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A Marriage of Convenience: Combining the Power of Isocyanide-Based Multicomponent Reactions with the Versatility of (Hetero)norbornene Chemistry

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Dedicated to Professor Giuseppe Guanti on the occasion of his retirement

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Isocyanide-based multicomponent reactions (I-MCRs) represent a milestone in combinatorial chemistry. Recently, efforts have been made to include I-MCRs in tandem or sequential pathways to synthesise more complex molecules, and the bicyclo[2.2.1]heptene (norbornene) moiety has been demonstrated to be a very versatile scaffold when employed to broaden the scope of the multicomponent approach, making it perfectly suited for diversity-oriented synthesis. In addition to this, the (hetero)norbornane/norbornene scaffold has been shown to influence the stereocontrol of the multicomponent condensation strongly, in some instances making this synthetic approach completely stereoselective. Finally, because of their intrinsic complexity, the resulting molecular entities can find many applications, from biology to polymer science. This review summarises the results obtained in this emerging field.

1. Introduction

The availability of step- and atom-economical processes capable of generating complexity and diversity in a limited number of synthetic operations is a crucial issue in the development of novel diversity-oriented methodologies.[1,2] In this context isocyanide-based multicomponent reactions (I-MCRs)[3,4] are undoubtedly a very efficient tool, able to assemble three or more diversity inputs in one-step fashion with minimal formation of waste. In addition, the introduction of straightforward post-transformations of the multicomponent adducts has increased the number of accessible molecular structures, mainly heterocyclic compounds. However, the need for building blocks with additional functional groups that will be inert during the multicomponent step rather limits the power of this approach. In addition, the typical poor stereoselectivity of I-MCRs complicates the whole scenario when more than one diastereoisomer is generated, and difficult purifications are often required in order to separate and isolate the final compounds.

The homonorbornane/ene or heteronorbornane/ene (oxa or aza) skeletons are privileged structures; they can indeed be found in natural products such as camphor, cantharidins, cineol and derivatives, terpenoids, carotenoids[5] or epibatidine,[6] as well as in other biologically relevant molecules such as prostaglandin analogues[5] and β-turn mimetics.[7] In addition, norbornenyl derivatives are highly valuable synthons (brilliantly defined as "molecular LEGO™"[5]) often employed, thanks to their unique reactivities and fixed geometries, as starting materials for the preparation of molecules with well defined stereo- and regiochemistry through elaboration of the bicyclic skeleton through particular reactions such as nucleophile[8] or metathesis[9] ring-opening reactions. One major limitation to the wider employment of these building blocks in diversity-oriented synthesis is the often not trivial decoration of the skeleton, especially when this has to be done in a combinatorial fashion.

A close analysis of the pros and cons of these two separate fields suggests that the use of a combination of I-MCRs with norbornene derivatives could overcome the weak points of both: the norbornene scaffold should increase the number of available post-transformations, and its rigid nature should enhance the stereoselectivity of the multicomponent process, whereas I-MCRs should facilitate the combinatorial decoration of the bicyclic moiety, leading to potentially biologically relevant entities. Methodologies perfectly suited for diversity-oriented synthesis could therefore be generated, confirming once more that "unity is strength" and that a marriage of convenience is not, in this case, to be despised.

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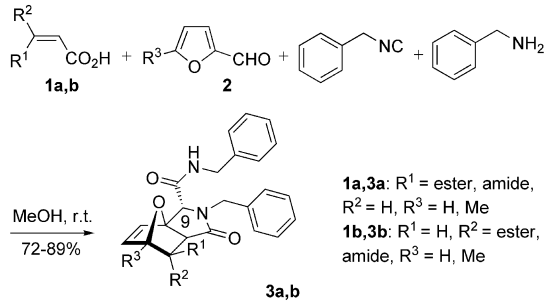
Despite the potential of this approach, the first attempt to combine the growing fields of multicomponent reactions and norbornene chemistry was made only ten years ago and so far not many actors have been taking part. This review is aimed at illustrating the progress made during the last decade, hopefully convincing other players to become part of the game.

From a general point of view, two distinct approaches to combining norbornene chemistry and I-MCRs can be envisaged: 1) the norbornenyl skeleton can be generated as a consequence of the multicomponent reaction, or 2) an appropriately functionalised norbornenyl derivative can be used as a building block for the I-MCR. Both these methodologies are discussed in detail in the following three sections, whereas Section 5 is devoted to illustrating the post-condensation elaborations that can follow these approaches.

2. I-MCRs with in-situ Generation of the Norbornene Skeleton

The idea of combining the advantages of I-MCRs with those of norbornene compounds was pioneered by Paulvannan,[10] who in 1999 reported the first synthesis of an Ugi-derived oxanorbornenyl derivative by coupling an I-MCR with an intramolecular Diels–Alder reaction of furan (IMDAF). This was achieved through the use of maleic or fumaric acid derivatives **1a** or **1b** and furaldehydes **2** as building blocks for the multicomponent reaction (Scheme 1). Interestingly, despite the formation of five new stereocentres, one diastereoisomer of **3** always predominated (isomer ratio ranging from 83:17 to 93:7). This could partly be explained by the fact that when the C-9 stereocentre generated during the Ugi step is incorporated into the final tricyclic system, it preferentially directs the attack of the diene onto one of the two diastereotopic faces of the dienophile.



Scheme 1. Four-component Ugi reaction with subsequent intramolecular Diels–Alder cycloaddition with furaldehydes as diene source.

As would be expected, when furaldehyde was substituted by furfurylamine (**4**) the C-2′ stereocentre, being outside the tricyclic system, is no longer able to direct the attack of the diene efficiently, and isomers **5** were isolated in a nearly 1:1 ratio (Scheme 2).

This approach was exploited one year later by Schreiber[11] to construct complex polycyclic molecules through further elaborations of the Ugi/Diels–Alder adducts. The same strategy was also applied to solid-phase synthesis by Oikawa.[12] Wright[13] also reported a similar approach that made use of the propiolic acid derivatives **6** (Scheme 3); although the Ugi intermediates were found to be slowly converted into the final cycloadducts **7** spontaneously at room temp., the IMDAFs were conveniently performed in toluene at 200 °C in sealed tubes. The reactions were highly diastereoselective, with less than 10% of any other isomer being detectable in the crude products. Moreover, the absolute

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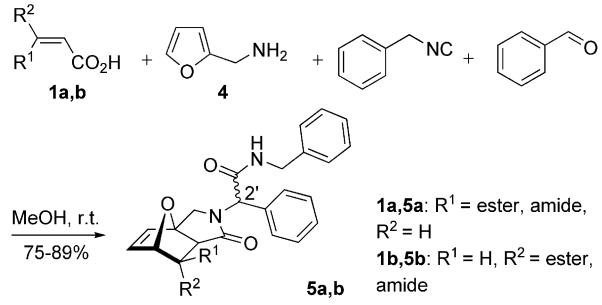
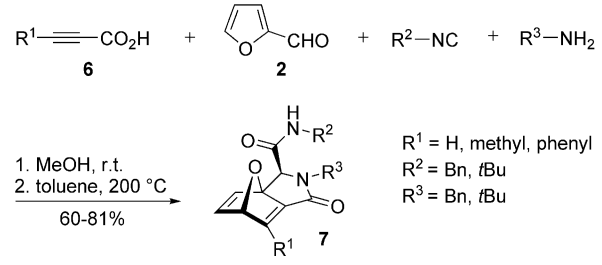
Luca Banfi graduated in Chemistry in 1981 from the University of Milano (Prof. Carlo Scolastico), and then in 1983 accepted a position as assistant professor at the University of Genova, where he joined the group of Prof. Giuseppe Guanti. He became associate professor in 1998 and full professor of organic chemistry in 2000. In 1986–1987 Luca Banfi spent a sabbatical in the U.S.A. working in the group of Prof. William R. Roush. During his scientific career, Luca Banfi has conducted studies in the field of organic synthesis, focusing especially on asymmetric synthesis, the synthesis of biologically active substances, multicomponent reactions and "diversity-oriented synthesis".

Renata Riva graduated in Chemistry at the University of Milan in 1982 where she obtained her Ph.D. working in the field of indole alkaloids under the supervision of Prof. Bruno Danieli and, in part, Prof. Giuseppe Guanti (University of Genova). After a post-doctoral period in the U.S.A. with Prof. William R. Roush (M.I.T. and Indiana University), she worked as a high school chemistry teacher from 1987 until 1992. She was then appointed assistant professor in organic chemistry at the University of Genova in 1992 and became associate professor in 2000. Her scientific interest are mainly focussed on the synthesis of biological active compounds through the diversity-oriented approach, including asymmetric methodologies (employing enzymes or organocatalysts) and multicomponent reactions.



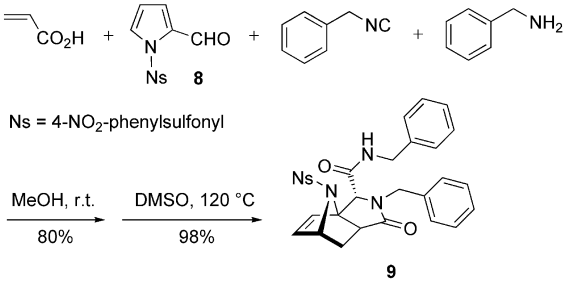
Scheme 2. Four-component Ugi reaction with subsequent intramolecular Diels–Alder cycloaddition with furfurylamine as diene source.

configuration of the main isomer of **7** (R^1 = Me, R^2 = R^3 = *t*Bu; see ref.[13]) was determined by X-ray diffraction. Curiously, the configuration of the Ugi-derived stereocentre (relative to the four stereocentres of the oxanorbornene ring) was the opposite of that in **3**.



Scheme 3. Four-component Ugi reactions and subsequent intramolecular Diels–Alder cycloadditions with propiolic acids as dienophile sources.

The number of possible applications of this strategy has yet to be exhausted, as demonstrated by recent papers published on this subject.[14–18] However, because of the poor reactivities of pyrrole derivatives in Diels–Alder reactions, this approach is so far essentially limited to the synthesis of oxanorbornene compounds, although one exception is represented by Paulvannan's report[19] in which the highly reactive *N*-nosylated pyrrole-2-carbaldehyde **8** is employed with formation of the desired cycloadduct **9** in two steps in a completely diastereoselective manner (Scheme 4). The



Scheme 4. Four-component Ugi reaction with subsequent intramolecular Diels–Alder cycloaddition for the assembly of azanorbornene derivatives.

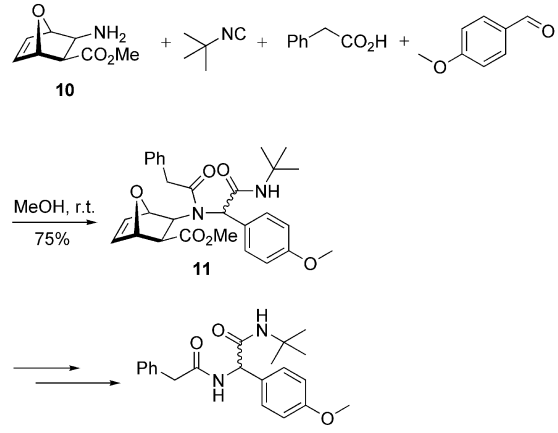
relative configuration of the Ugi-derived stereocentre, also determined in this case by X-ray crystallography, again parallels the results obtained for **3**.

Andreana[20] recently also reported the first example of a tandem Ugi/Diels–Alder process starting with 2-thiophenecarbaldehyde to give a thianorbornene lactam in a 10:1 diastereomeric ratio.

3. Norbornane/ene Derivatives as Monofunctional Building Blocks in I-MCRs

The generation of the oxa- or azanorbornene skeleton in situ after/during a multicomponent condensation is a classic example of how easily complexity can be generated by coupling I-MCRs with post-condensation transformations. However, this approach is rather limited in scope, due to the restricted number of dienes and dienophiles that can be successfully employed.

In 2002 we started to explore an alternative approach based on the employment in I-MCRs of building blocks already containing the norbornenyl structure. We thus prepared compound **10** (Scheme 5) with the purpose of using it as a chiral auxiliary in analogy with the amino sugars developed by Kunz[21] and Ugi:[22] its removal under very mild conditions by means of a retro-Diels–Alder reaction as the key step (see Section 5 for further details) would have been a significant advantage in comparison with the existing auxiliaries. The results, however, were disappointingly poor in terms of selectivity, because no or little inducing power was observed and the mixture of the two possible epimers **11** was isolated in nearly 1:1 ratio.



Scheme 5. An oxanorbornenylamino ester as a chiral auxiliary for a four-component Ugi reaction.

A few attempts based on the norbornenyl isocyanide **12** (Figure 1) were also carried out but, unsurprisingly (chiral isocyanides are known to have no or little inducing power, at least in Ugi reactions), equally poor results were obtained. To the best of our knowledge there are only two other reports of I-MCRs in which norbornene derivatives have been employed as monofunctional inputs, one involving the use of the camphor-derived isocyanide **13**[23] (Figure 1) and another involving aldehyde **14**.[24] Interestingly,

13 can be very efficiently employed as a chiral auxiliary in some Passerini reactions, although in Ugi condensations much lower diastereoselectivity is observed. On the other hand, the aldehyde **14**, known to give excellent asymmetric induction in reactions with C-nucleophiles other than isocyanides, gave only low or moderate diastereoisomeric ratios (up to 2:1) when employed in I-MCRs.

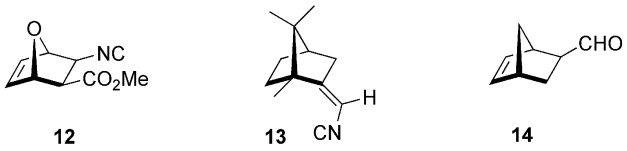
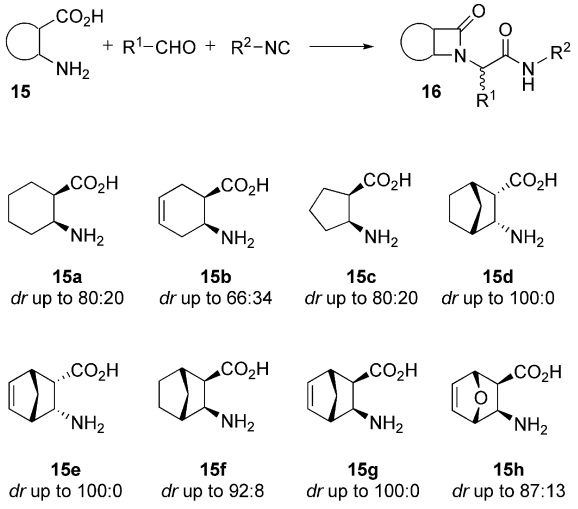


Figure 1. Different norbornane-derived building blocks employed in four-component Ugi reactions.

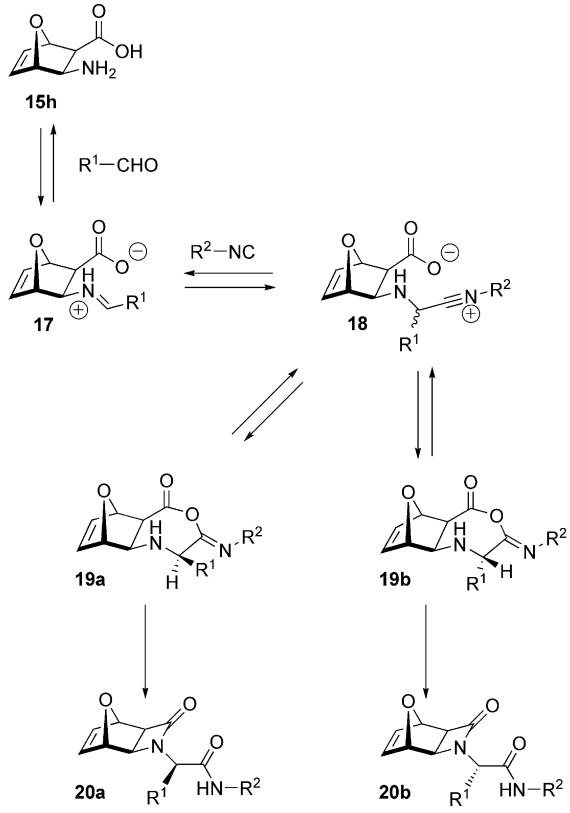
4. Norbornane/ene Amino Acids as Bifunctional Building Blocks in I-MCRs

More success has been met with use of bifunctional norbornane/ene amino acids: Fülöp[25,26] reported Ugi reactions with various cyclic β-amino acids **15**, including norbornane/ene derivatives, for the assembly of the bi- and tricyclic β-lactam derivatives **16** by a 4-centre-3-component Ugi reaction (U-4C-3CR) mechanism (Scheme 6).



Scheme 6. Different mono- and bicyclic amino acids employed in 4-centre-3-component Ugi reactions.

Although the use of β-amino acids to prepare β-lactams had already been reported by Ugi in 1961,[27] the interesting feature of these reports is that good stereoselectivities were observed, especially when the bicyclic systems **15d**–**h** were employed. The reason for the unusual stereoselectivity probably lies in the assumed particular mechanism of this reaction (U-4C-3CR), as exemplified by compound **15h** in Scheme 7: after the iminium ion formation between the aldehyde and the bicyclic amino acid has taken place, interaction of **17** with the isocyanide generates, via **18**, a seven-membered ring intermediate **19** fused with the norbornanyl skeleton. Because of the complexity of the events, not yet fully clarified, that take place during the Ugi reaction it is difficult to argue whether the observed stereoselectivity (in favour of **20a**) originates from the different stabilities of the two diastereomeric seven-membered ring intermediates **19a** and **19b**, in thermodynamical equilibrium through **18**, or from faster removal of **19a** from the equilibrium. Compound **19a** could in fact more easily undergo a Mumm's rearrangement, evolving to the final β-lactam **20a**. As a matter of fact, however, the stereoselectivity is lower when the linear or monocyclic β-amino acids **15a**–**c** are employed, confirming the importance of a rigid system.

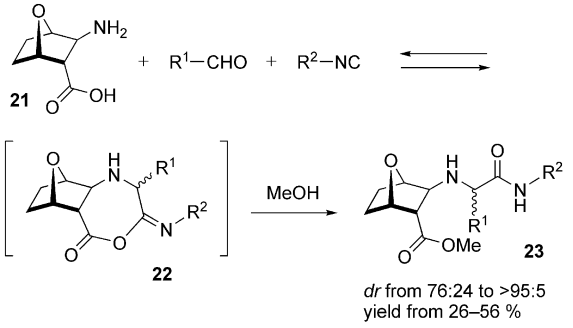


Scheme 7. Mechanism of the 4-centre-3-component Ugi reaction with an oxanorbornenylamino acid.

Generalisation is nevertheless difficult and the final outcome strongly depends on the particular aldehyde and isocyanide employed in the multicomponent step. Aliphatic carbonyl inputs give lower stereoselectivities than aromatic aldehydes, for example. Fülöp[28] has recently also studied the effect of the solvent in reactions of this kind: he has reported a comparison between the reaction behaviour of **15h** in methanol and in water, although finding only modest differences in stereoselectivity. Moreover, no general trend could be traced: stereoselectivity was in some cases higher in water (*dr* up to 100:0), whereas in others it was higher in methanol.

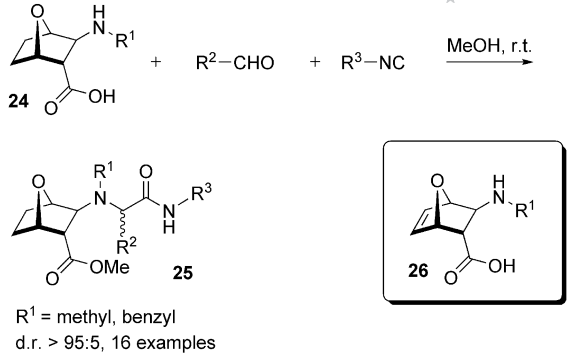
A very different outcome was observed when the *trans* derivative **21** (Scheme 8) was employed instead. In this case the intermediate **22**, generated by interaction with the aldehyde and the isocyanide, cannot be transformed into the corresponding *trans*-fused β-lactam because of steric bias,

and an alternative mechanism operates, accounting for the formation of compound **23**. A 5-centre-4-component Ugi reaction (U-5C-4CR),[29] which is typical when α-amino acids are employed, takes place with the formation of the methyl ester **23** through displacement of **22** by the methanol used as the solvent. The results were promising in that, at least in few cases, very high diastereoselectivities were observed. However, levels of conversion were disappointingly low.[30]



Scheme 8. The 5-centre-4-component Ugi reaction that occurs when a *trans*-oxanorbornanylamino acid is employed.

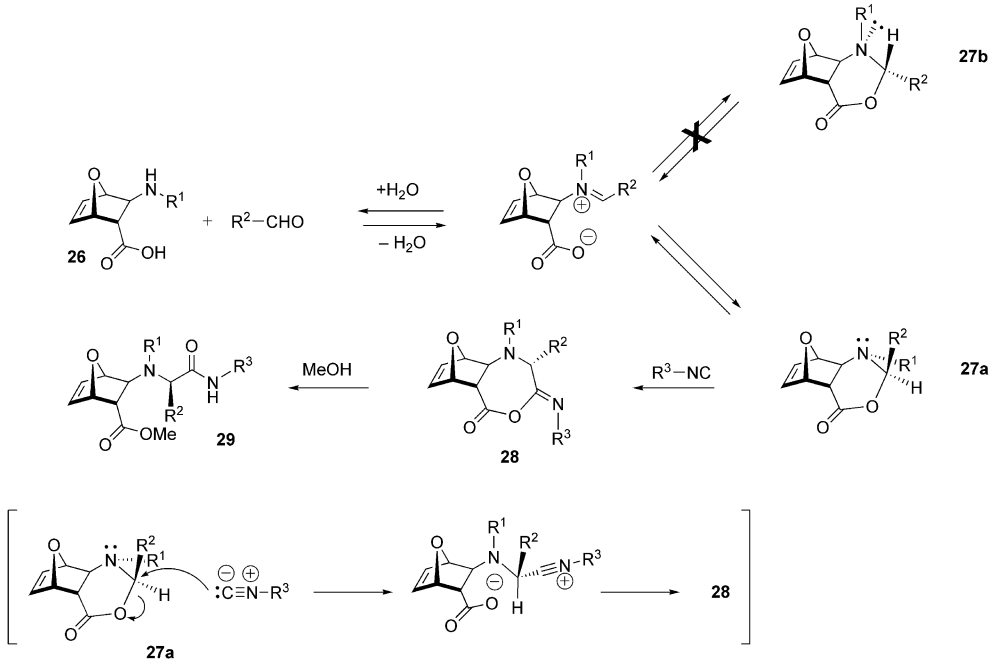
Because derivative **21** behaves as an α-amino acid, it was speculated that the oxanorbornanylamino acid **24** ($R^1 \neq H$, Scheme 9), featuring a secondary amine, might react similarly to proline, which is known to follow the U-5C-4CR mechanism smoothly and to give good to very good stereoselectivities.[31] This was indeed the case, and Ugi reactions of **24** with several different aldehydes and isocyanides always furnished compounds **25** as single diastereoisomers with good to very good levels of conversion,[30] outclassing the selectivity of proline.



Scheme 9. The 5-centre-4-component Ugi reaction that occurs when a *N*-alkylated *trans*-oxanorbornanylamino acid is employed.

The oxanorbornene derivative **26** (Scheme 9) also behaved in the same manner. Although its synthesis was more complex,[32] the additional value of the double bond will become evident below.

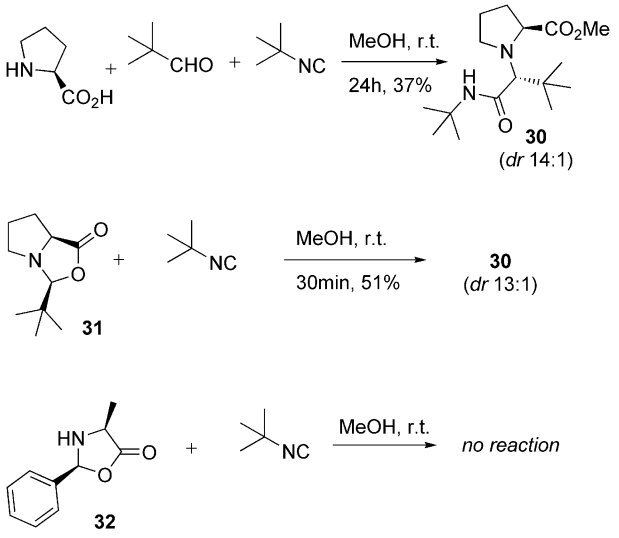
The introduction of alkyl substituents onto the nitrogen atoms in amino acids **24** or **26** cannot explain the dramatic differences in reactivity and stereoselectivity observed between them and **21** on a purely steric basis, and so a different mechanism was postulated. According to our hypothesis the adduct between a norbornenyl amino acid **26** and an aldehyde exists preferentially in the cyclic form **27**, and this is the species that rapidly reacts with the isocyanide to afford the usual seven-membered ring intermediate **28** (Scheme 10). Stereoselectivity might therefore be enhanced by the constrained cyclic nature of **27** and be governed by the preferential formation of **27a** over **27b**. The isocyanide would then attack intermediate **27** and subsequently form the seven-membered ring intermediate **28** by interaction



Scheme 10. Postulated mechanism for the 5-centre-4-component Ugi reaction that occurs when a *N*-alkylated *trans*-oxanorbornenylamino acid is employed.

with the carboxylate; as a consequence, inversion of the configuration at the stereocentre bearing the R^2 substituent would occur. Indeed, according to this hypothesis, compound **29** (determination of its absolute configuration is discussed in Section 5) originates from diastereoisomer **27a**, which according to MMFF94 calculations is more stable than **27b** by about 4 kcal mol^{-1} when both R^1 and R^2 are methyl groups.

We never managed to isolate an intermediate **27**, but some analogies with α-amino acids corroborated our hypothesis. In parallel studies (Scheme 11) we first treated proline with pivaloyl aldehyde and *tert*-butyl isocyanide in methanol and after 24 h we isolated the desired adduct **30** (37% yield) as a 14:1 diastereomeric mixture. In a second experiment we prepared the adduct **31** by the stereoselective procedure described by Seebach[33] and treated it with *tert*-butyl isocyanide in methanol: after just 30 min we isolated adduct **30** (51% yield) with a very similar diastereomeric ratio (13:1, the major isomer being the same in both cases). A different outcome was observed with alanine in place of proline. The isolated compound **32**, prepared from alanine by a known procedure,[34] gave only hydrolysed products upon treatment with *tert*-butyl isocyanide, whereas on mixing benzaldehyde, alanine and the same isocyanide in methanol the expected U-5C-4CR product was regularly obtained.



Scheme 11. Evidence corroborating the hypothesis of the formation of a cyclic adduct after condensation of a *N*-alkylated amino acid with a carbonyl derivative.

An added benefit of using secondary amines such as those of general formula **26** is the potential to introduce a third diversity input, represented by the R^1 group, in the synthetic sequence. During the last five years different compounds (with R^1 = methyl, allyl, propargyl, benzyl) have been prepared and used in I-MCRs. Apart from in a very few cases, the reactions always proceeded with complete stereoselectivity regardless of the aldehyde and isocyanide employed. However, this behaviour seems to be specific to this class of bicyclic β-amino acids; erratic results were obtained when norbornanylamino acids structurally different from **25** were employed instead. The oxa- and azanorbornanyl derivatives **33**,[30] **34**[35] and **35**[36] (Figure 2) were designed and synthesised by the same principle of maintaining a carboxylic group and a secondary amine in the β-position, but although reactivity was generally acceptable, allowing for recovery of final products in good yields, the stereoselectivity was satisfactory only in a limited number of cases. Interestingly, a strong dependence on the bulkiness of the isocyanide was observed, rather contradicting the mechanism hypothesised for compound **25**, in which the structure of the isocyanide was expected to have no influence on the stereoselectivity.

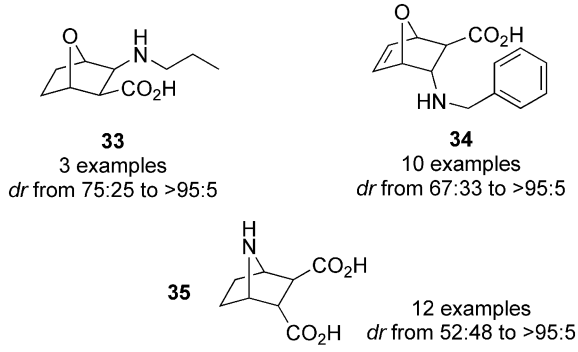
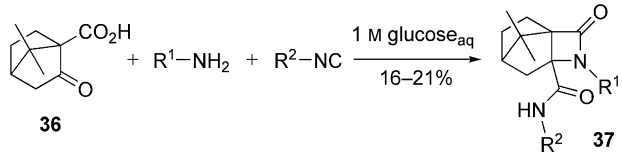


Figure 2. Various *N*-alkylated norbornanyl/norbornenylamino acids employed in 5-centre-4-component Ugi reactions.

Additional studies to determine whether factors such as temperature, solvent, concentration or presence of additives can influence the stereoselectivities of these reactions are currently being carried out in our laboratories.

Although most of the work in this area has been focussed on bicyclic amino acids, it is also worth mentioning Pirrung's example[37] in which the camphor carboxylate **36** (Scheme 12) is employed to generate the tricyclic β-lactams **37** through an intramolecular Ugi reaction with isocyanides and amines in water. Unfortunately no details of stereoselectivity are given, although it is reasonable that only *exo*-fused β-lactams are isolated.

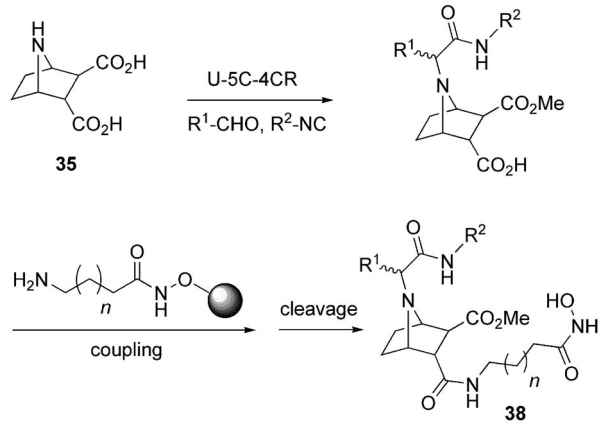


Scheme 12. An example of an Ugi reaction with a camphor-derived oxo acid.

5. Applications of the Ugi-Derived Norbornane/Norbornene Derivatives

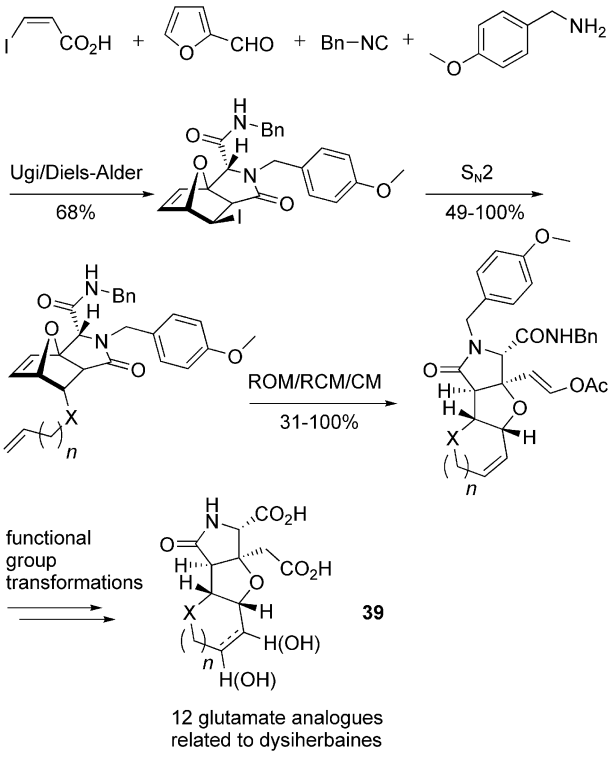
As anticipated in the Introduction, the importance of the approach described in this review is strictly related to the properties of the norbornene scaffold, which can be used as a privileged structure without further manipulations or can be transformed by exploitation of its particular reactivity.

The azabicyclic derivative **35** described above, for example, has been used to build, on solid-phase, a small library of hydroxamates **38** (Scheme 13) through the exploitation of the acid functionality left untouched by the multicomponent step. These compounds have been evaluated as HDAC (histone deacetylase) inhibitors.[38]



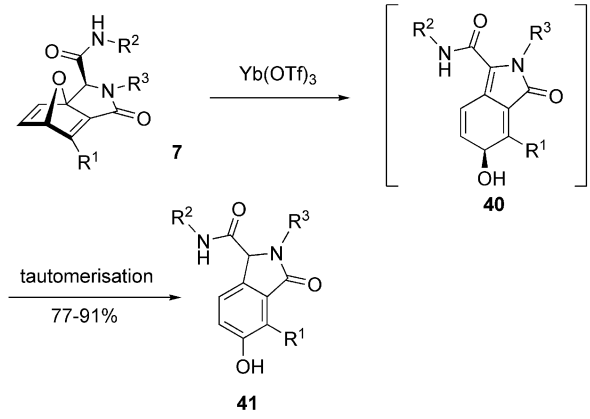
Scheme 13. Solid-phase synthesis of a Ugi-derived library of azanorbornanyl hydroxamic acids.

Oikawa, using an approach similar to that pioneered by Schreiber, has coupled the Ugi reaction/Diels–Alder cycloaddition process with a regioselective domino metathesis leading to the biologically active glutamate analogues **39** (Scheme 14).[16]



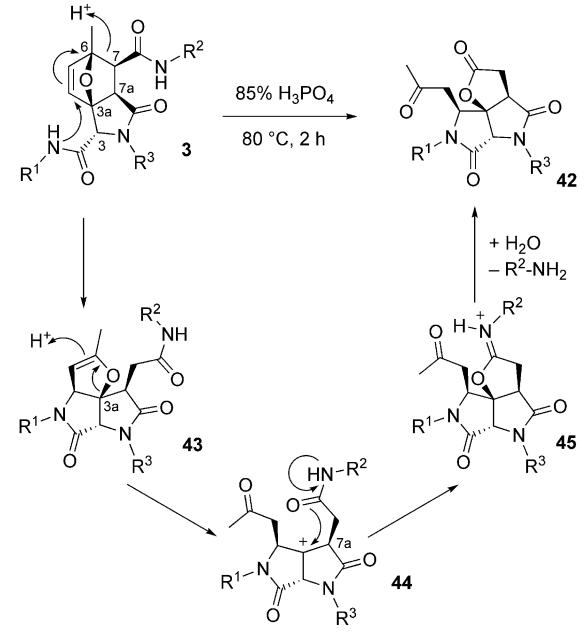
Scheme 14. Synthesis of glutamate analogues by elaboration of the adduct derived from a tandem Ugi/Diels–Alder reaction sequence.

Moreover, Wright[13] has reported the conversion of oxabicyclo[2.2.1]heptadienes of general formula **7**, described in Section 1, into the isoindolinones **41** (Scheme 15) through Lewis-acid-promoted opening of the oxa-bridge and elimination to afford the unsaturated amides **40**, which spontaneously tautomerise to the phenols **41**.



Scheme 15. Synthesis of indolinones from an Ugi/Diels–Alder adduct.

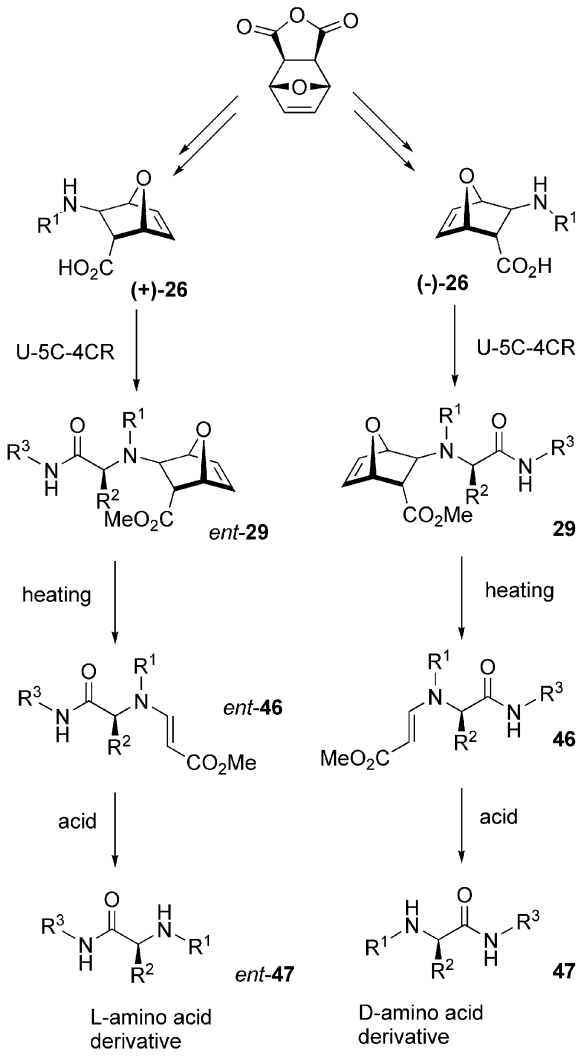
On the other hand, Ivachtchenko[15] reported that the similar substrates **3** rearrange by a complex mechanism to afford the natural product-like tricyclic bis-lactams **42** when treated with 85% H_3PO_4 (Scheme 16). The authors propose a tentative mechanism involving the formation, via C^3-carboxamide-assisted heterolytic cleavage of the C^6–C^7 bond of **3**, of the transient cyclic enol ethers **43**. Acid-promoted opening of **43** (to liberate the 2-oxopropyl side chain) then generates the C^{3a} tertiary carbocations **44**, which are intercepted by the proximal C^{7a} carboxamide. Finally, hydrolysis of the protonated iminolactams **45** leads to the loss of R^2–NH_2 and to the formation of lactones **42**.



Scheme 16. Rearrangement of an Ugi/Diels–Alder adduct mediated by strong acid, with postulated mechanism.

In the area of polymer sciences, Wright[24] has employed norbornenyl Ugi adducts derived from **14** (Figure 1) in ring-opening metathesis polymerisation (ROMP) reactions to prepare functional polymers reminiscent of polypeptides.

We have recently started to investigate the chemical properties of the oxanorbornene derivatives **26** (Scheme 9), intrigued not only by the fact that the multicomponent step proceeds in a completely stereoselective fashion, but also because the resulting bicyclic adducts can undergo various different post-condensation transformations independently of one another, making these compounds real pluripotent substrates in diversity-oriented synthesis. In analogy with the approach illustrated in Section 3, we first investigated the use of the bicycles **26** as chiral auxiliaries and found that the optically pure α-aminoamides **47** (Scheme 17) could be conveniently obtained by a simple two-step procedure involving retro-Diels–Alder reactions of Ugi adducts **29** with loss of furan and acid-mediated cleavage of the resulting enamines **46**.[32]



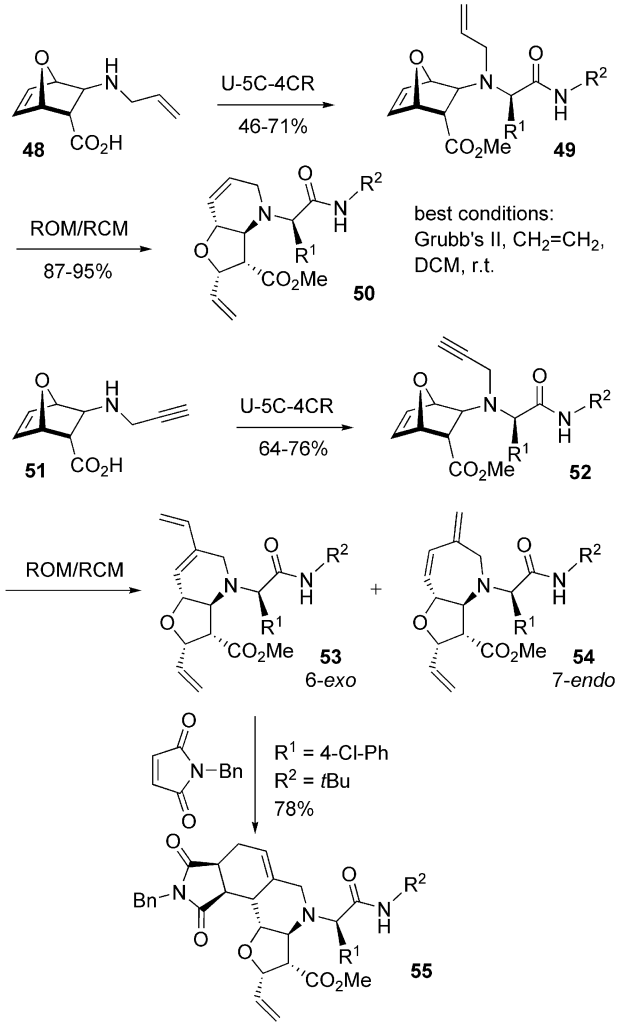
Scheme 17. Ugi-mediated synthesis of enantiomerically pure α-amino acid derivatives through employment of an oxanorbornenyl chiral auxiliary.

Both steps proceeded in a very straightforward manner and produced only volatile secondary products, thus allowing for the isolation of the final compounds without any need for additional purification procedures. In addition, depending on the structure of the aldehyde (= R^2) and on which enantiomer of **26** had been employed during the multicomponent step, both D- and L-series natural and unnatural amino acid derivatives could be obtained with the same ease. Finally, determination of the signs of the optical rotatory powers of **47** or *ent*-**47** and comparison with those of real samples allowed identification of the absolute configuration in compounds **29**, thus confirming that they originated from the more stable intermediates **27a** (Section 4).

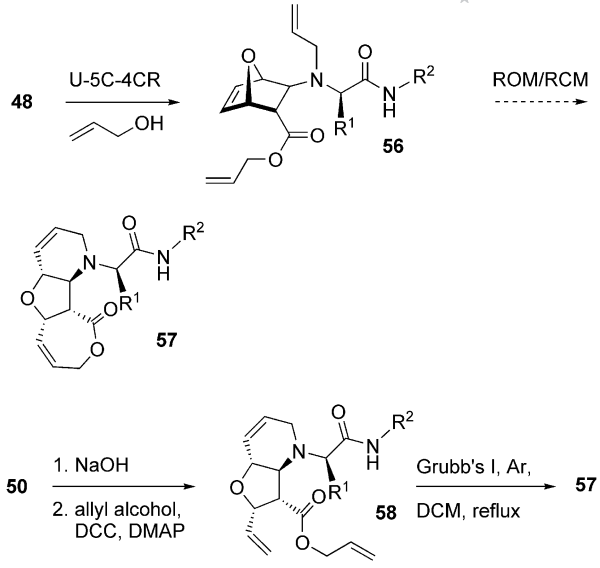
Although we have not yet investigated this potential application, the optically pure enamines **46**, derived from the retro-cycloaddition and not easily obtainable by other routes, are reactive substrates that might, for example, undergo Michael additions or dipolar cycloadditions to generate novel peptidomimetic compounds in an enantioselective manner.

The power of ring-opening/ring-closing metathesis (ROM/RCM) processes to produce new heterobicyclic systems from oxa- and azanorbornene derivatives with complete control of stereochemistry has recently been illustrated by Plumet in a comprehensive review.[9] With the aim of investigating whether norbornene/Ugi adducts were potential substrates for this kind of synthetic approach, we prepared the bicyclic derivatives **48** and **51** (Scheme 18) and employed them in various Ugi reactions with aldehydes and isocyanides.[39] The resulting adducts **49** and **52** were subjected to ROM/RCM reactions under various sets of conditions, it being found that an ethylene atmosphere was beneficial for both ene/ene and ene/yne metathesis. Interestingly, the second-generation Grubbs' catalyst gave better yields, but in the case of ene/yne metathesis the first-generation catalyst was essential for providing the 6-*exo* adducts **53** selectively. These adducts could be further elaborated through Diels–Alder reactions with activated dienophiles, with exploitation of the diene system generated in the metathesis reaction. Once more the cycloadditions proceeded in completely stereoselective fashion and compounds **55**, despite their eight stereocentres, were obtained in enantiomerically pure form as single diastereoisomers (Scheme 18).

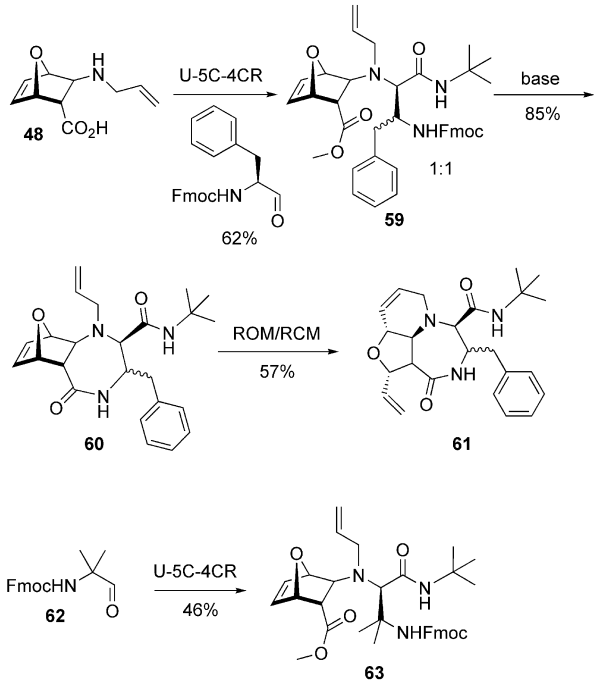
The presence, in structures **50**, of additional terminal double bonds deriving from the norbornene scaffold prompted us also to investigate the possibility of a double ROM/RCM process through the incorporation of an additional double bond in the ester moiety. The allyl esters **56** (Scheme 19) could be conveniently prepared by Ugi condensation in allyl alcohol, thus making the solvent a real diversity input of the multicomponent reaction. Unfortunately all attempts to perform double ROM/RCM processes on compounds **56** failed, the reasons becoming clear when we investigated RCM of the allyl esters **58** in more detail: these reactions proceeded well only with the first-generation Grubbs' catalyst under argon in dichloromethane at reflux, conditions that had previously been found to be deleterious for the ROM process. Compounds **57** could be assembled



Scheme 18. Sequential ring-opening and ring-closing metathesis reactions with Ugi-derived oxanorbornenyl compounds.



Scheme 19. Studies directed towards the synthesis of a double ring-closing metathesis adduct.



Scheme 20. 5-Centre-4-component Ugi reactions with carbonyl derivatives bearing additional amino groups.

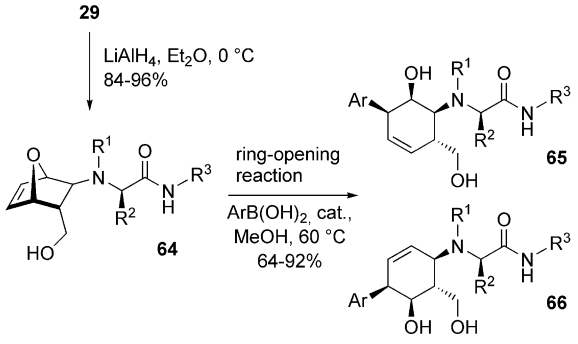
anyway in three steps from **50**, but the synthetic pathway was not as appealing as the one-pot reaction from **56** and was therefore not pursued further.

Whereas the transformations illustrated above affected the oxanorbornenyl skeleton, the use of α-aminoaldehydes as carbonyl components in the Ugi reaction led to the spontaneous formation of the oxabicyclo-fused diazepinone **60** (Scheme 20) upon Fmoc removal from **59**. However, when D- or L-*N*-Fmoc-phenylalaninal were used in the Ugi condensation, two distinct diastereoisomers were obtained in nearly 1:1 ratio. Our experience in the use of α-aminoaldehydes in multicomponent reactions suggested that racemisation during the formation of the immonium ion was more likely than poor selectivity of the U-5C-4CR; indeed, when the aldehyde **62**, lacking α-hydrogen atoms, was employed instead, only the single isomer **63** was isolated.

Compound **60** could be further elaborated by coupling the lactam formation with a ROM/RCM step, leading to the tricycle **61**. This strategy confirmed that distinct post-condensation transformations on these norbornene derivatives could be performed alternatively or in combination, increasing the variety of accessible structures (Scheme 20).

Very recently we have introduced an additional transformation exploiting metal-catalysed nucleophile-mediated ring-opening,[40] by methods developed mainly by Lautens.[8] In this particular case the labilities of the Ugi adducts **29** to heating (because of retro-Diels–Alder processes) were a major drawback, because these reactions are usually performed at high temperatures when poorly reactive sub-

strates are employed. In order to circumvent this problem, the Ugi adducts **29** were first reduced to the corresponding primary alcohols **64** (Scheme 21), and only at this stage were ring-opening reactions with various aryl boronic acids performed. Because of the asymmetric natures of the Ugi adducts, two distinct regioisomers could be generated, depending on the particular C–O bond broken during the S_N2' process and this was indeed observed in most cases; however, the pairs of regioisomeric cyclohexenols **65** and **66** were obtained with complete control of all the stereocentres as a result of *exo* attack of the nucleophile on the oxabicyclic unit. The potential to direct the reaction towards the selective formation of single regioisomers has not yet been investigated, although in principle the nature of the ligands of the metal catalyst could have an important effect. This strategy served in the discovery of a novel class of inhibitors for the BcL-xL protein,[41] and studies directed towards increasing the potencies of such compounds through the addition of additional appendages are underway.



Scheme 21. Transition-metal-catalysed ring-opening of reduced Ugi adducts.

6. Conclusions

During the last two decades multicomponent reactions have attracted many scientists and found many applications both in target-oriented synthesis[42] and in combinatorial chemistry.[43] Efforts to combine multicomponent reactions with post-condensation transformations have been made in recent years, mainly to generate heterocyclic compounds with straightforward step-economical procedures.[44,45] The number of such methodologies is increasing day by day, together with the variety of molecular scaffolds achievable. Very often, however, a single post-condensation transformation is associated with a single multicomponent-derived scaffold, thus again falling in the field of combinatorial chemistry, in which the appendages are varied but the skeleton is kept fixed.

One possible strategy by which to overcome this limitation and thus to allow multicomponent reactions truly to fit into diversity-oriented synthesis[46] is to employ substrates, called pluripotent, that are able to undergo a number of orthogonal transformations. Norbornenyl compounds can

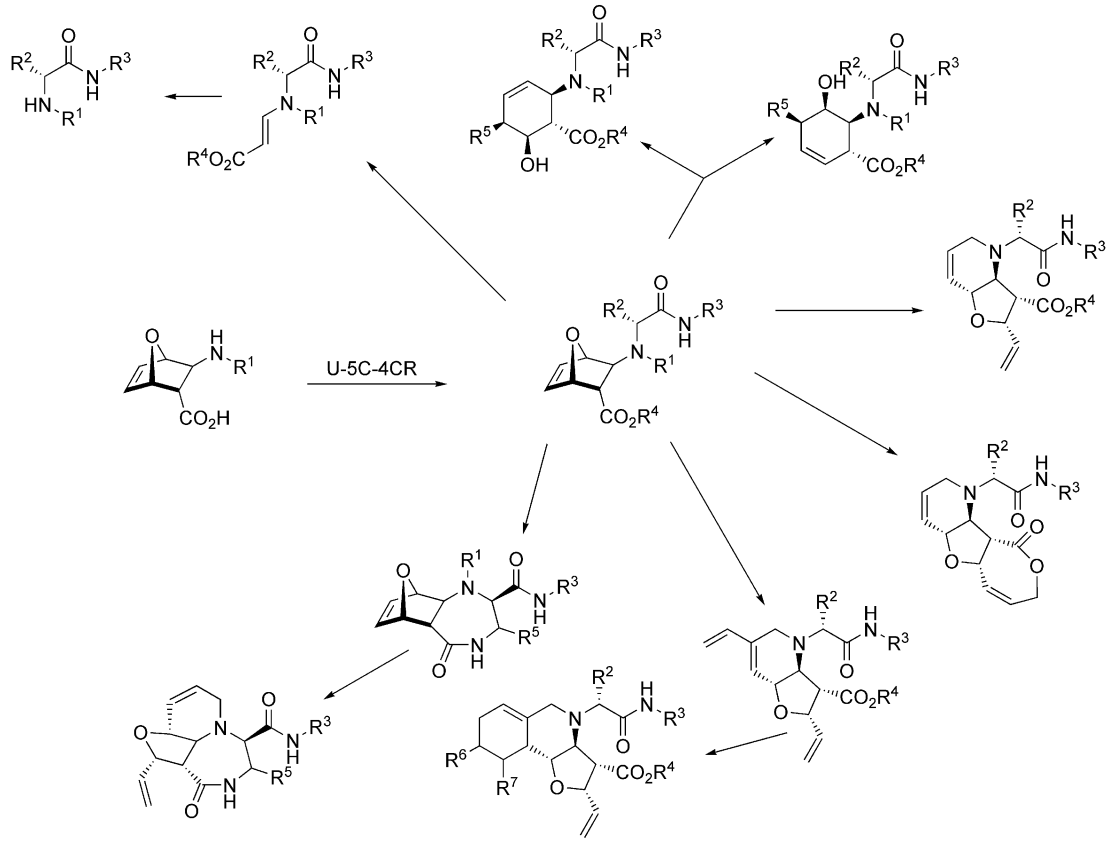


Figure 3. A DOS approach employing Ugi-derived oxanorbornene derivatives as pluripotent substrates.

be conveniently employed in this way, as in the examples summarised in Figure 3, but many other pluripotent substrates and many other transformations are still possible and the challenge to the diversity-oriented synthetic chemist will be to discover and to apply them. It is possible to argue about the significance and utility of such an approach and at the moment no conclusive answer can be given, although some pros can already be seen in the particular cases illustrated in this review: 1) most of the structures illustrated in Figure 3 possess features already displayed by natural products and therefore have a good chance of interacting with biological targets, because this is what natural products are for, 2) biological activities have already been demonstrated for some compounds,[41] by application of a multidisciplinary approach combining synthetic chemistry, molecular docking and NMR screening, and 3) according to a recent study,[47] drug candidates often lack basic nitrogens, resulting in failures at later stages of the drug validation, from which point of view the presence of tertiary amines in all the compounds shown in Figure 3 is indeed an advantage not often achievable when classic I-MCRs are employed.

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