WILEY-VCH

Edited by
Erik V. Van der Eycken and Upendra K. Sharma

Multicomponent Reactions towards Heterocycles

Concepts and Applications

Multicomponent Reactions towards Heterocycles

Multicomponent Reactions towards Heterocycles

Concepts and Applications

Edited by

Erik V. Van der Eycken
Upendra K. Sharma

WILEY-VCH

Editors

Prof. Dr. Erik V. Van der Eycken
Katholieke Universiteit Leuven
Department of Chemistry
Celestijnenlaan 200F
3001 Heverlee
Belgium

Dr. Upendra K. Sharma
Katholieke Universiteit Leuven
Department of Chemistry
Celestijnenlaan 200F
3001 Leuven
Belgium

Cover Image: DenisKot (globe)

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at <http://dnb.d-nb.de>.

Print ISBN: 978-3-527-34908-1
ePDF ISBN: 978-3-527-83242-2
ePub ISBN: 978-3-527-83244-6
oBook ISBN: 978-3-527-83243-9

Cover Design: Adam-Design, Weinheim, Germany
Typesetting Straive, Chennai, India

Printed on acid-free paper

10 9 8 7 6 5 4 3 2 1

Contents

Preface

Owing to the countless plausible combinations of carbon, hydrogen, and various heteroatoms, heterocyclic chemistry has remained as the foundation of novel chemical compounds in the sphere of natural product chemistry, pharmaceuticals, agrochemicals, and material sciences. They can serve as useful tools to facilitate tunable interactions with biological targets, thereby providing improved pharmacological and physicochemical properties of biomolecules as well as drug candidates. Recently, heightened cognizance of environmental issues is directing our society toward more sustainable solutions. Ever since the 12 principles of Green Chemistry were articulated, chemists answered the call to play their part in generating more sustainable syntheses. Multicomponent reactions (MCRs) appear as an obvious solution since most of the reactants' atoms are often incorporated in the final product. Moreover, a vast literature has been produced showing the power of MCRs as well as post-MCRs, in simplifying the synthetic design and yet obtaining high complexity and diversity in the construction of privileged structures. This is crucial in the development of novel bioactive molecules, wherein the production of libraries of compounds is necessary for the search of optimal drug candidates. Given the broad applications of heterocycles in the plethora of scientific fields, the current book title "*Multicomponent Reactions towards Heterocycles. Concepts and Applications*" is well warranted. In addition, recent advances in the field of MCR chemistry along with the plausible scope toward the synthesis and functionalization of biologically relevant heterocycles has encouraged us to compile this volume.

As the vast majority of small molecule drugs are of heterocyclic nature, the interplay of heterocycles with MCRs becomes therefore significant. The first chapter focuses on the recent progress made in the area according to the main reactivity mode involved in the transformation: concerted, radical, metal-catalyzed, carbonyl/imine, and isocyanide-based processes. The chapter itself provides an overview of heterocycles as input in MCRs. The next chapter "Heterocycles and Multi-Component Polymerizations" highlights some of the latest examples in this emerging field. The third chapter highlights examples from the viewpoint of target-oriented synthesis, the use of MCR in medicinal chemistry, from drug discovery, synthesis of drugs, to screening libraries, and biopharmaceutical applications. Further, heterocyclic chemistry has traditionally relied on solution-phase synthesis as technological platform to discover and produce bioactive scaffolds. The

next chapter "*Solid-phase Heterocycle Synthesis using Multicomponent Reactions*" highlights methodological aspects of the implementation of on-resin MCRs to produce heterocycle compounds. Different name reactions, synthetic strategies, and solid-supports are analyzed critically in this chapter.

In the synthesis of heterocyclic compounds, MCRs have inherent advantage on pot, atom, and step economy (PASE) and are simple in operation, consume less energy, and release a reduced amount of waste. The fifth chapter discusses MCR-based green synthetic methods, including high-order MCRs, consecutive MCRs, MCRs followed by cyclization, and cycloaddition reactions, for the synthesis of heterocycles. Further, the use of enabling methods viz. continuous flow approaches has been beneficial in terms of yield, selectivity, reaction time, real-time monitoring. The next chapter is focused on different methodologies that can be used to perform heterocycle multicomponent syntheses in a continuous flow, to highlight the advantages over batch synthesis. Similarly, the next chapter analyzes a merging of C–H functionalization and MCRs approaches toward synthesis and modification of heterocyclic compounds.

MCRs have demonstrated their reliability and effectiveness as a synthetic approach that provides rapid access to chemical complexity. Among the many factors that bring this about, the MCR effect stands out, based on the fact that a changed number of reagents becomes the main differentiating factor of the reaction direction, that enables *multicomponent-switched heterocyclizations*, the topic of the next chapter in the book. Alkynoyl functionalities are densely substituted bifunctional electrophiles and prerequisite in many heterocycle syntheses via cyclocondenzations or cycloadditions. The 10th chapter of the book summarizes, explains, and highlights recent endeavors in the catalytic alkynoyl generation and their application to diversity-oriented multicomponent syntheses of heterocycles. The next chapter of the book is focused on the MCR synthesis of saturated heterocycles, encompassing the synthesis of small ring size (from 3 to 7) heterocycles, macroheterocycles, fused rings, and spirocyclic compounds. This is followed by the topic *asymmetric MCRs* where the development of enantioselective versions of these reactions have led to optimized reaction conditions, broader scopes, and increased chemo- and enantioselectivities. At last, the final chapter focuses on the recent advances made in MCRs built upon transition metal-catalysis directed toward the synthesis of heterocycles. In conclusion, this volume offers a versatile overview of the topic alongside discussing the recent progress in the flourishing area of MCR chemistry. This would, in turn, provide a platform for future innovations toward the designing of novel green transformations for heterocyclic synthesis.

Finally, we are extremely grateful to all authors for their excellent contributions to this volume. We are also thankful to the Wiley editors in particular Dr. Elke Maase and Ms. Katherine Wong for their professional support and assistance during this endeavor.

University of Leuven (KU Leuven)
Belgium
21 June 2021

Dr. Upendra K. Sharma
Prof. Dr. Erik V. Van der Eycken

1

Heterocycles as Inputs in MCRs: An Update

Ouldouz Ghashghaei, Marina Pedrola, Carmen Escolano, and Rodolfo Lavilla

University of Barcelona, Laboratory of Medicinal Chemistry, Faculty of Pharmacy and Food Sciences, and Institute of Biomedicine IBUB, Av. de Joan XXIII, 27-31, Barcelona 08028, Spain

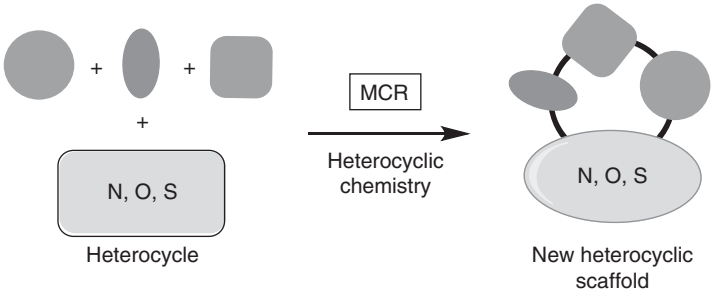
1.1 Introduction

Multicomponent reactions (MCRs) hold a privileged position in organic synthesis and are currently gaining momentum in the fields where a fast access to high levels of structural diversity is needed. This is especially important in medicinal chemistry and key to drug discovery. In this endeavor, as the vast majority of small-molecule drugs are of heterocyclic nature, the interplay of heterocycles with MCRs becomes significant [1]. Although the majority of work has been devoted to the synthesis of heterocyclic adducts from non-heterocyclic reactants [2, 3], we will focus, however, on the intrinsic reactivity of basic heterocycles as a source of synthetically useful MCRs (Scheme 1.1). This approach, still quite unexplored in the MCR context, is arguably a rich source of novel, complex scaffolds. There is a wide choice of commercially available heterocyclic inputs, which together with their often-exclusive reactivity make this perspective simple, conceptually attractive, and synthetically productive. In this chapter, we describe a representative selection of relevant results in the last six years, as the field has experienced impressive growth since our last revision [4], and an exhaustive account is out of scope. This update groups the highlighted processes according to the main reactivity modes defining the MCRs: concerted, radical, metal-catalyzed, carbonyl/imine, and isocyanide-based processes. Finally, a miscellany section is included to cluster those MCRs that do not clearly fit in the classification. Occasionally, some significant post-transformations and applications have been detailed.

1.2 Concerted MCRs

The impact of heterocycle-based concerted MCRs in organic synthesis is quite relevant, with recent contributions arising from Povarov reactions, hetero Diels–Alder processes, and dipolar cycloadditions. The Povarov MCR, the interaction of an

Multicomponent Reactions towards Heterocycles: Concepts and Applications, First Edition.
Edited by Erik V. Van der Eycken and Upendra K. Sharma.



Scheme 1.1 Heterocycles as inputs in MCRs.

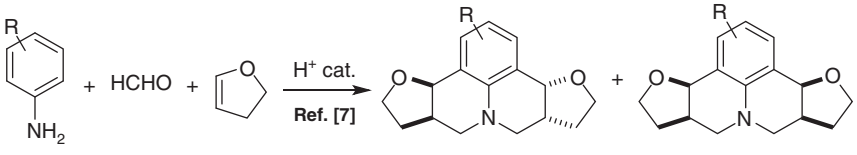
aromatic amine, an aldehyde, and an activated alkene, remains one of the best synthetic approaches to access tetrahydroquinolines (THQs) [5] and is especially productive in medicinal chemistry [6]. Although the concerted cycloaddition is a well-founded hypothesis for the reaction mechanism, there is evidence on polar stepwise processes in some cases, and both pathways are considered here.

For instance, a double Povarov process led to julolidine derivatives: the first MCR generates a secondary amine, which under calixarene-based polysulfonic acid catalysis spontaneously triggers a second MCR, leading to the final five-component adducts with good yields and modest stereoselectivity (Scheme 1.2) [7].

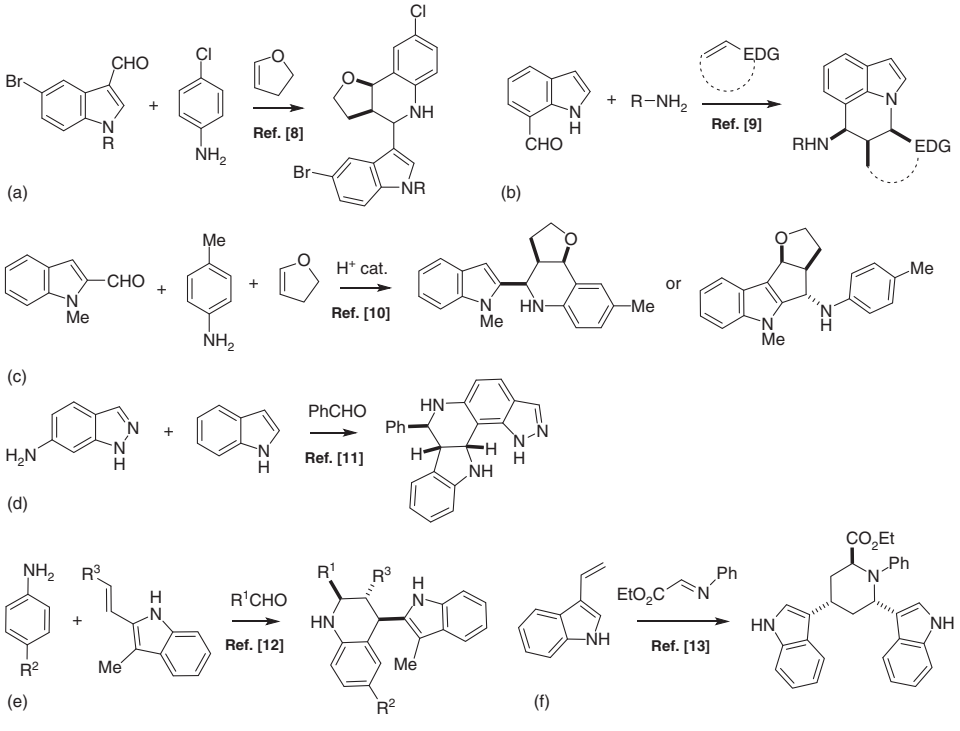
Indole derivatives participate in Povarov MCRs not only as aldehyde or olefin inputs, but also as aniline surrogates. Their specific structural arrangement, and the catalytic conditions used, determines the outcome. In this way, while indole-3-carbaldehyde gives the expected Povarov adduct [8], indole-7-carbaldehyde reacts in a different way, leading to fused adduct where the indole nitrogen closes a six-membered ring [9]. Interestingly, indole-2-carbaldehyde, depending on the catalysts used, may lead to the *normal* Povarov adduct or to a different scaffold, with a distinct connectivity through an alternative [3 + 2] cycloaddition mode (Scheme 1.3) [10].

As olefin inputs, indoles unsubstituted at C2 and C3 yield the THQ adduct, losing the aromaticity at the pyrrole ring [11]. In this respect, 2-vinylindoles react exclusively at the olefin moiety to yield the expected THQ adduct [12]. However, the isomeric 3-vinyl derivatives react quite differently, leading to bisindole-piperidines in a stereo- and enantio-controlled fashion, using chiral catalysts (Scheme 1.3) [13].

Regarding heterocyclic inputs, the interaction of aldehydes, 1,4-dhydropyridines as activated olefins, and aminocoumarin, as aniline surrogate, leads to complex



Scheme 1.2 Access to julolidines via double Povarov MCRs.



Scheme 1.3 Indoles as inputs in Povarov MCRs.

functionalized chromenonaphthyridines [14]. Relevantly, 3-aminopyridine imines react with alkynes (terminal or internal) to regioselectively afford the naphthyridine scaffold [15]. Similarly, 3-aminopyridones also lead to oxidized Povarov adducts (Scheme 1.4) [16].

There are mechanistic variations that dramatically modify the connectivity pattern of standard Povarov MCRs. For instance, a Ferrier rearrangement was promoted during a Povarov process involving glycals [17]. An interesting example of interrupted Povarov process with salicylaldehydes, anilines, and dihydrofurans, instead of yielding the expected THQ adduct, follows a Mannich-type process with the enol ether, and the resulting intermediate is trapped by the phenolic hydroxyl, yielding the MCR adduct in a stereoselective fashion (Scheme 1.5) [18].

In a remarkable photoredox-catalyzed process, aldimines, dihydrofurans and trimethylsilyl azide, afforded azidotetrahydrofurans. The observed polarity reversal can be explained through a mechanism involving an azido radical, which adds on the β-position of the enol ether to promote the imine addition (Scheme 1.5) [19].

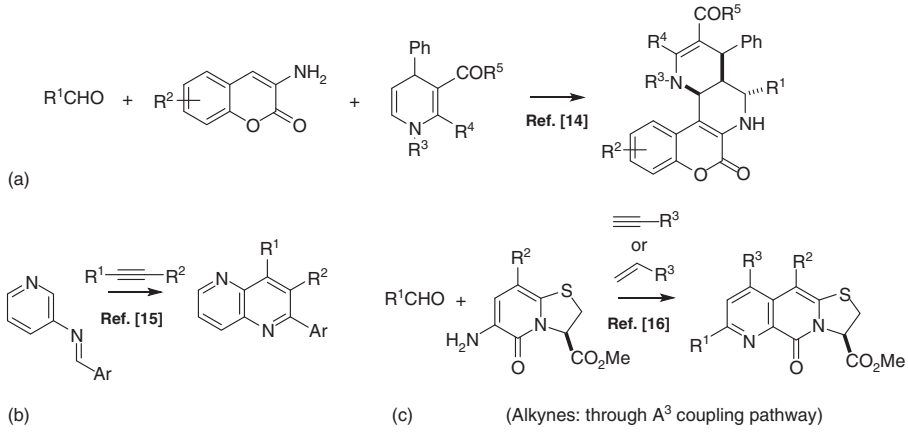
Finally, the Povarov MCR has enabled the selective tagging of benzaldehyde-functionalized DNA chains through the reaction with anilines and an *N*-protected dihydropyrrole [20].

Isochromenylium ions react with dienophiles in a [4 + 2] cycloaddition to yield adducts, which go through a Ritter-type domino process with acetonitrile to afford complex tetracyclic compounds [21]. Also, a formal concerted MCR connects *in situ* generated isoquinolinium salts with unsaturated aldehydes and alcohols in a process promoted by *N*-heterocyclic carbenes to give bridged azaheterocycles [22]. A [4 + 3] cycloaddition process is triggered by the condensation of an iminoindole with aldehydes to give an azadiene that reacts *in situ* with a sulfur ylide to yield azepinoindoles (Scheme 1.6) [23].

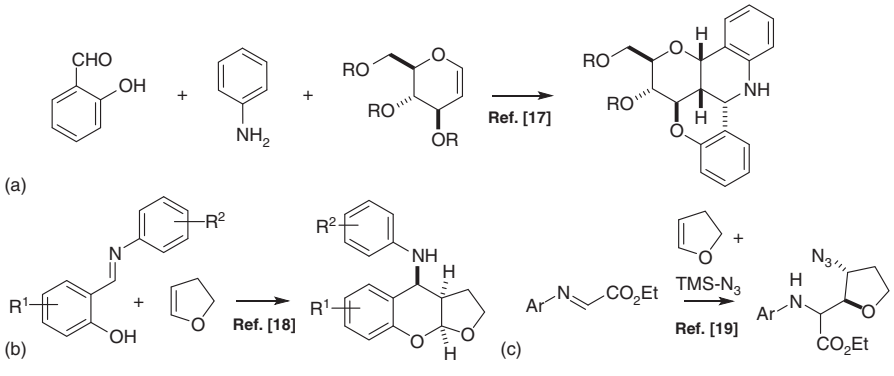
MCRs involving [3 + 2] cycloadditions have produced a substantial number of new transformations. The processes involving azinium ions have been reviewed [24]. The interaction of heterocyclic secondary amines with carbonyl inputs to generate dipoles is a common motif in the field. For instance, THQs, aldehydes, and ketomalonate afford the corresponding oxazolidine adducts [25].

Azomethine ylides, mostly generated by condensation or decarboxylation of α-amino acids, have been thoroughly used in MCRs in the presence of suitable dipolarophiles, often with applications in drug discovery [26]. The synthesis of pyrrolizidines and indolizidines through this MCR methodology has been reviewed [27]. A remarkable five-component interaction based on a double [3 + 2] cycloaddition of azomethine ylides has led to tetracyclic adducts in high yields in a stereoselective manner (Scheme 1.7) [28].

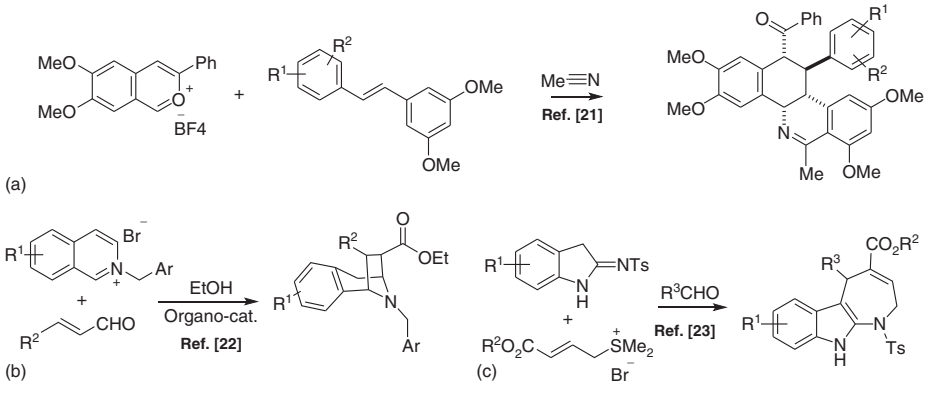
Azines are also present in this reactivity. α-Methylquinolines, aldehydes and alkynoates yield a fused adduct in a domino process starting with the formation of the dehydrated aldol-like intermediate [29]. Moreover, quinoline and pyridine dipoles react with azomethine ylides in an unprecedented fashion to yield complex fused pyrrolidine cycloadducts [30]. Finally, isatin undergoes a series of complex transformations triggered by the initial [3 + 2] cycloadduct generated through its interaction with proline and alkynoates (Scheme 1.8) [31].



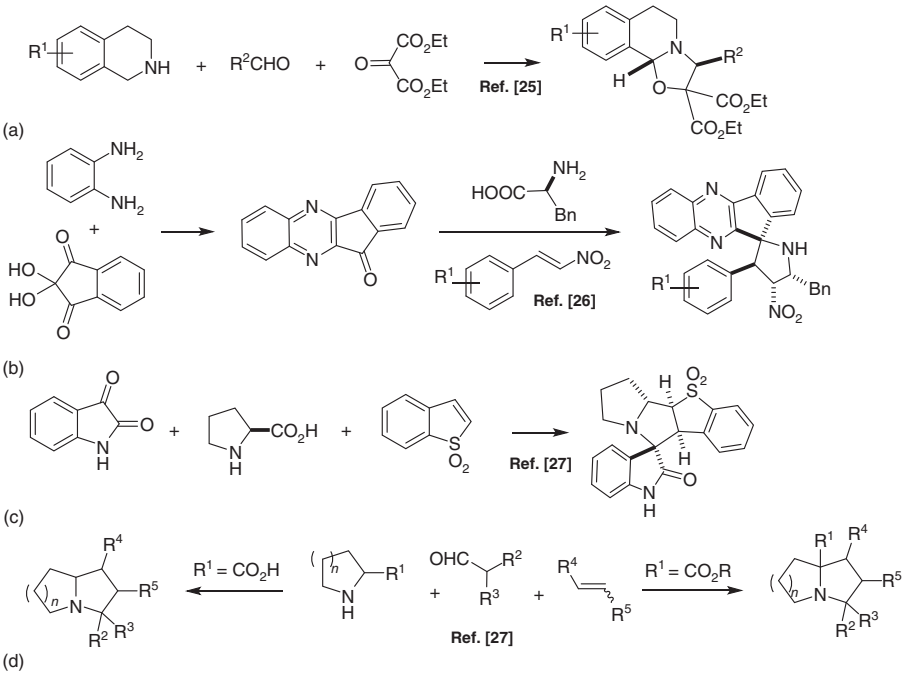
Scheme 1.4 Aminoheterocycles in Povarov MCRs.



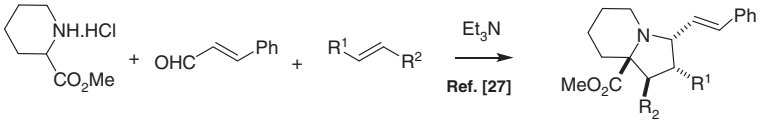
Scheme 1.5 Mechanistic variations of the Povarov-type processes.



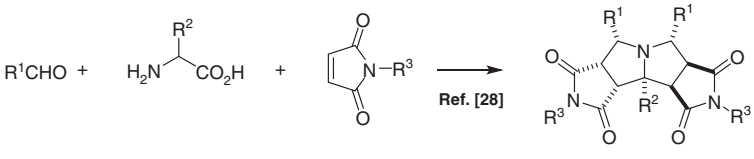
Scheme 1.6 Cycloaddition-type MCRs.



Scheme 1.7 [3 + 2] Dipolar cycloaddition MCRs.

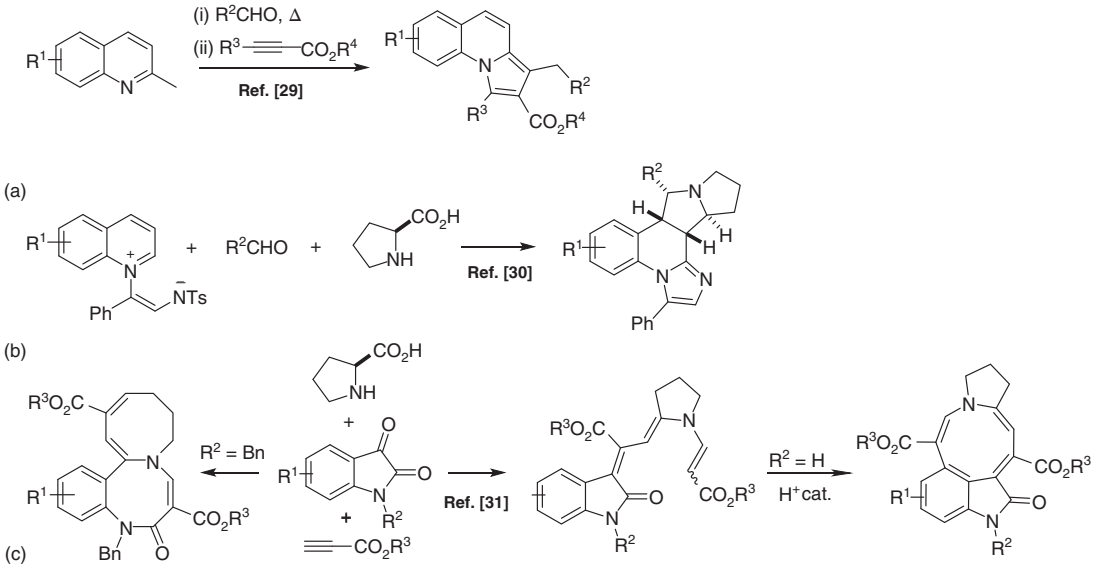


(e)



(f)

Scheme 1.7 (*Continued*)



Scheme 1.8 Azines and isatins in dipolar MCRs.

Arynes yield dipoles through interaction with nucleophilic species. Their participation in MCRs has been recently reviewed [32]. Azines are *N*-arylated, and the resulting dipole interacts with carbonyl groups in an addition/cyclization mode or through proton transfer to generate second nucleophiles that trap the azinium intermediate. Also, the azine dipoles react with the aryne in [3 + 2] dipolar cycloaddition MCRs (Scheme 1.9).

In a series of related processes, epoxides, aziridines, and also four-membered cyclic amines and (thio)ethers react with arynes and protonucleophiles leading to the corresponding adduct featuring a substituted chain originated in the heterocycle (Scheme 1.10) [32].

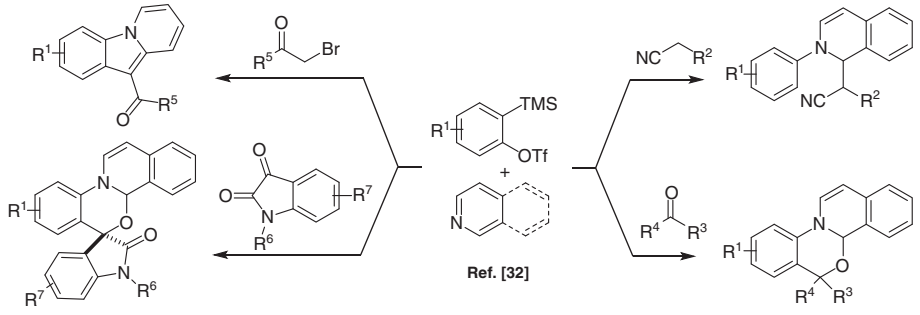
1.3 Radical MCRs

The incorporation of radical chemistry into MCRs has unlocked access to new synthetic pathways unavailable through conventional polar reactions. Radical MCRs generally consist of a proradical, a relay reagent, and a trapping component [33]. Novel radical MCRs exploiting photochemical approaches have experienced rapid growth in recent years [34]. However, their pairing with heterocyclic inputs has been mainly restricted to the functionalization of the heterocyclic component. In this regard, the multicomponent versions of Minisci reaction stand out [35]. In these processes pyridine-type heterocycles get alkylated in the presence of a suitable alkene and an initiator amenable to produce the radical species [36]. β-Dicarbonyl radicals [37] as well as heteroatomic radicals including azido [38], sulfonyl, and phosphonyl [39] species have been reported to yield Minisci adducts in a similar fashion. As for the alkene components, *N*-vinylacetamide has been coupled with suitable azines and the proradical, to enantioselecitvely afford γ-aminoesters in the presence of a chiral phosphoric acid (Scheme 1.11) [40].

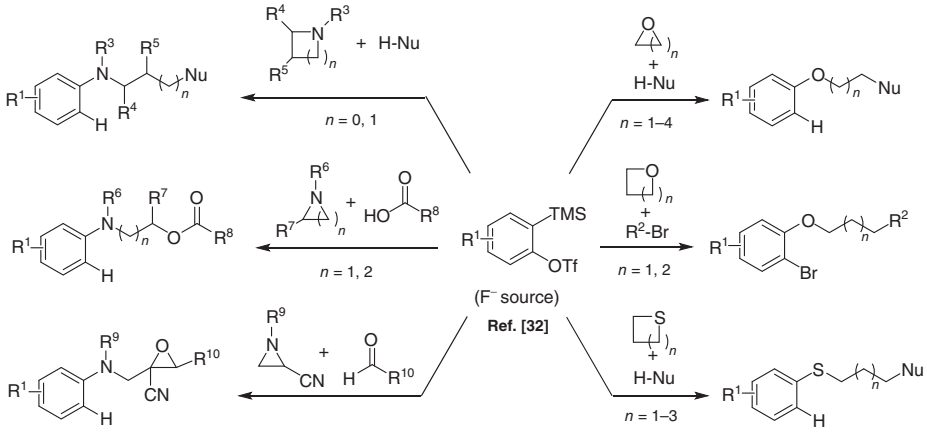
The scope of the heterocycic inputs in Minisci MCRs is mainly restricted to pyridine-type systems, usually substituted at some reactive positions (C2/C4) to block undesired regioisomer formation. In an alternative approach, the use of 4-cyanopyridine allows the γ-selective functionalization under a variety of conditions, involving the favored generation of pyridyl radicals [41, 42]. Interestingly, the use of Tf_2O as the azine activator and a CF_3 radical source results in the regioselective *p*-trifluoromethyl-alkylation of pyridines and quinolines [43]. In a related process, the use of pyridyl halides directs the functionalization upon the C4 position in a Ni-catalized radical process. It also features an interesting [1,5]-H shift that enables the heteroatom addition upon the β position of the initiating carbon radical (Scheme 1.12) [44].

Other heterocyclic systems have also been functionalized through radical MCRs. For instance, the C-sulfonylation of imidazoles has been reported in an Eosin-catalyzed photoredox transformation (Scheme 1.13) [45].

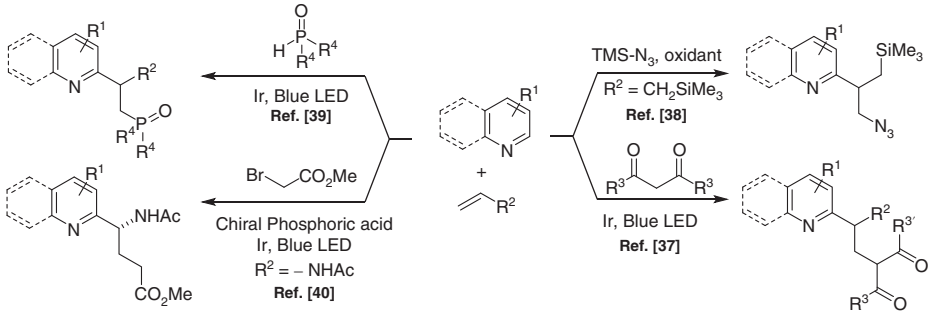
Dearomatization of indoles and related heterocycles has also been achieved through radical MCRs. In a remarkable approach, C3-spiro trifluoromethylindolines have been assembled in a copper-catalyzed radical MCR with β-aminomethylindoles,



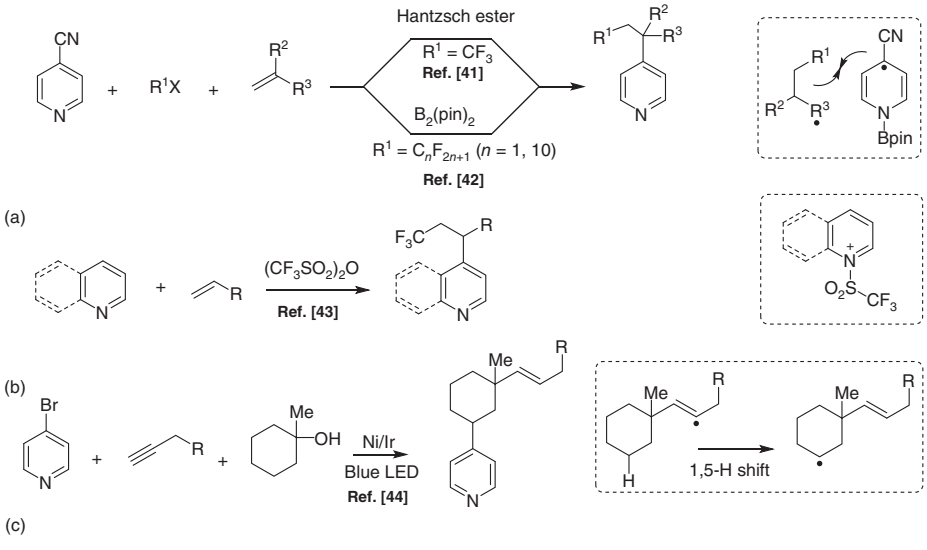
Scheme 1.9 Azine-aryne MCRs.



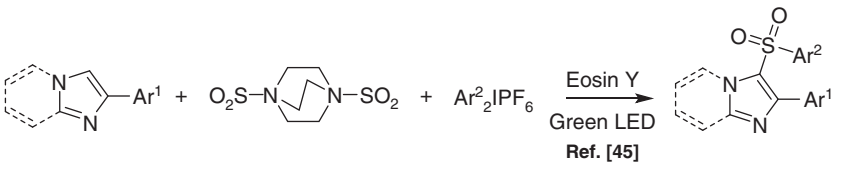
Scheme 1.10 3/4-Membered heterocycles in aryne MCRs.



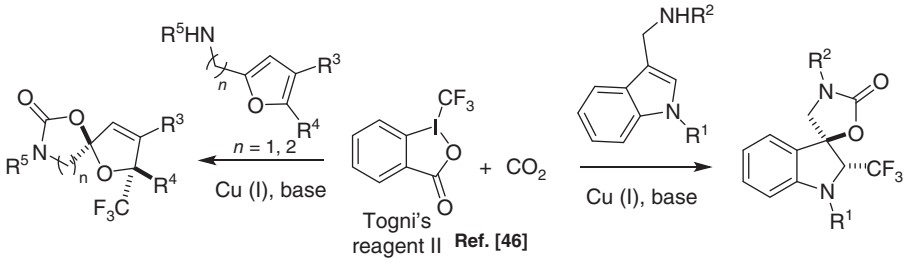
Scheme 1.11 Minisci-type radical MCRs.



Scheme 1.12 Site-selective azine-based radical MCRs .



Scheme 1.13 SO_2 photoredox MCR.



Scheme 1.14 Heterocycle dearomatization in radical MCRs.

carbon dioxide, and a trifluoromethyl radical source. The CF_3-indole radical is intramolecularly trapped by the copper carbamate, which is formed *in situ*, through the condensation of amine and CO_2. Furans with similar side chains have successfully afforded the corresponding spiro adducts (Scheme 1.14) [46].

Finally, maleimides have been involved in a remarkable Minisci-type MCR, in which the initiating alkyl radical was generated through a novel mild process [47]. Moreover, the assembly of fused quinolines through the condensation of 3-arylaminoacrylates, maleimides, and an electrophilic radical source has been achieved, matching the radical affinities in a domino process (Scheme 1.15) [48].

1.4 Metal-catalyzed MCRs

Transition metal-catalyzed MCRs featuring heterocyclic inputs have also experienced immense progress in recent years. Regarding the C–H activation processes, the direct functionalization of azoles through the insertion of an isocyanide, followed by the attack of a heterocycle, has been reported for the synthesis of di(hetero)aryl-ketones and-alkylamines [49]. The methodology involves the reaction of azoles, haloarenes, and isocyanides resulting in the formation of an imine, which can be hydrolyzed or reduced to yield the final adducts. Other examples of C—H bond functionalization include the preparation of fused imidazo-heterocycles starting from methyl ketones, *o*-tosylhydroxylamine and 2-pyridinone or thiazo/benzo[d]thiazol-2(3H)-ones [50]. This MCR consists of the copper catalyst coordination, the formation of the C–H functionalized intermediate, followed by a tandem addition-cyclization process. A relevant C–H glycosylation via a Catellani-type arylation allows the synthesis of C-aryl glycosides, which can undergo further transformations, such as Heck, Suzuki, and Sonogashira cross-couplings (Scheme 1.16) [51].