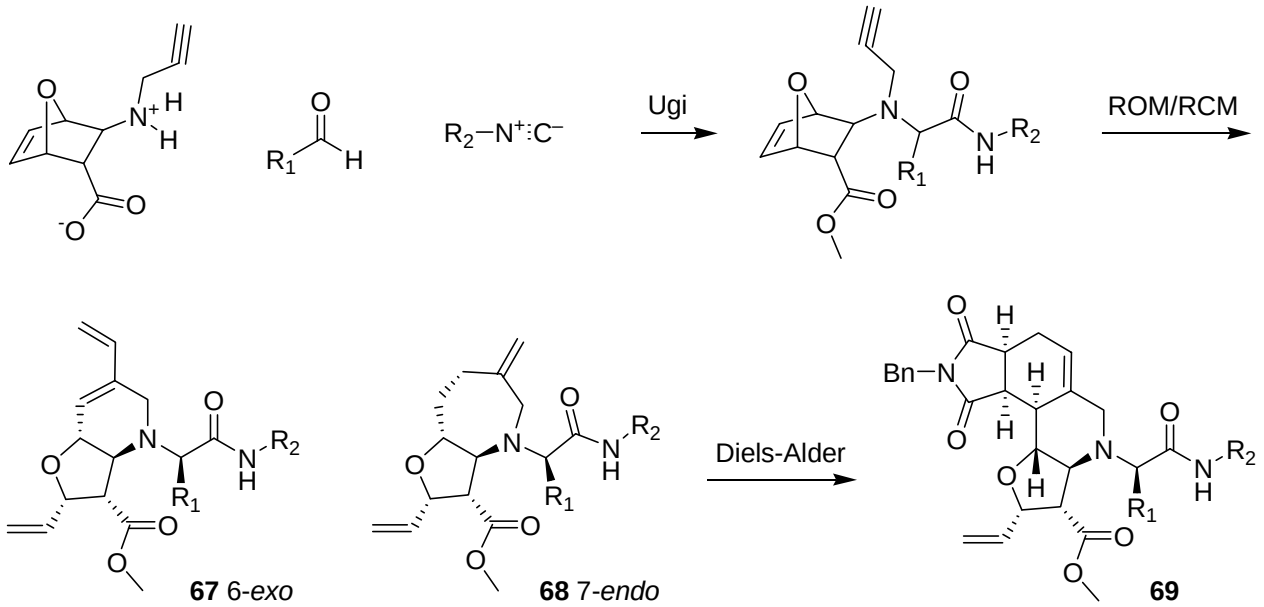
Ugi/ROM/RCM/Diels-Alder

An eloquent application of the Ugi-post-condensation concept was the preparation of optically pure fused polycyclic structures by the combination of the Ugi reaction with ROM/RCM and Diels-Alder sequences.[37] Optically pure starting material **63** (Scheme 23) was transformed to intermediate Ugi products **64**, which upon ROM/RCM with Grubbs II catalyst yielded compounds **65** in 61-95% yields. These products could be further modified by introduction of additional unsaturated moieties to participate in RCM reactions. An example was given in the case of R_1 = *i*-propyl and R_2 = cyclohexyl where the final product **66** was obtained in 78% yield.



Scheme 23

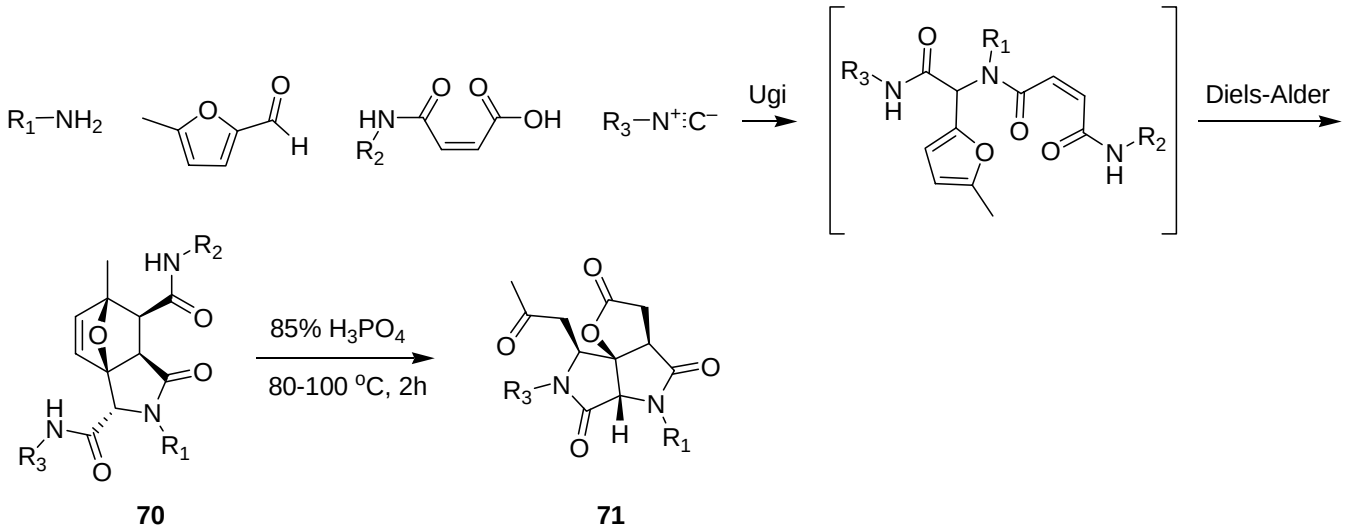
The use of a propargyl instead of an allyl group as the nitrogen substituent provides the opportunity for enyne metathesis reactions (Scheme 24). In these reactions the use of Grubbs II catalyst resulted in mixtures of 6-*exo* and 7-*endo* products, **67** and **68** respectively, while Grubbs I provided exclusively the 6-*exo* product **67**. Compound **67** was further subjected to Diels-Alder reactions to yield highly complex structures of type **69**.



Scheme 24

Ugi/Diels-Alder

A series of Ugi/intramolecular Diels-Alder adducts **70** (Scheme 25) have been prepared following previously reported procedures[11] in good yields (68-92%).[38] When compounds **70** were subjected to 85% H_3PO_4 under thermal conditions an unexpected rearrangement occurred providing diastereomerically pure tricyclic bis-lactam lactone-containing products **71** in 66-90 % yields. Mechanistic rationale for the H_3PO_4 promoted rearrangement was also provided by the authors and tentatively supported by additional experiments.

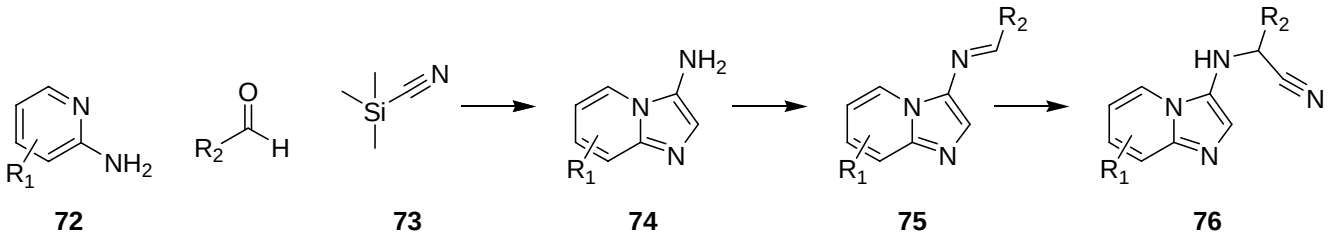


Scheme 25

Ugi/Strecker

Hulme and co-workers at Eli-Lilly[39] have reported a unique one step microwave sequence employing TMSCN **73** (Scheme 26) as an isocyanide replacement in the Ugi-type reaction of aminopyridines **72**.

The reaction mixture was irradiated in the microwave at 140 ºC. Depending on the stoichiometry of each component three different products could be obtained. Amino-imidazopyridines **74** were obtained with one equivalent of each component, iminoaryl-imidazopyridines **75** with two equivalents of the aldehyde component and imidazopyridines **76** with excess of the aldehyde and TNSCN components. Compound **76** derived from a subsequent Strecker reaction of imines **75**. Higher yields were obtained when non aromatic aldehydes were used (39-92%), presumably due to the higher reactivity of imines **75** towards the Strecker reaction.

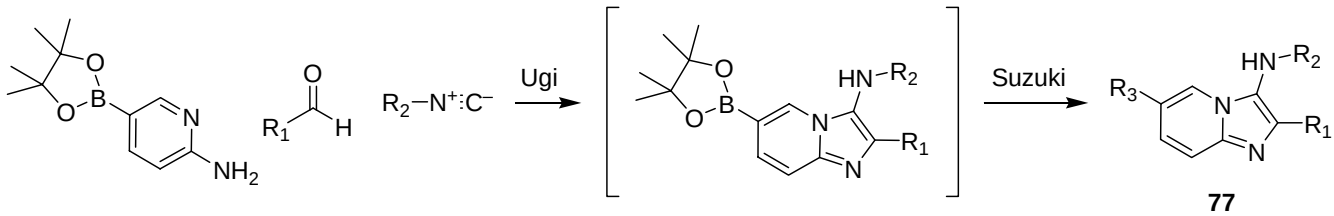


Product	Amine (equiv)	Aldehyde (equiv)	TMSCN (equiv)	PS-Sc(OTf)3 (mol%)	Rxn Time (min)	Temperature (ºC)
74	1	0.9	1	5	5	140
75	1	2.2	1	5	5	140
76	1	4.0	3	5	5	140

Scheme 26

Ugi/Suzuki

The first example of an aminopyridine substituted with boronate functionality participating in the Ugi reaction followed by a Suzuki coupling has been reported.[40] The reaction sequence was carried in a two step one pot procedure employing 4% $MgCl_2$ as the catalyst in the Ugi step (Scheme 27) and heating in the microwave at 160 ºC for 10 min, followed by Suzuki coupling using 10% $Pd(dppf)Cl_2$ and heating in the microwave at 90 ºC for 30 min to provide substituted amino-imidazopyridines **77** in moderate overall yields (42-68%)

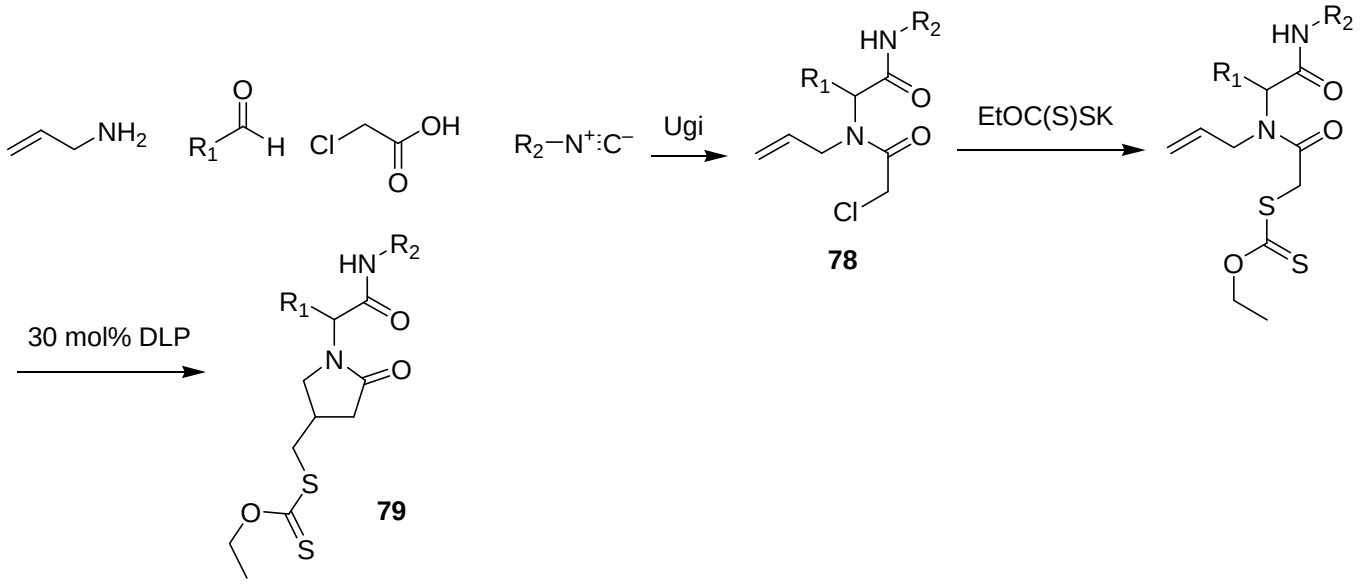


Scheme 27

Ugi/xanthate radical cyclizations

The El Kaïm group reported[41] the first combination of the Ugi reaction with a radical cyclization to obtain 5-8 membered rings. The reaction sequence incorporates the necessary for radical cyclizations xanthate group by nucleophilic displacement of a chlorine group in the Ugi adduct **78** (Scheme 28). The radical cyclizations proceed with dilauroyl peroxide as initiator to provide pyrrolidinones **79** in good yields

(63-70%). Alternatively, 2-xanthyl acetic acid could be used directly as an input in the Ugi reaction. Following this strategy six and eight membered lactams, **80** and **81** respectively (Figure 5), were also obtained.



Scheme 28

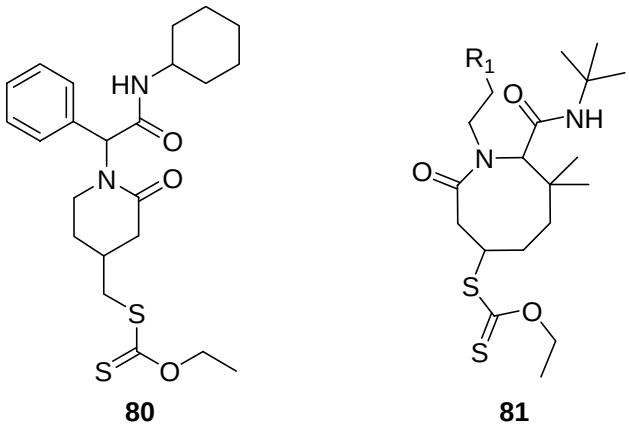
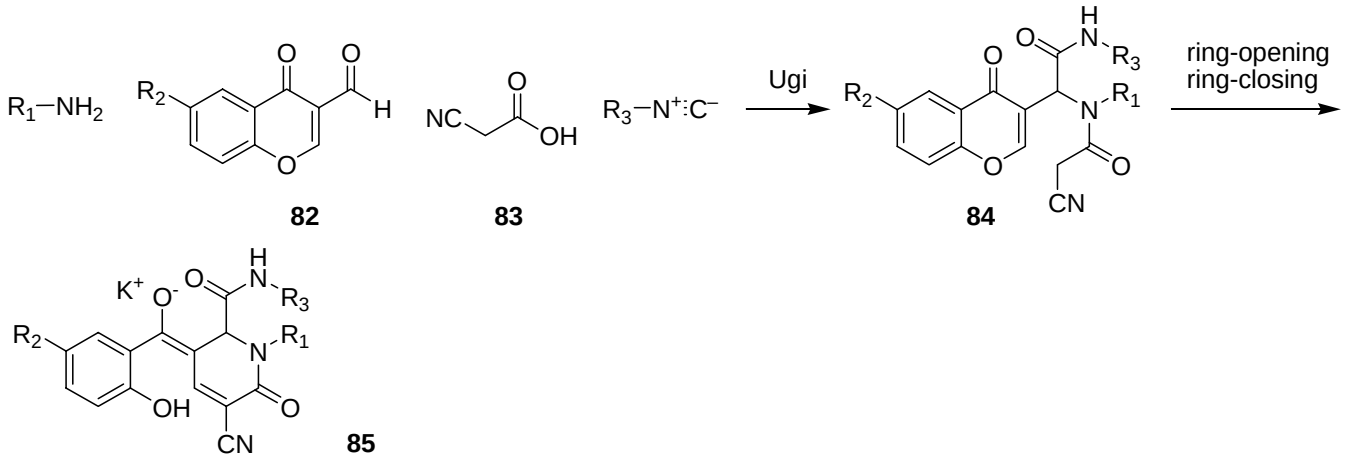


Figure 5

Ugi/Ring-opening/ring-closing

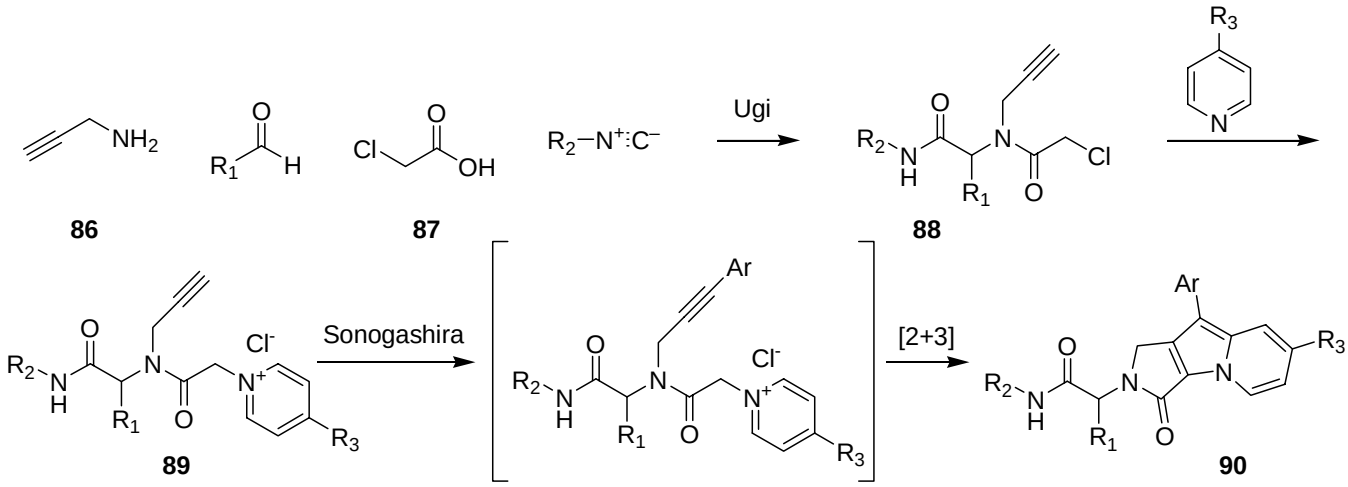
A novel methodology for the synthesis of functionalized pyridones by sequential Ugi/base promoted ring-opening and then ring-closing has been reported.[42] Formylchromones **82** and cyanoacetic acid **83** participate in the Ugi reaction to provide adducts **84** (Scheme 29) in 27-68% yields. Typically, the products were powders that could be isolated by simple filtrations. Upon treatment with KOH the chromone ring was opened and a new pyridone ring **85** was formed in 22-84% yields.



Scheme 29

Ugi/Pyridine addition/Sonogashira/[2+3] cycloaddition/oxidation

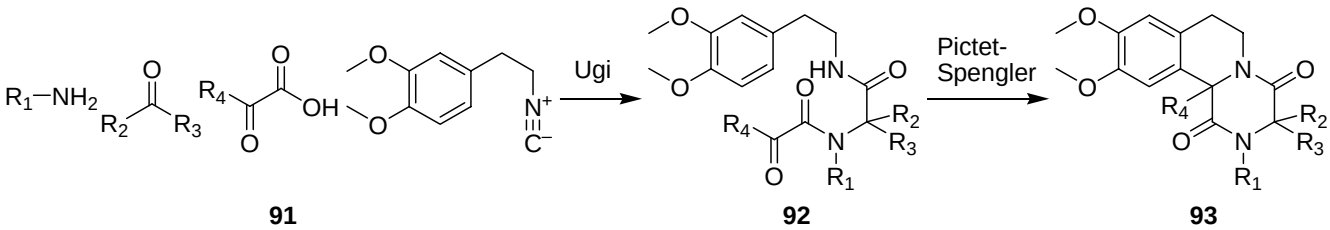
The El Kaim group reported a sequence of reactions starting with the Ugi transformation using propargyl amine **86** (Scheme 30) and chloroacetic acid **87**, followed by pyridine addition to the Ugi adduct **88**, Sonogashira coupling of alkyne **89**, cycloaddition and oxidation to obtain indolizines **90**.[43] In several examples the procedure could be simplified by combining the Ugi reaction with the pyridine addition step in a one pot procedure (rt overnight, then pyridine and heating 50 ºC) and performing the remaining three steps in another one pot sequence using ArI, $Pd(OAc)_2$, CuI and PPh_3 in a mixture of THF and *i*-Pr_2NH.



Scheme 30

Ugi/Pictet-Spengler

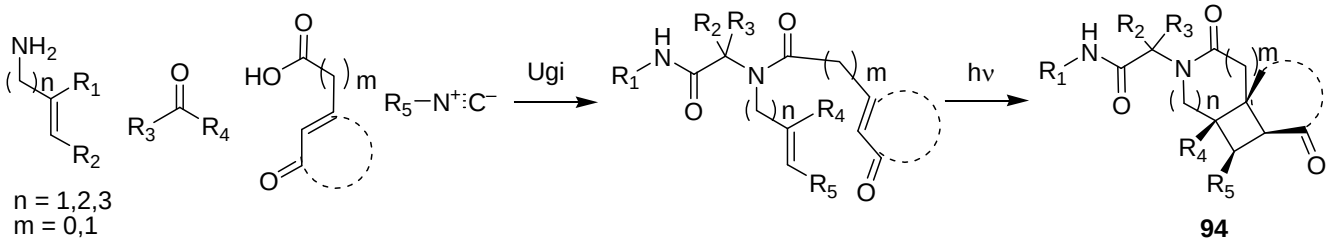
The same group reported on the combination of the Ugi reaction with a Pictet-Spengler cyclization.[44] The efficiency of the Ugi reaction was found to be dependent upon the fast formation of the imine intermediate prior to addition of the ketocarboxylic acid **91** (Scheme 31). The Ugi adducts **92** were not isolated but treated with TFA to provide the final products **93** in good overall yields (41-73%) as mixtures of diastereomers.



Scheme 31

Ugi/[2+2] ene-enone photocycloadditions

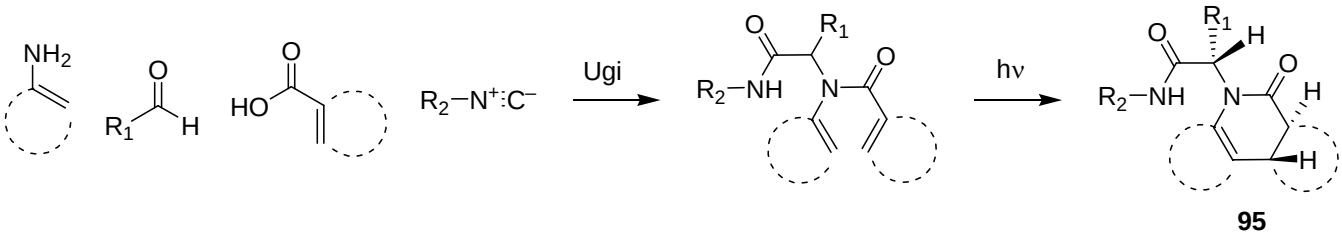
The Abbott group reported on the first combination of the Ugi reaction with [2+2] ene-enone photocycloadditions to provide complex three-dimensional structures with up to five stereocenters.[45] Typically the photocyclizations were high yielding (58-93%) and proceeded with high diastereoselectivity. In most cases only two diastereomeric azabicyclo octanones **94** (Scheme 32) were observed due to the stereocenter of the Ugi reaction. The relative stereochemistry of products **94** was determined by extensive NMR experiments and X-ray crystallography.



Scheme 32

Ugi/Acrylanilide [6π]-Photocyclizations

The same group has also reported on the combination of the Ugi reaction with an acrylanilide [6π]-photocyclization.[46] The photocyclization reactions provide dihydroquinolinones **95** (Scheme 33) in excellent yields (59-96%) with preferential trans-selectivity for the newly formed ring system. NMR experiments and X-ray crystallography were used to determine the diastereomeric ratio of products **95**.

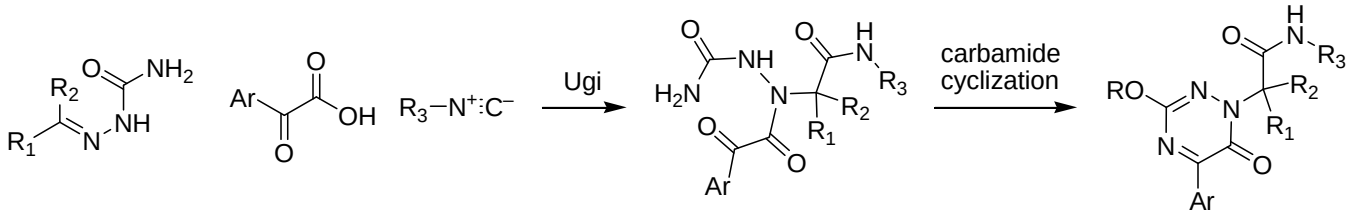


Scheme 33

Ugi/Carbamate Cyclization

Semicarbazones **96** underwent Ugi reactions in 46-73% yields to give compounds **97** (Scheme 34), which upon treatment with EtONa cyclized to provide cyclic dipeptidyl ureas **98** in 53-84% yields.[47]

Compounds **98** were further treated with diazomethane to get the *O*-methyl derivatives **99**. Compounds **98** and **99** both represent new classes of pseudopeptidic triazines.

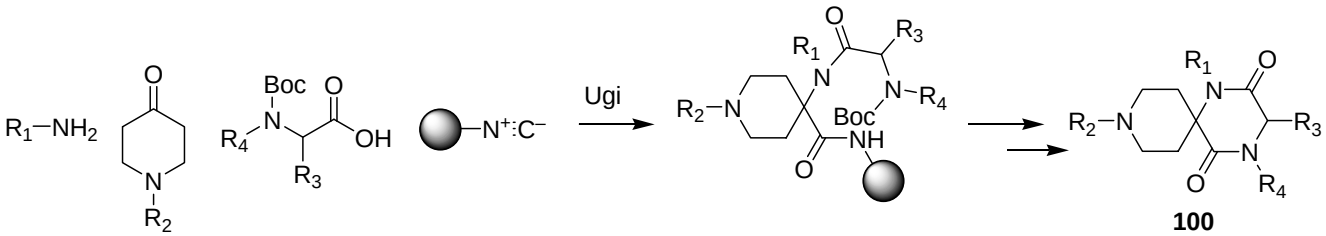


96 **97** **98** R = H **99** R = Me

Scheme 34

Ugi/de-Boc/cyclization

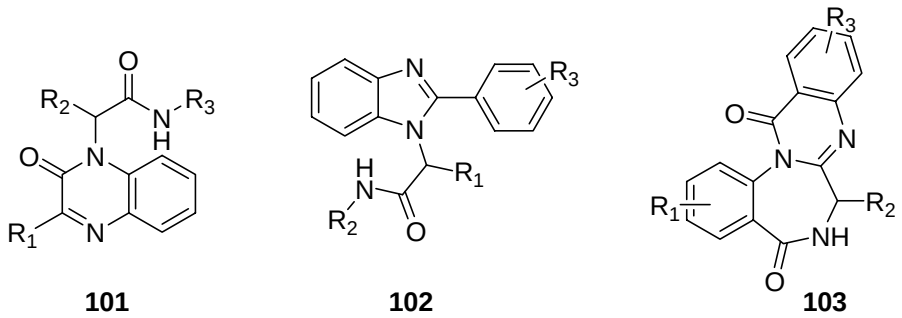
A library of spirodiketopiperazine analogs was synthesized on solid support by employing an Ugi/de-Boc/cyclization protocol (Scheme 35).[48] The final spirodiketopiperazines **100** were obtained after cleavage from the resin in 42-100% purities and 15-99% yields. After further optimization of the initial hits through library reiteration single digit nanomolar CCR5 antagonists were identified.



100

Scheme 35

Zhang[49] offered a summary of the applications of fluorous chemistry in UDC type reactions. In addition to the previously described[50] quinoxalinones **101** and benzimidazoles **102** (Figure 6)**,** benzodiazepine-quinazolinone scaffolds **103** were synthesized by employing F-Bn amines for the Ugi reaction and F-SPE for purifications. A comparison of fluorous versus regular chemistry techniques was also given.

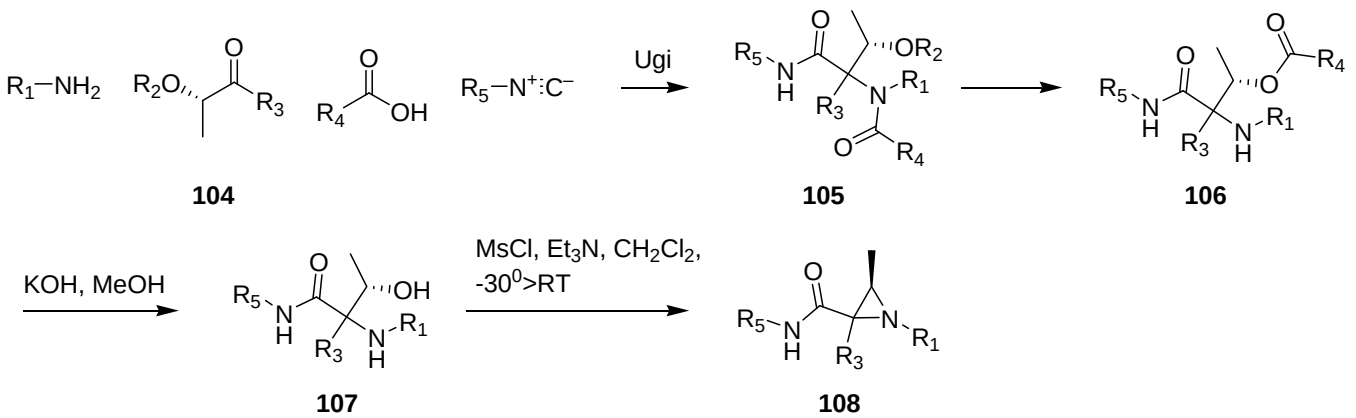


101 **102** **103**

Figure 6

Ugi/acylmigration/S_N2

Banfi, Riva and co-workers[51] have described a highly convergent entry to functionalized aziridines based on an Ugi/acylmigration/nucleophilic substitution sequence. Initially, a set of lactate derived carbonyl compounds **104** (Scheme 36) were subjected to Ugi-conditions to provide adducts **105** in good to excellent yields (30-93%). *O*-deprotection of compounds **105**, under a variety of conditions (depending on protecting group, BOM-H_2/Pd/C, TBDMS-CSA, MeOH and THP-HCO_2H, THF, H_2O) unexpectedly provided the rearranged products **106**. The authors suggested that the observed transacylation was due to release of steric strain as the acyl group migrated from the more to less hindered environment. Synthesis of the desired aziridines **108** was then accomplished by sequential removal of the acyl group (R_4CO) followed by exposure of the alcohol **107** to mesyl chloride. The structure of the aziridine was demonstrated by careful NMR studies, including NOE experiments.



Scheme 36

Ugi/Ugi

A new strategy coined MiBs (*m*ultiple *m*ulticomponent *m*acrocyclizations *i*ncluding *b*ifunctional *b*uilding ***b***locks) has been employed by the Wessjohann group to build macrocycles. Thus peptoid-based Cryptands, Cages and Cryptopanes,[52] Steroid-Biaryl ether hybrid mycrocycles,[53] Biaryl-Ether-Cyclopeptoid macrocycles[54] dye-modified and photoswitchable macrocycles[55] as well as combinatorial libraries of macrocycles[56] have been synthesized by using combinations of at least two bifunctional Ugi inputs.

CONCLUSIONS

The field of post-Ugi modifications continues to expand with additional reactions being explored in unique combinations. The number of potential outcomes appears to be endless if one considers all the possible Ugi variations combined with additional reactions. In addition to the combination of the Ugi reaction with frequently used in organic synthesis transformations, such as Pd catalysed transformations, cycloadditions and nucleophilic substitutions, we have also seen the use of radical and photochemical

reactions. Further exploration of underutilized transformations, efficient methodologies to affect the sequences, as well as unexpected products from future combinations, are expected to continuously energize this field of research. At the same time we expect to see a surge in the applications of these diversity and complexity generating reactions in other research areas such as materials sciences and pharmaceutical discovery.

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Dr. Stevan Djuric is responsible for the Medicinal Chemistry Technology and Structural Chemistry groups at Abbott Laboratories. Their current efforts are focused on new initiatives in the areas of high throughput synthesis and purification and the design and construction of novel compound libraries for lead targeting and identification. During his tenure at Abbott Laboratories, Dr Djuric has been a Project Leader for groups in the Immunoscience, Metabolic Disease, and Antiinfective areas. Several of these programs have advanced compounds into clinical development including Abbott's proprietary rapamycin analog, Zotarolimus, used for the Endeavour stent currently marketed in Europe. Dr Djuric

has over 125 scientific publications, and patents/applications pending. He has also given over 20 invited lectures at universities and national meetings. He is a member of the Editorial Advisory Board for the Journal of Medicinal Chemistry and, in addition, holds an Adjunct Professorship in the Department of Medicinal Chemistry at the University of Kansas.