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Heterocycles as Key Substrates in Multicomponent Reactions: The Fast Lane towards Molecular Complexity

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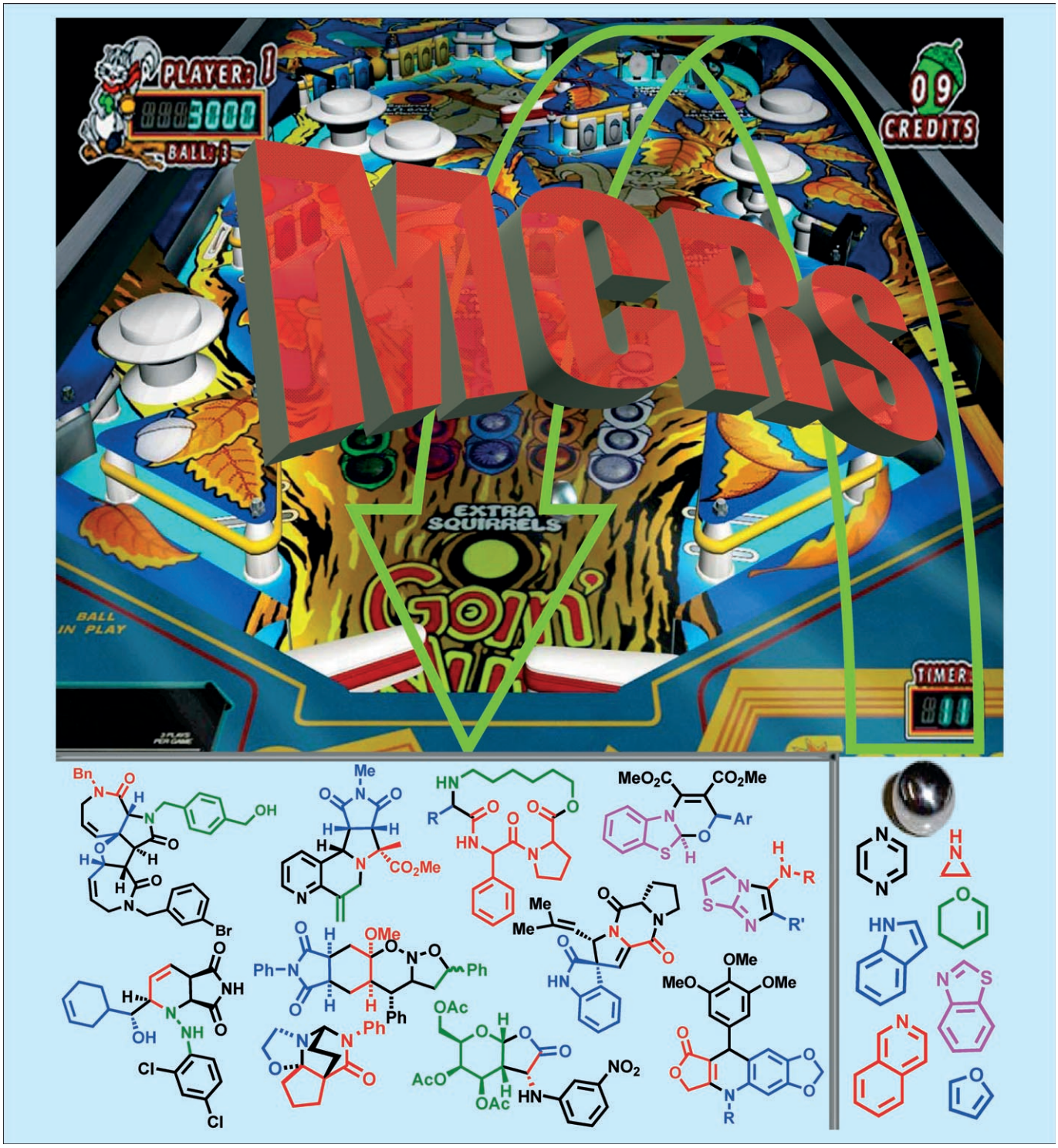


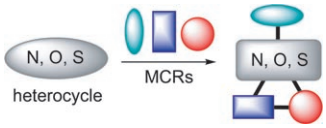
Abstract: Heterocycles display an intrinsic reactivity which enables rich, versatile and productive transformations. Taking into account their ubiquitous presence in natural products and drugs, the development of new, fast and efficient preparative protocols for these structures remains an urgent task in Organic Synthesis. Multicomponent reactions using heterocyclic chemistry offer new possibilities to exploit this exclusive reactivity. Recent results show relevant examples of such transformations. Several approaches which allow the construction of complex heterocyclic compounds from simple starting materials using this principle have been analyzed.

Keywords: domino reactions · heterocycles · molecular diversity · multicomponent reactions · synthetic methods

Introduction

Organic Synthesis is one of the main driving forces in the development of chemistry and makes a significant contribution to addressing several of the scientific challenges currently faced by our society. The capacity to generate new chemical entities in a programmed and efficient manner is pivotal in many fields, for instance in medicinal chemistry, and is increasingly gaining relevance in disciplines such as chemical biology and materials science, among others. The possibility to use small molecules as probes in those fields, linked to the vastness of the chemical space, demand new and more suitable synthetic methods. In this regard, although classical issues such as selectivity, molecular complexity and synthetic efficiency are still the focus of much research effort, new features should be examined (sustainability, diversity-oriented synthesis, etc.) in order to meet current needs.[1] Regarding modern organic synthesis, multicomponent reactions (MCRs) hold a privileged position because they allow the connectivity of three or more starting materials to generate an adduct in a single operation with high atom economy and bond-forming efficiency.[2] Step economy becomes critical when preparing collections of compounds in which short synthetic sequences are often mandatory. In addition to the inherent usefulness of the MCRs, the study of the behavior of these complex systems and the design and implementation of the ensuing domino processes will serve to enhance our chemical knowledge.[3]

On the other hand, heterocycles constitute the most common structural motif found in bioactive compounds and drugs, and can be considered privileged substructures.[4] The straightforward synthesis of these compounds is therefore one of the main goals of medicinal chemistry.[5] Traditionally, MCRs have contemplated heterocycles as the products (for instance in the classic Hantzsch and Biginelli MCRs) or as the substituents of reactive functional groups, allowing, in this case, the incorporation of the heterocyclic moiety in the final adduct. A third (complementary and more versatile) possibility involves the direct use of heterocycles as reagents in MCRs (Scheme 1). This modular approach takes advantage of the rich heterocyclic reactivity and leads to the preparation of new drug-like scaffolds that carry heterocyclic motifs. Furthermore, it allows the exploration of the reactivity pathways in these systems. In this article, we outline several representative research results that highlight the power of this methodology.



Scheme 1. Heterocycles as reagents in MCRs.

Mannich-Type Reactions and Related Processes

The interaction of a variety of heterocycles with imines formed in situ has provided a broad array of structures of interest. Several 3CRs involving amines, aldehydes and indoles give the corresponding 3-substituted indoles.[6] Mechanistically related Pictet–Spengler cyclizations have been performed both in solution and in solid-phase to afford valuable β-carboline derivatives in multicomponent protocols.[7] The interaction of indoles with aldehydes or synthetic equivalents has been explored and access to the indolocarbazole and furooxepine ring systems has been described (Scheme 2).[8] These reaction cascades can be rationalized considering the generation of early cationic intermediates ready to trap nucleophilic partners to yield the final adducts.

The Povarov reaction consists of the interaction of an aniline, a carbonyl (usually an aldehyde) and an activated olefin to yield a tetrahydroquinoline adduct.[9] This stepwise process is related to the Pictet–Spengler reaction and can be explained mechanistically through the generation of an imine, which is attacked by the π nucleophile under acid activation, followed by an intramolecular cyclization upon the activated aryl group to close the nitrogen ring. The use of cyclic enol ethers greatly enriches the molecular diversity of the adducts formed, thereby allowing access to furo and pyrano derivatives with relevant biological activities

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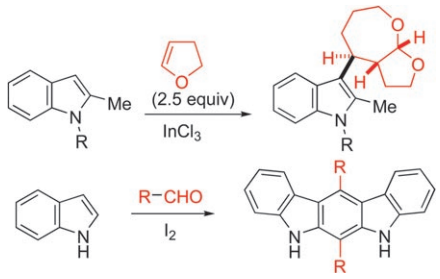
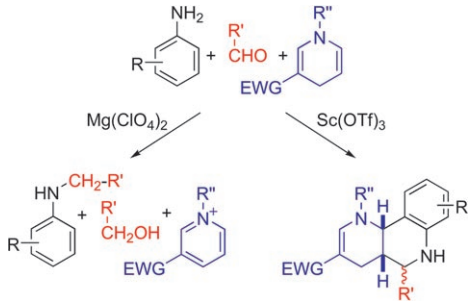
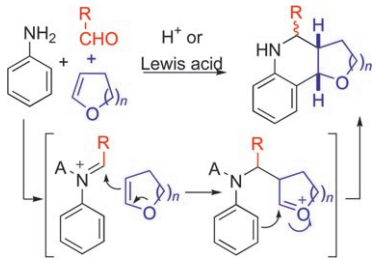


Scheme 2. Access to furooxepines and indolocarbazoles through indole MCRs.



Scheme 5. Dihydropyridines in Povarov reactions.

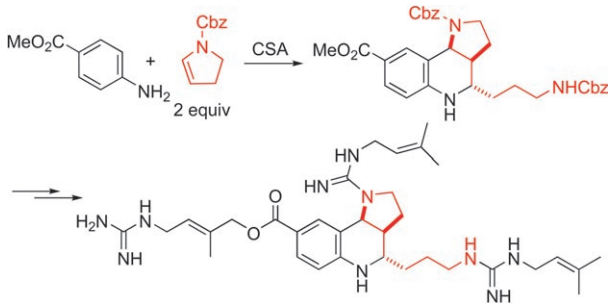
(Scheme 3).[10] Crucial to the development of this transformation are studies on the catalyst and reaction conditions that allowed its straightforward and general implementation with high efficacy. Therefore through the use of Sc, In and lanthanide ions as Lewis acid catalysts, the process is amenable to the preparation of libraries of compounds.[11]



Scheme 3. Povarov reaction involving cyclic enol ethers.

The use of cyclic enamines enables the incorporation of nitrogen rings fused to the tetrahydroquinoline core.[12] Particularly attractive are the applications of this methodology to the rapid synthesis of natural products. For instance, martinelline was prepared by Batey's group in a short sequence where the key step was a modified Povarov reaction using two equivalents of the enamine component (Scheme 4).[13]

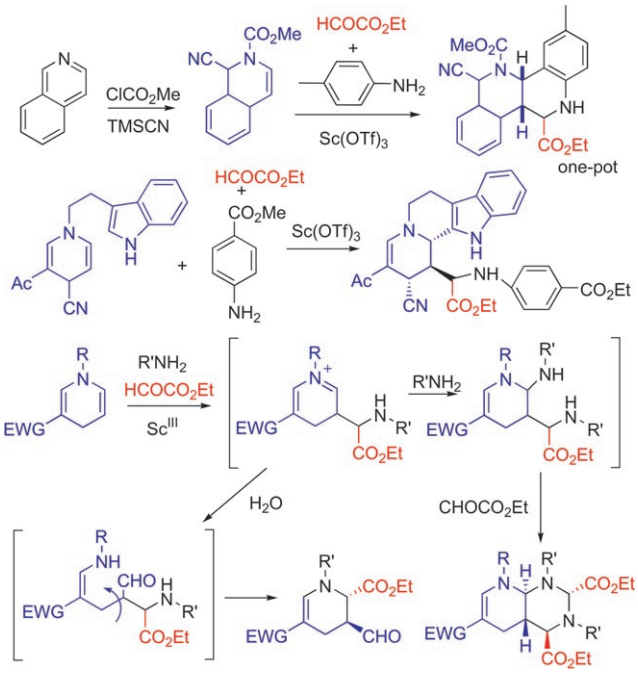
The participation of dihydropyridines, as enamine surrogates, in this process is of interest as these compounds allow the formation of pyrido-fused systems (benzonaphthyrydines). The reducing power of dihydropyridines (NADH analogues) may impair the MCR, as carbonyls and imines are present in the reaction medium. Although some catalysts promote the biomimetic redox process, the Povarov reaction takes place efficiently with lanthanide ions and related species (Scheme 5).[14]



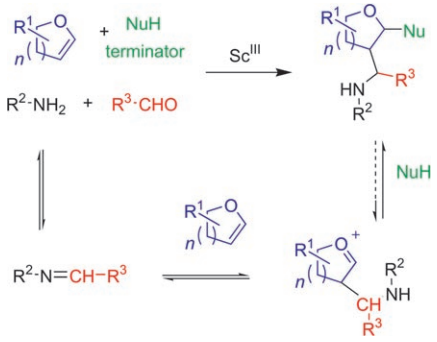
Scheme 4. Batey's synthesis of martinelline through a modified Povarov reaction.

This process has been conducted in solid-phase conditions, linking the aldehyde or the aniline to the solid support. The reaction has been modified by generating the dihydropyridine in situ. A mechanistic variation consisted of a final cyclization from an indole ring attached to the dihydropyridine nitrogen, thereby generating a new scaffold type (a substituted indoloquinolizidine). The participation of primary aliphatic amines affords two new structural types, which can be prepared stereoselectively (Scheme 6).[14]

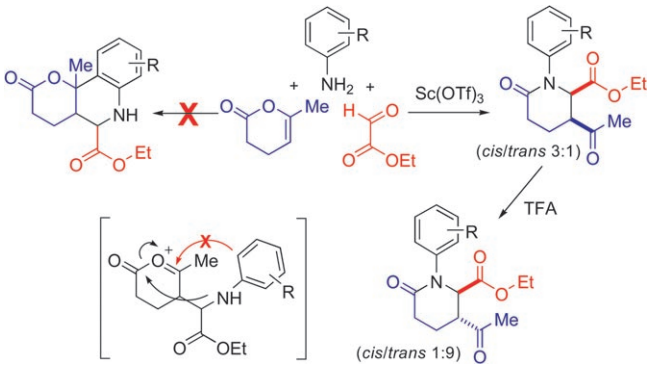
Taking into account the manifold mechanistic profile shown in the above processes, the next step was to explore the feasibility of a true 4CR based on the intermolecular trapping of the cationic Mannich intermediate. This hypothesis was confirmed, and in a series of reactions, cyclic enol



Scheme 6. Mechanistic variations in dihydropyridine Povarov reactions.



Scheme 7. 4CR between enol ethers, aldehydes, amines and nucleophilic species.



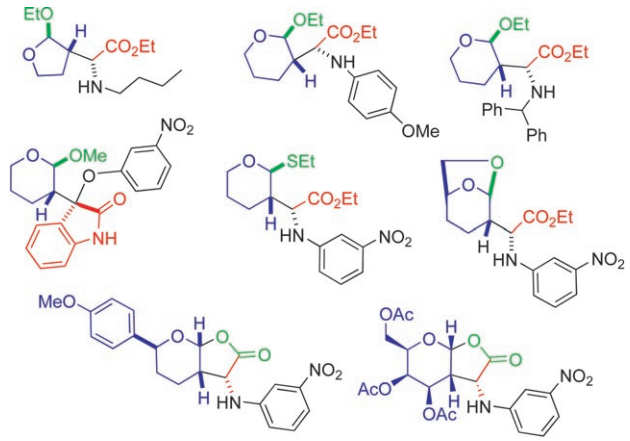
Scheme 9. Cyclic enol esters in Mannich-type MCRs.

ethers, aldehydes, amines and several nucleophiles (terminators) afforded, under $Sc(OTf)_3$ catalysis, the four-component adduct in a stereoselective manner (Scheme 7).[15]

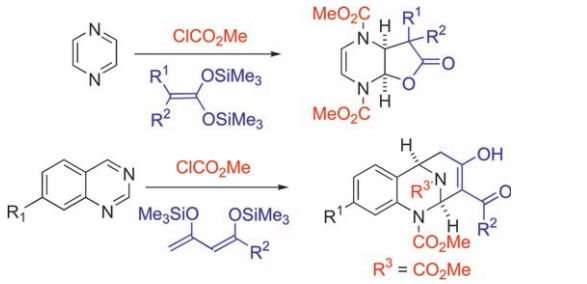
This orchestrated sequence constitutes a general reaction, which tolerates a wide range of reactive carbonyl compounds, amines, terminators (alcohols, thiols and water) and cyclic enol ethers (including glycals) (Scheme 8). The protocol simply requires mixing the components and the catalyst and stirring the resulting solution. Ghosh developed a conceptually related approach involving the initial reaction of cyclic enol ethers with pre-generated tosylimines and a subsequent nucleophilic trapping with allyltrimethylsilane to stereoselectively yield highly substituted tetrahydrofurans and pyrrolidines.[16]

When the Povarov process was tested on a cyclic enol ester, a dramatic change in the reaction mechanism altered the synthetic outcome, leading to disubstituted *N*-aryl lactams.[17] This result can be explained through the interruption of the normal Povarov cascade at the Mannich intermediate, followed by the acylation of the aniline nitrogen with the activated carbonyl species generated in the imine addition step (Scheme 9).

The mechanistically related Reissert reaction has recently been developed into efficient solid-phase and asymmetric versions.[18,19] The addition of distinct nucleophiles to the activated azinium ions has widened the synthetic applications of these processes.[20] Interesting transformations have been disclosed by the groups of Rudler and Langer, where the addition of silyloxy alkenes to activated azines afforded a variety of highly substituted heterocyclic derivatives (Scheme 10).[21]



Scheme 8. Array of adducts prepared through the 4CR.[15]

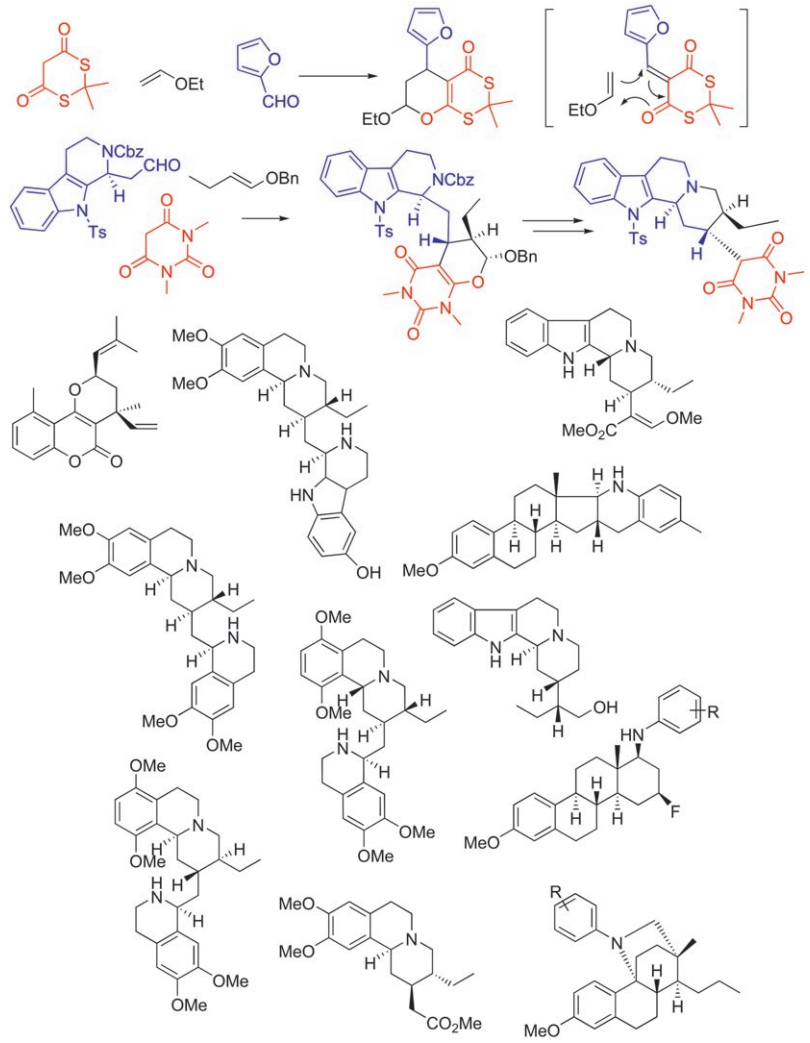


Scheme 10. MCRs with azines, chloroformate and silyloxyalkenes.

β-Dicarbonyl Chemistry

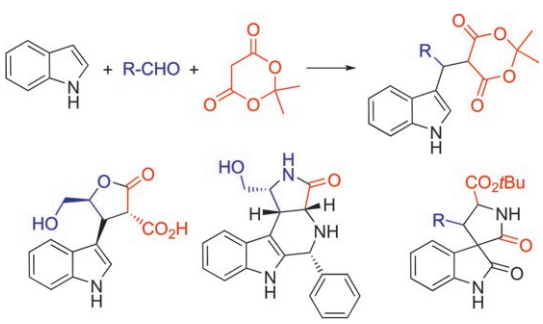
The Knoevenagel reaction has been successfully used as the starting point for many MCRs. Tietze designed a family of processes which are considered milestones in this field. In his work, the Knoevenagel adduct in situ reacts with an olefin in a hetero Diels–Alder cycloaddition.[3a,22] The chemistry of these systems has been extensively studied in his laboratories and numerous examples of this reaction have been described. Intramolecular versions of this Domino process have been used as the key steps in the synthesis of many targets. Complex structural types, particularly alkaloids belonging to diverse biogenetic classes, azasteroids and coumarins, have been efficiently accessed following this protocol (Scheme 11).

The Yonemitsu reaction, a useful MCR involving Meldrum's acid, indoles and aldehydes, has been widely used for the synthesis of tryptophyl derivatives. Enantiomerically pure aldehydes lead to a good level of stereocontrol, thereby allowing the preparation of substituted tetrahydro-β-carbolines (Scheme 12).[6,23]



Scheme 11. Tietze's MCR and an array of compounds synthesized from it.

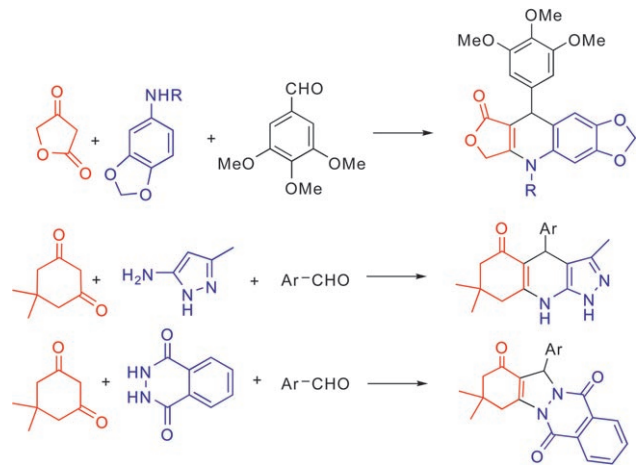
A related MCR, initiated by a Knoevenagel condensation, has been applied to the one-step synthesis of an azapodophyllotoxin derivative. This process involves the interaction of tetronic acid, an activated aniline and 3,4,5-trimethoxybenzaldehyde.[24] The reactions have also been implemented with different inputs, including heteroaromatic amines, amides, and β-dicarbonyl compounds (Scheme 13).[25]



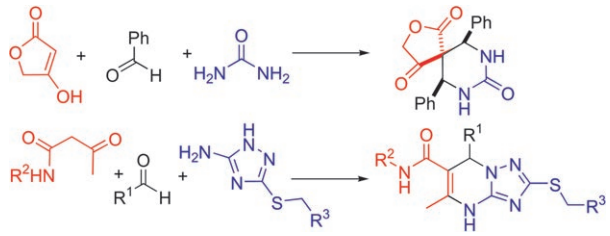
Scheme 12. Yonemitsu MCR and representative targets from this transformation.

The traditional use of β-dicarbonyl compounds in MCRs continues to provide novel heterocyclic scaffolds of interest.[26] Among these processes, the Biginelli MCR (the acid-catalyzed condensation of β-dicarbonyls, urea and aldehydes yielding dihydropyrimidinones) is the focus of intense research.[27] In this context, the use of tetronic acid yields spiroheterocyclic systems in a stereoselective manner.[28] Recently, Kappe disclosed an interesting modification by formally replacing the urea component by an aminotriazole. This approach allowed the preparation of complex and functionalized bicyclic systems in one step (Scheme 14).[29]

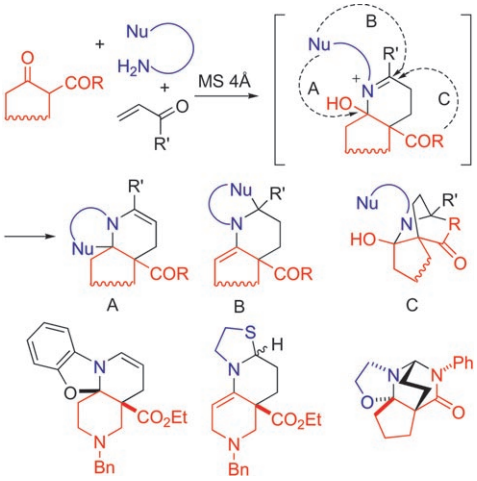
MCRs based on Michael addition processes have been mastered by Rodriguez's group and displayed a high synthetic versatility.[30] The participation of transient heterocycles, formed in the course of the reaction cascade, has recently enabled access to novel scaffolds, including bridged structures (Scheme 15).



Scheme 13. Knoevenagel-initiated MCRs.



Scheme 14. Biginelli MCRs with heterocyclic inputs.

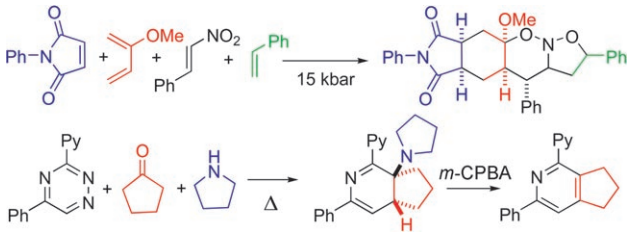


Scheme 15. Michael-triggered MCRs and several structural types derived from them.

Hetero Diels–Alder Transformations

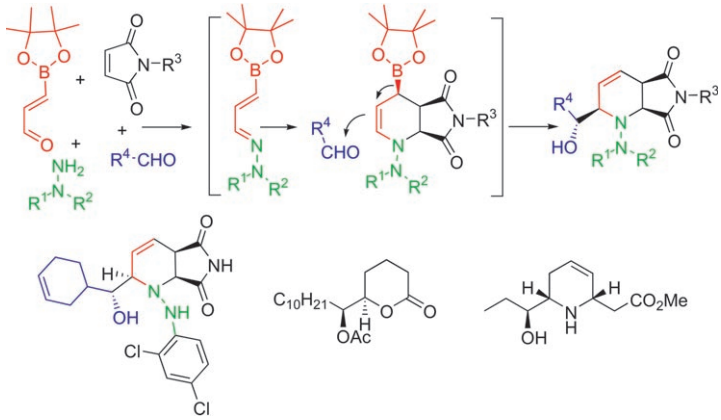
The hetero Diels–Alder methodology has found its place in the MCR arena. Apart from the examples listed in the dicarbonyl section,[3a,22] a number of applications dealing with heterocyclic processes deserve attention. For instance, the tandem [4+2]/[3+2] cycloadditions studied by Denmark involve the formation of a transient nitronate from the interaction of an activated olefin and a nitroalkene, which subsequently undergoes a cycloaddition with an electron-deficient dipolarophile.[31] Recently, Scheeren performed a related 4CR using high pressure conditions.[32] Taylor disclosed a useful synthesis of substituted pyridines by reacting a 1,2,4-triazine, a ketone, and a cyclic secondary amine (the two latter generating the enamine in situ) to initially yield an adduct which is aromatized by a Cope elimination (Scheme 16).[33]

Hall developed a sharp approach to the stereocontrolled synthesis of polysubstituted piperidines. The tandem protocol involves an aza-Diels–Alder cycloaddition, which generates an heterocyclic allylborane ready to interact with an aldehyde to yield the α-hydroxyalkylpiperidine derivative in a selective manner.[34] In a further improvement of this method, the 1-azadiene can be generated in situ by interaction of a boronoacrolein and an hydrazine, thus leading to a general and useful 4CR. Implementation of this methodology using chiral catalysts, chiral auxiliaries and combinatorial



Scheme 16. Hetero Diels–Alder MCRs.

techniques has allowed the total synthesis of complex natural products and bioactive compounds (Scheme 17).[35]



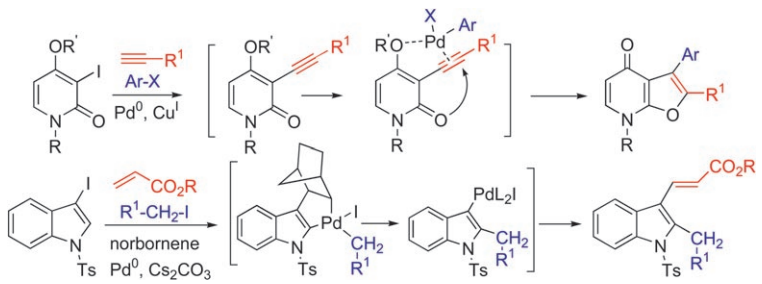
Scheme 17. Hall's aza-[4+2]/allylboration.

Organometallic Cascades

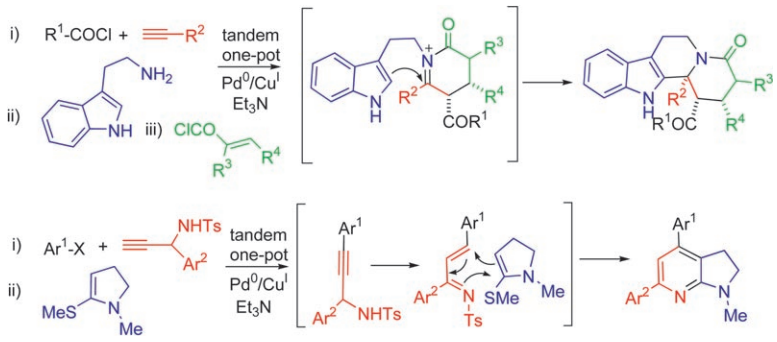
Organometallic chemistry has made a significant contribution to the development of new MCRs. Palladium catalysts continue to be the most used and recent reviews have covered the field.[36] The groups led by Balme[37] and Lautens[38] have disclosed useful tandem processes aimed at the formation of diversely substituted furopyridones, thiophenes and indoles using simple heterocycles as inputs in these MCRs (Scheme 18).

Müller et al. devised a family of tandem MC protocols that exploit Sonogashira reactions coupled to isomerization, cycloaddition, and polar processes to yield a wide array of heterocyclic structures. The versatility of this approach relies on the fact that the initially formed alkynes are efficiently trapped or converted into reactive species in a subsequent one-pot transformation (Scheme 19).[39]

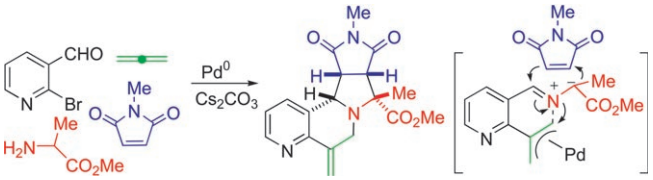
Grigg developed an elegant series of reaction cascades in which palladium chemistry is engaged with a dipolar cycloaddition to yield polycyclic adducts in a stereoselective manner. Key to the process is the participation of heterocyclic nucleophilic species in the capture of the allyl–palladium intermediate, generated from an allene. Remarkably, these processes are also flexible enough to be accommodated to several non-organometallic reactions, such as Pictet–Spengler cyclizations (Scheme 20).[40]



Scheme 18. Balme's and Lautens' palladium-mediated MCRs.



Scheme 19. Müller Sonogashira-initiated MCRs.



Scheme 20. Grigg's palladium-catalyzed allenylation-dipolar cycloaddition cascade.

It is worth to mention that the MCR concept also has applications in materials science and nanotechnology. A striking example has recently been provided by Severin and involves the metal complex which acts as a component to be incorporated in the final adduct in a multiple 4CR. The process is based on the self-assembly of a nanodimensional structure through the orthogonal formation of boronates, imines and, noteworthy, the ligand exchange of the pyridine moieties with the metal centers (Scheme 21).[41]

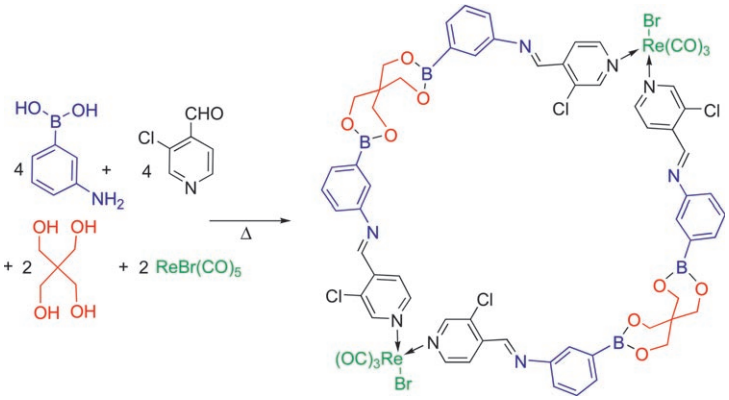
Isocyanide-Based Reactions

The high versatility of isocyanide MCRs can be further extended by the use of heterocycles in these processes.[2f] A selection of new transformations (not intended to be comprehensive) is listed below. The ring opening of epoxides and aziridines with isocyanides, and subsequent trapping with carboxylic acids gives rise to a family of scaffolds in a Passerini-like reaction.[42] The acid-catalyzed double insertion of isocyanides into epoxides yields ring-expanded iminofuran derivatives (Scheme 22).[43]

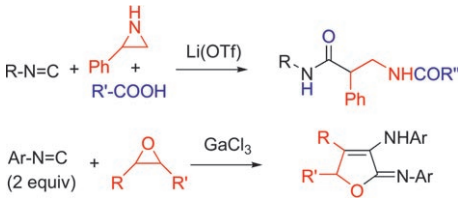
The Joullié–Ugi coupling reaction has been used to synthesize a variety of glyco- and peptidomimetics by a direct procedure. The addition of imines (instead of forming them in situ) allows the participation of a variety of heterocyclic structures, which could not otherwise be prepared in a straightforward manner.[44] In this regard, the use of dihydropyridines and cyclic enol ethers is also promising, as they can be activated by electrophiles to generate the cationic species ready to interact with the isocyanides and give the adduct.[45] The mixing of iodine, isocyanides and 1,4-dihydropyridines produced an unexpected result: a complex cascade process led to rearranged benzimidazolium systems in high yields (Scheme 23).[46]

The participation of azines in these reactions also proved fruitful in terms of structural diversity and reactivity pathways. For instance, a family of MCRs based on the interaction of isocyanides with distinct azines and activating agents (protic acids, acylating and related species) has recently been described. The processes normally start with the generation of the azinium intermediate, which undergoes the isocyanide attack in a Reissert-like reaction (Scheme 24).[47]

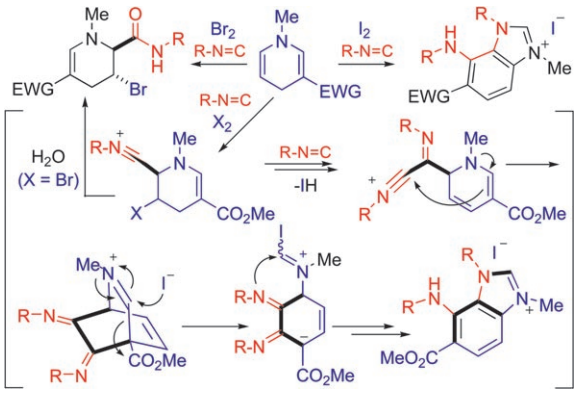
The Bienaymé–Blackburn–Groebcke reaction,[48] which involves the interaction of α-aminoazines with aldehydes and isocyanides, has been developed into a powerful tool for drug discovery. Among recent achievements, combinatorial



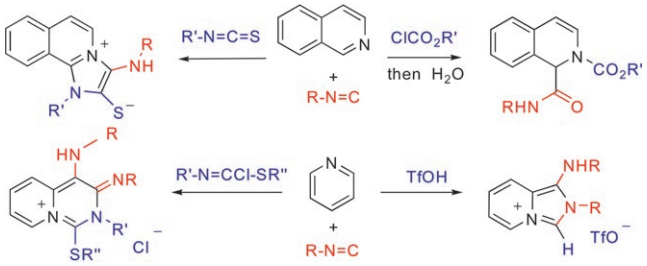
Scheme 21. Formation of macrocycle in a [4+4+2+2] condensation reaction.



Scheme 22. Isocyanide reactions with aziridines and epoxides.

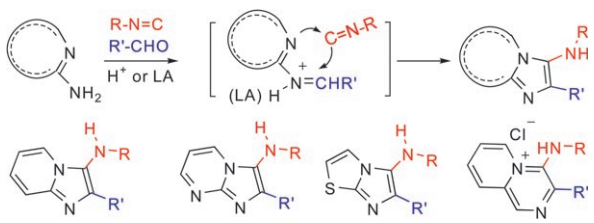


Scheme 23. Isocyanide–dihydropyridine MCRs and mechanistic proposal.



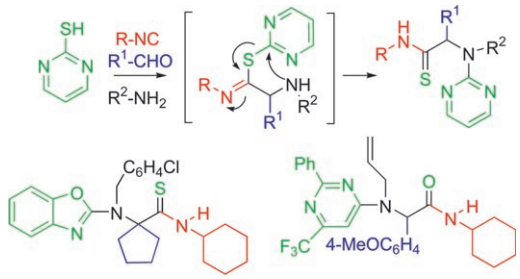
Scheme 24. Isocyanide–azine MCRs.

chemistry techniques, the use of diversely functionalized azines and the extension to modified carbonyl and heterocyclic systems have made a remarkable contribution to the production of large and structurally diverse libraries (Scheme 25).[2f,49]



Scheme 25. Bienaymé–Blackburn–Groebcke MCR and selected scaffolds.

El Kaïm has recently linked the Ugi MCR with the Smiles rearrangement in phenolic substrates. The application of this methodology to a variety of heterocyclic surrogates has allowed efficient protocols for the functionalization of these systems (Scheme 26).[50]



Scheme 26. El Kaïm Ugi Smiles MCRs with heterocyclic substrates.

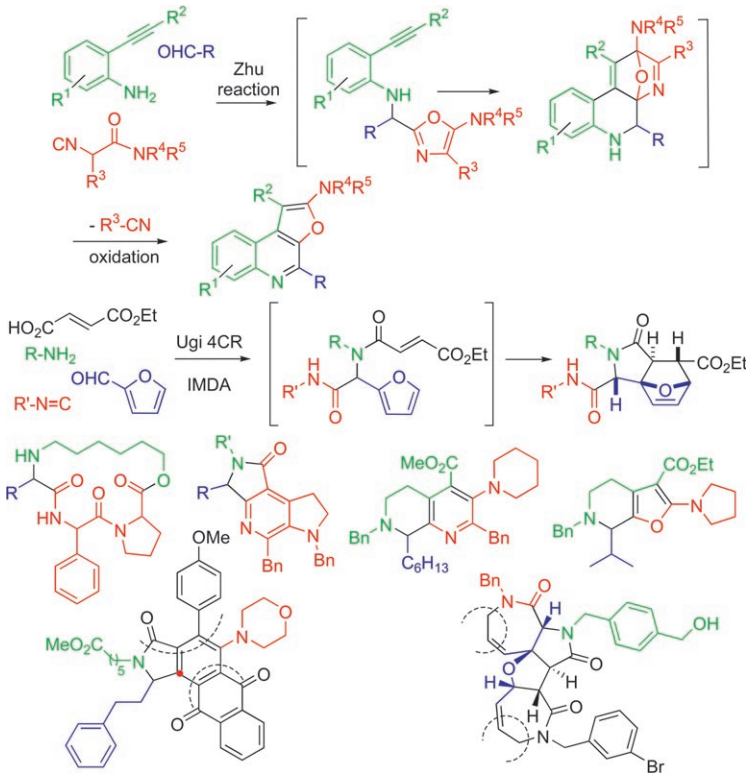
In a series of seminal papers, Zhu and co-workers described the use of oxazoles as transient intermediates in isocyanide MCRs. This strategy allows extraordinary synthetic versatility. In this way, the use of α- acetamidoisocyanides in Ugi reactions yields highly substituted oxazoles which in situ react intramolecularly to afford complex heterocyclic systems and cyclodepsipeptides, thereby leading to broad scaffold diversity.[51] In a related approach, Schreiber reported examples of diversity-oriented syntheses using furan-containing Ugi and Passerini adducts, which are subsequently transformed in a flexible manner (Scheme 27).[52]

Dipole-Mediated Processes

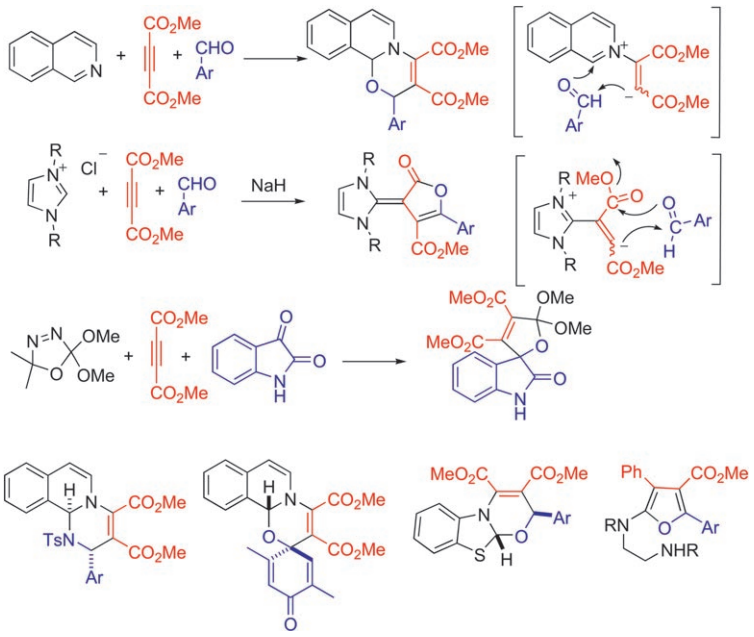
The interaction of certain nucleophiles (carbenes, azines, isocyanides, etc.) with electron-deficient π systems generates dipolar intermediates capable of promoting further bond-forming events. In this way a series of MCRs have been developed.[53] The participation of heterocycles in this chemistry greatly amplifies the synthetic outcome of these transformations. Nair has reported relevant examples of this concept using azines (isoquinoline, quinoline, benzothiazoles, etc.) and (heterocyclic) carbenes as nucleophilic triggers.[54] Perhaps the only limitation of this methodology lies in the need for strongly activated π acceptors (dimethyl acetylenedicarboxylate in most of the cases), which permits few variations regarding this component (Scheme 28).

In a series of related processes, Ma explored the reactivity of imidazoles and thiazolium salts (the latter as carbene precursors), which, together with the novel use of ketenes, allows a rich reactivity leading to novel heterocyclic systems.[55] Mironov further explored this family of MCRs by screening a wide array of combinations of the three partners: isoquinolines, electron-deficient olefins and the acceptor-donor species (Scheme 29).[56]

[3+2] Dipolar cycloadditions have also found their place in this field, and have led to novel MCRs. Representative examples include Tepe's reaction of oxazolones with aldehydes and primary amines to afford imidazolines in a stereoselective manner, presumably through a cycloaddition between the in situ generated *N*-silyl munchnone and imine species.[57] Williams reported the remarkable preparation of



Scheme 27. Zhu's and Schreiber's use of transient heterocycles in MCR sequences.



Scheme 28. Nair's nucleophilic-triggered dipolar MCRs.

a variety of complex natural products with spiranic cores through the interaction of an heterocyclic azomethine ylide and an activated olefin.[58] Later, Schreiber used this methodology to prepare a large collection of diversified analogues using macrobeads in a diversity oriented synthesis approach.[59] Arndtsen reported an efficient synthesis of pentasubstituted pyrroles via the participation of a transient imidazole dipole, which is formed by the interaction of an imine, an acid chloride and an isocyanide.[60] The dipole undergoes cycloaddition with an alkyne present in the reaction mixture to form an adduct, which evolves to the pyrrole by a retrocycloaddition that expels an isocyanate unit (Scheme 30).

Conclusion

The MCR approach is having a dramatic impact on modern organic synthesis by improving our capacity to tackle the preparation of complex molecules in short sequences. Furthermore, MCRs are also reshaping retrosynthetic analysis by providing new and general transformations. The findings reported here highlight that heterocycles, with their intrinsic reactivity, are extremely valuable substrates for these processes, particularly when dealing with library production and diversity oriented synthesis issues. Although many aspects of heterocyclic MCRs are poorly understood (mechanisms, catalysis, regio- and stereo-control, etc.) and our capacity to design new reaction cascades of this type is somewhat limited; rapid progress can be expected in the field. This progress will be fuelled by the synthetic achievements that the use of this concept has already made possible. The ideal synthesis of complex heterocyclic systems is still far away, however, with these advances, we are definitely getting closer!

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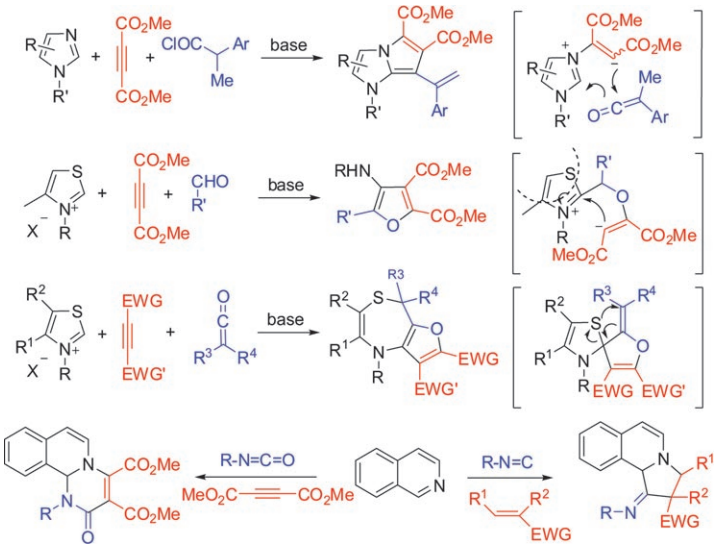
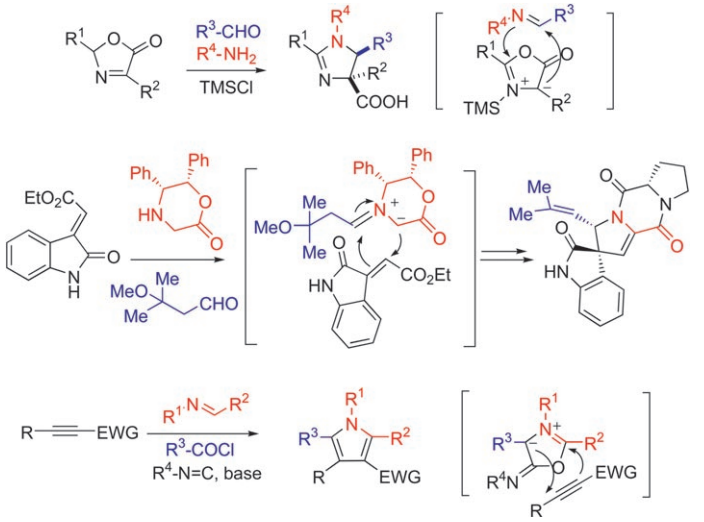


Scheme 29. Ma's and Mironov's imidazole, thiazolium and isoquinoline MCRs.



Scheme 30. Tepe's, Williams' and Arndtsen's dipolar cycloaddition MCRs.

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[1] For some sharp reflections on this topic, see: a) B. M. Trost, *Science* **1991**, *254*, 1471–1477; b) P. A. Wender, *Chem. Ind.* **1997**, 765–769; c) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 2056–2075; *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; d) M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2004**, *116*, 48–60; *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58; e) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res.* **2008**, *41*, 40–49.

[2] For an overview, see: Multicomponent reactions, (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**; for recent reviews, see: a) A. Dömling, I. Ugi, *Angew. Chem.* **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210; b) H. Bienaymé, C. Hulme, G. Oddon, P. Schmitt, *Chem. Eur. J.* **2000**, *6*, 3321–3329; c) R. V. A. Orru, M. de Greef, *Synthesis* **2003**, 1471–1499; d) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; e) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628–1661; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602–1634; f) A. Dömling, *Chem. Rev.* **2006**, *106*, 17–89.

[3] For an overview, see: a) Domino reactions in Organic Synthesis (Eds.: L. F. Tietze, G. Brasche, K. M. Gericke), Wiley-VCH, Weinheim, **2006;** for seminal reviews, see: b) G. H. Posner, *Chem. Rev.* **1986**, *86*, 831–844; c) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger. *Angew. Chem.* **2006**, *118, 7292–7344; Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186.

[4] a) C. Merlot, D. Domine, C. Cleva, D. J. Church, *Drug Discovery Today* **2003**, *8*, 594–602; b) L. Constantino, D. Barlocco, *Curr. Med. Chem.* **2006**, *13*, 65–85.

[5] a) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930; b) for an overview of the field, see: G. Wess, M. Urmann, B. Sickenberger, *Angew. Chem.* **2001**, *113*, 3443–3453; *Angew. Chem. Int. Ed.* **2001**, *40*, 3341–3350.

[6] For an excellent review on indole MCRs, see: J. Sapi, J.-Y. Laronze, *Arkivoc* **2004**, 208–222.

[7] For instance, see: N. Srinivasan, A. Ganesan, *Chem. Commun.* **2003**, 916–917.

[8] a) M. L. Deb, B. Baruah, P. J. Bhuyan, *Synthesis* **2008**, 286–292; b) J. S. Yadav, B. V. S. Reddy, G. Satheesh, A. Prabhakar, A. C. Kunwar, *Tetrahedron Lett.* **2003**, *44*, 2221–2224.

[9] L. S. Povarov, *Russ. Chem. Rev.* **1967**, *36*, 656–670.

[10] a) S. Kobayashi, H. Ishitani, S. Nagayama, *Synthesis* **1995**, 1195–1202; b) J. Legros, B. Crousse, M. Ourévitch, D. Bonnet-Delpon, *Synlett* **2006**, 1899–1902.

[11] a) A. S. Kiselyov, R. W. Armstrong, *Tetrahedron Lett.* **1997**, *38*, 6163–6166; b) S. Kobayashi, R. Akiyama, H. Kitagawa, *J. Comb. Chem.* **2001**, *3*, 196–204.

[12] a) R. A. Batey, P. D. Simoncic, D. Lin, R. P. Smyj, A. J. Lough, *Chem. Commun.* **1999**, 651–652; b) P. J. Stevenson, M. Nieuwenhuyzen, D. Osborne, *Chem. Commun.* **2002**, 444–445.

[13] D. A. Powell, R. A. Batey, *Org. Lett.* **2002**, *4*, 2913–2916.

[14] I. Carranco, J. L. Díaz, O. Jiménez, M. Vendrell, F. Albericio, M. Royo, R. Lavilla, *J. Comb. Chem.* **2005**, *7*, 33–41, and references therein.

[15] O. Jiménez, G. de la Rosa, R. Lavilla, *Angew. Chem.* **2005**, *117*, 6679–6683; *Angew. Chem. Int. Ed.* **2005**, *44*, 6521–6525.

[16] See: A. K. Ghosh, S. S. Kulkarni, C.-X. Xu, P. E. Fanwick, *Org. Lett.* **2006**, *8*, 4509–4511, and references therein.

[17] N. Isambert, M. Cruz, M. J. Arévalo, E. Gómez, R. Lavilla, *Org. Lett.* **2007**, *9*, 4199–4202.

[18] B. A. Lorsbach, J. T. Bagdanoff, R. B. Miller, M. J. Kurth, *J. Org. Chem.* **1998**, *63*, 2244–2250, and references therein.

[19] E. Ichikawa, M. Suzuki, K. Yabu, M. Albert, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 11808–11809, and references therein.

[20] For instance, see: a) J. Pabel, C. E. Hösl, H. Maurus, M. Ege, K. Th. Wanner, *J. Org. Chem.* **2000**, *65*, 9272–9275; b) A. R. Katritzky, S. Zhang, T. Kurz, M. Wang, *Org. Lett.* **2001**, *3*, 2807–2809; c) S. Yamada, M. Inoue, *Org. Lett.* **2007**, *9*, 1477–1480.

[21] For a detailed review, see: a) P. Langer, *Eur. J. Org. Chem.* **2007**, 2233–2238; b) O. Sieck, M. Ehwald, J. Liebscher, *Eur. J. Org. Chem.* **2005**, 663–672.

[22] For reviews, see: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) Domino reactions in Organic Synthesis (Eds.: L. F. Tietze, G. Brasche, K. M. Gericke), Wiley-VCH, Weinheim, **2006**, Chapter 2.

[23] E. Dardennes, Á. Kovács-Kulyassa, M. Boisbrun, C. Petermann, J.-Y. Laronze, J. Sapi, *Tetrahedron: Asymmetry* **2005**, *16*, 1329–1339.

[24] C. Tratrat, S. Giorgi-Renault, H.-P. Husson, *Org. Lett.* **2002**, *4*, 3187–3189.

[25] a) C.-L. Shi, D. Q. Shi, S. H. Kim, Z.-B. Huang, S.-J. Ji, M. Ji, *Tetrahedron* **2008**, *64*, 2425–2432; b) M. Sayyafi, M. Seyyedhamzeh, H. R. Khavasi, A. Bazgir, *Tetrahedron* **2008**, *64*, 2375–2378.

[26] C. Simon, T. Constantieux, J. Rodriguez, *Eur. J. Org. Chem.* **2004**, 4957–4980.

[27] For recent review, see: C. O. Kappe in *Multicomponent reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**, Chapter 4.
[28] G. Byk, H. E. Gottlieb, H. Herscovici, F. Mirkin, *J. Comb. Chem.* **2000**, *2*, 732–735.
[29] V. A. Chebanov, E. A. Muravyova, S. M. Desenko, V. I. Musatov, I. V. Knyazeva, S. V. Shishkina, O. V. Shishkin, C. O. Kappe, *J. Comb. Chem.* **2006**, *8*, 427–434.
[30] a) Liéby-Muller, C. Simon, T. Constantieux, J. Rodriguez, *QSAR Comb. Sci.* **2006**, *25*, 432–438, and references therein.
[31] S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137–165.
[32] a) L. W. A. van Berkom, G. J. T. Kuster, F. Kalmoua, R. de Gelder, H. W. Scheeren, *Tetrahedron Lett.* **2003**, *44*, 5091–5093; b) L. W. A. van Berkom, G. J. T. Kuster, H. W. Scheeren, *Mol. Diversity* **2003**, *6*, 271–282.
[33] Y. Fernández Sainz, S. A. Raw, R. J. K. Taylor, *J. Org. Chem.* **2005**, *70*, 10086–10095.
[34] B. B. Touré, H. R. Hoveyda, J. Tailor, A. Ulaczyk-Lesanko, D. G. Hall, *Chem. Eur. J.* **2003**, *9*, 466–474.
[35] a) A. Ulaczyk-Lesanko, E. Pelletier, M. Lee, H. Prinz, H. Waldmann, D. G. Hall, *J. Comb. Chem.* **2007**, *9*, 695–703; b) X. Gao, D. G. Hall, *J. Am. Chem. Soc.* **2003**, *125*, 9308–9309; c) B. B. Touré, D. G. Hall, *Angew. Chem.* **2004**, *116*, 2035–2038; *Angew. Chem. Int. Ed.* **2004**, *43*, 2001–2004.
[36] a) G. Balme, D. Boussy, N. Monteiro in *Multicomponent reactions* (Eds.: J. Zhu, H. Bienaymé), Wiley-VCH, Weinheim, **2005**, Chapter 8; b) J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, *J. Organomet. Chem.* **2005**, *690*, 539–587; c) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680; d) N. Patil, Y. Yamamoto, *Synlett* **2007**, 1994–2005.
[37] E. Bossharth, P. Desbordes, N. Monteiro, G. Balme, *Org. Lett.* **2003**, *5*, 2441–2444.
[38] K. Mitsudo, P. Thansandote, T. Wilhelm, B. Mariampillai, M. Lautens, *Org. Lett.* **2006**, *8*, 3939–3942.
[39] For a review, see: a) D. M. D'Souza, T. J. J. Müller, *Chem. Soc. Rev.* **2007**, *36*, 1095–1108; b) O. Schramm, T. Oester, T. J. J. Müller, *J. Org. Chem.* **2006**, *71*, 3494–3500.
[40] a) H. A. Dondas, C. W. G. Fishwick, X. Gai, R. Grigg, C. Kilner, N. Dumrongchai, B. Kongkathip, N. Kongkathip, C. Polysuk, V. Sridharan, *Angew. Chem.* **2005**, *117*, 7742–7746; *Angew. Chem. Int. Ed.* **2005**, *44*, 7570–7574; b) R. Grigg, M. R. A. Sarkar, A. Thayaparan, V. Sridharan, C. W. G. Fishwick, *Tetrahedron* **2007**, *63*, 7213–7228, and references therein.
[41] a) N. Christinat, R. Scopelliti, K. Severin, *Angew. Chem.* **2008**, *120*, 1874–1878; *Angew. Chem. Int. Ed.* **2008**, *47*, 1848–1852; b) for MCRS leading to macrocyclizations, see: F. Leon, D. G. Rivera, L. A. Wessjohann, *J. Org. Chem.* **2008**, *73*, 1762–1767, and references therein; for a recent review see: c) H. Eckert, *Heterocycles* **2007**, *73*, 149–158.
[42] a) O. T. Kern, W. B. Motherwell, *Chem. Commun.* **2003**, 2988–2989; b) O. T. Kern, W. B. Motherwell, *Chem. Commun.* **2005**, 1787.
[43] a) G. Bez, C.-G. Zhao, *Org. Lett.* **2003**, *5*, 4991–4993; for a related process, see: b) M. Tobisu, A. Kitajima, S. Yoshioka, I. Hyodo, M. Oshita, N. Chatani, *J. Am. Chem. Soc.* **2007**, *129*, 11431–11437.
[44] For recent work, see: a) L. Banfi, A. Basso, G. Guanti, R. Riva, *Tetrahedron Lett.* **2004**, *45*, 6637–6640; b) T. M. Chapman, I. G. Davies, B. Gu, T. M. Block, D. I C. Scopes, P. A. Hay, S. M. Courtney, L. A. McNeill, C. J. Schoefield, B. G. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 506–507, and references therein.
[45] C. Masdeu, E. Gómez, N. A. Williams, R. Lavilla, *QSAR Comb. Sci.* **2006**, *25*, 465–473.
[46] C. Masdeu, E. Gómez, N. A. O. Williams, R. Lavilla, *Angew. Chem.* **2007**, *119*, 3103–3106; *Angew. Chem. Int. Ed.* **2007**, *46*, 3043–3046.
[47] a) The complementary mechanism (the activation of the isocyanide) has also been observed; b) E. Marchand, G. Morel, *Tetrahedron Lett.* **1993**, *34*, 2319–2322; c) J. L. Díaz, M. Miguel, R. Lavilla, *J. Org. Chem.* **2004**, *69*, 3550–3553; d) M. Mironov, S. S. Maltsev, V. S. Mokrushin, V. A. Bakulev. *Mol. Diversity* **2005**, *9*, 221–227; for related processes, see: e) J.-C. Berthet, M. Nierlich, M. Ephritikhine, *Eur. J. Org. Chem.* **2002**, 375–378; f) N. A. O. Williams, C. Masdeu, J. L. Díaz, R. Lavilla, *Org. Lett.* **2006**, *8*, 5789–5792.
[48] a) H. Bienaymé, K. Bouzid, *Angew. Chem.* **1998**, *110*, 2349–2352; *Angew. Chem. Int. Ed.* **1998**, *37*, 2234–2237; b) C. Blackburn, B. Guan, P. Fleming, K. Shiosaki, S. Tsai, *Tetrahedron Lett.* **1998**, *39*, 3635–3638; c) K. Groebcke, L. Weber, F. Mehlin, *Synlett* **1998**, 661–663.
[49] a) M. Umkehrer, G. Ross, N. Jäger, C. Burdack, J. Kolb, H. Hu, M. Alvim-Gaston, C. Hulme, *Tetrahedron Lett.* **2007**, *48*, 2213–2216; b) E. F. DiMauro, J. M. Kennedy, *J. Org. Chem.* **2007**, *72*, 1013–1016; c) S. Caballares, J. F. Espinosa, *Org. Lett.* **2005**, *7*, 2329–2331; d) M. A. Lyon, T. S. Kercher, *Org. Lett.* **2004**, *6*, 4989–4992.
[50] a) L. El Kaïm, L. Grimaud, J. Oble, *Angew. Chem.* **2005**, *117*, 8175–8178; *Angew. Chem. Int. Ed.* **2005**, *44*, 7961–7964; b) L. El Kaïm, M. Gizolme, L. Grimaud, J. Oble, *Org. Lett.* **2006**, *8*, 4019–4021; c) L. El Kaïm, M. Gizolme, L. Grimaud, J. Oble, *Synlett* **2007**, 465–469.
[51] For an excellent review, see: a) J. Zhu, *Eur. J. Org. Chem.* **2003**, 1133–1144; for more recent work, see: b) A. Fayol, J. Zhu, *Org. Lett.* **2004**, *6*, 115–118; c) A. Fayol, J. Zhu, *Org. Lett.* **2005**, *7*, 239–242; d) A. Fayol, J. Zhu, *Tetrahedron* **2005**, *61*, 11511–11519; e) C. Bughin, G. Zhao, H. Bienaymé, J. Zhu, *Chem. Eur. J.* **2006**, *12*, 1174–1184; f) D. Bonne, M. Dekhane, J. Zhu, *Angew. Chem.* **2007**, *119*, 2537–2540; *Angew. Chem. Int. Ed.* **2007**, *46*, 2485–2488; g) T. Pirali, G. C. Tron, G. Masson, J. Zhu, *Org. Lett.* **2007**, *9*, 5275–5278.
[52] a) D. Lee, J. K. Sello, S. L. Schreiber, *Org. Lett.* **2000**, *2*, 709–712; b) J. K. Sello, P. R. Andreana, D. Lee, S. L. Schreiber, *Org. Lett.* **2003**, *5*, 4125–4127; c) P. R. Andreana, C. C. Liu, S. L. Schreiber, *Org. Lett.* **2004**, *6*, 4231–4233.
[53] For recent reviews, see: a) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal, *Acc. Chem. Res.* **2003**, *36*, 899–907; b) V. Nair, S. Bindu, V. Sreekumar, *Angew. Chem.* **2004**, *116*, 5240–5245; *Angew. Chem. Int. Ed.* **2004**, *43*, 5130–5135; c) V. Nair, R. S. Menon, A. R. Sreekanth, N. Abhilash, A. T. Biju, *Acc. Chem. Res.* **2006**, *39*, 520–530.
[54] For recent work, see: a) V. Nair, A. Deepthi, M. Poonoth, B. Santhamma, S. Vellalath, B. P. Babu, R. Mohan, E. Suresh, *J. Org. Chem.* **2006**, *71*, 2313–2319; b) A. N. Pillai, B. R. Devi, E. Suresh, V. Nair, *Tetrahedron Lett.* **2007**, *48*, 4391–4393; c) V. Nair, S. Devipriya, S. Eringathodi, *Tetrahedron Lett.* **2007**, *48*, 3667–3670; d) V. Nair, B. P. Babu, S. Vellalath, E. Suresh, *Chem. Commun.* **2008**, 747–749; e) V. Nair, S. C. Mathew, S. Vellalath, A. N. Pillai, E. Suresh, *Synthesis* **2008**, 551–554.
[55] a) C. Ma, H. Ding, G. Wu, Y. Yang, *J. Org. Chem.* **2005**, *70*, 8919–8923; b) C. Ma, H. Ding, Y. Wang, *Org. Lett.* **2006**, *8*, 3133–3136; c) C. Ma, H. Ding, Y. Zhang, M. Bian, *Angew. Chem.* **2006**, *118*, 7957–7961; *Angew. Chem. Int. Ed.* **2006**, *45*, 7793–7797; d) H. Ding, Y. Zhang, M. Bian, W. Yao, C. Ma, *J. Org. Chem.* **2008**, *73*, 578–584.
[56] a) M. A. Mironov, V. S. Mokrushin, S. S. Maltsev, *Synlett* **2003**, 943–946; b) M. A. Mironov, *QSAR Comb. Sci.* **2006**, *25*, 423–431; c) for a recent reference of the isocyanate process, see: M. Adib, M. Mollahosseini, H. Yavari, M. H. Sayahi, H. R. Bijanzadeh, *Synthesis* **2004**, 861–864.
[57] S. Peddibhotla, S. Jayakumar, J. J. Tepe, *Org. Lett.* **2002**, *4*, 3533–3535.
[58] a) P. R. Sebahar, R. M. Williams, *J. Am. Chem. Soc.* **2000**, *122*, 5666–5667; b) T. Onishi, P. R. Sebahar, R. M. Williams, *Org. Lett.* **2003**, *5*, 3135–3137; c) K. A. Ahrendt, R. M. Williams, *Org. Lett.* **2004**, *6*, 4539–4541.
[59] M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086.
[60] D. J. St. Cyr, N. Martin, B. A. Arndtsen, *Org. Lett.* **2007**, *9*, 449–452.

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