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Heterocycles as Inputs in MCRs: An Update

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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.
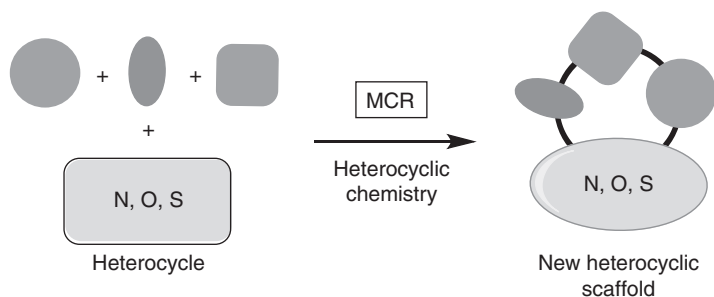
1.2 Concerted MCRs

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

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-dyhydropyridines as activated olefins, and aminocoumarin, as aniline surrogate, leads to complex
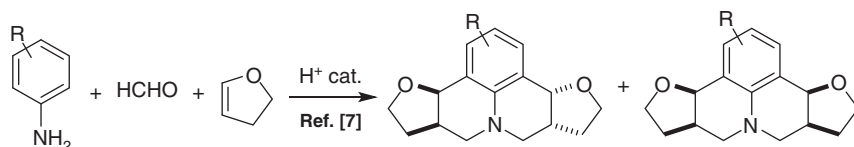
Scheme 1.2 Access to julolidines via double Povarov MCRs.
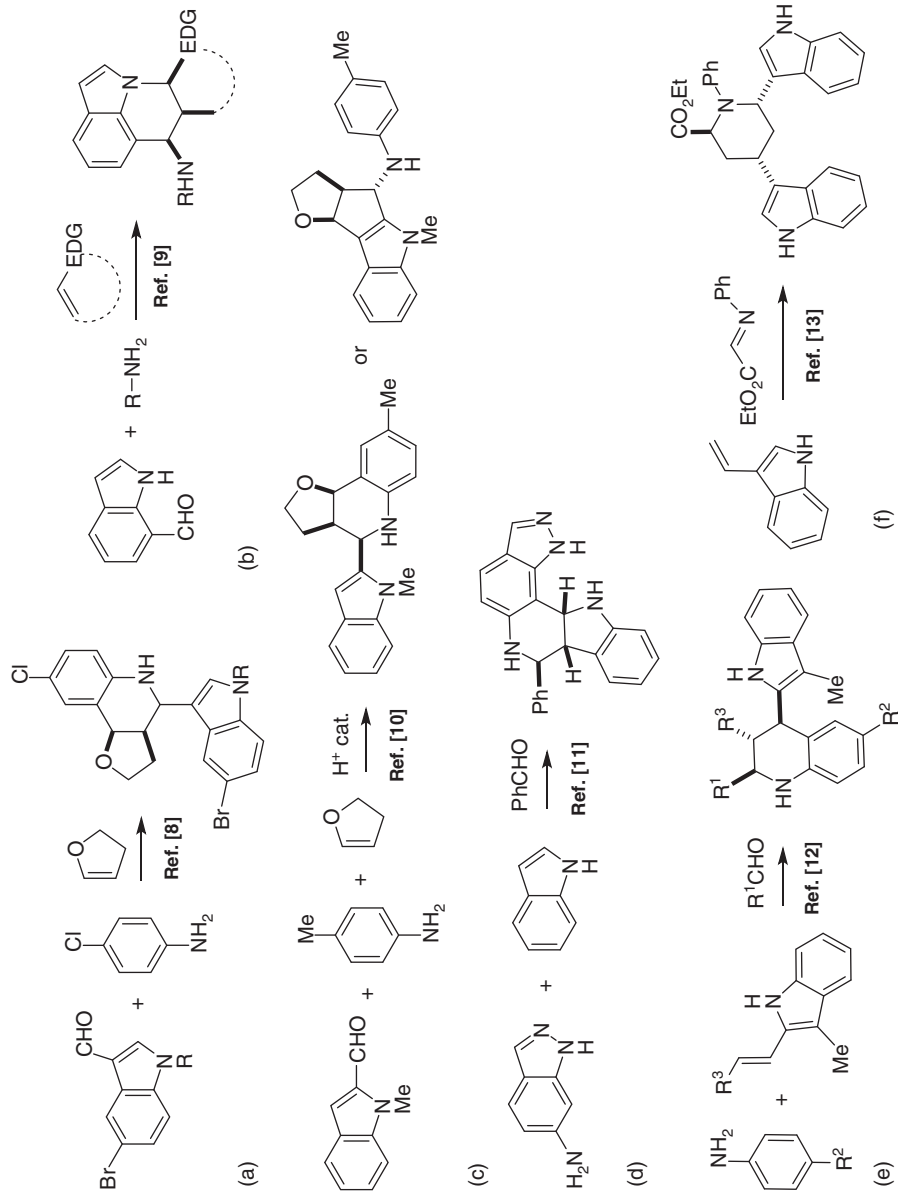
Scheme 1.3 Indoles as inputs in Povarov MCRs.

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].

(a)

R^1CHO +

(b)

Ref. [15]

(c)

R^1CHO +

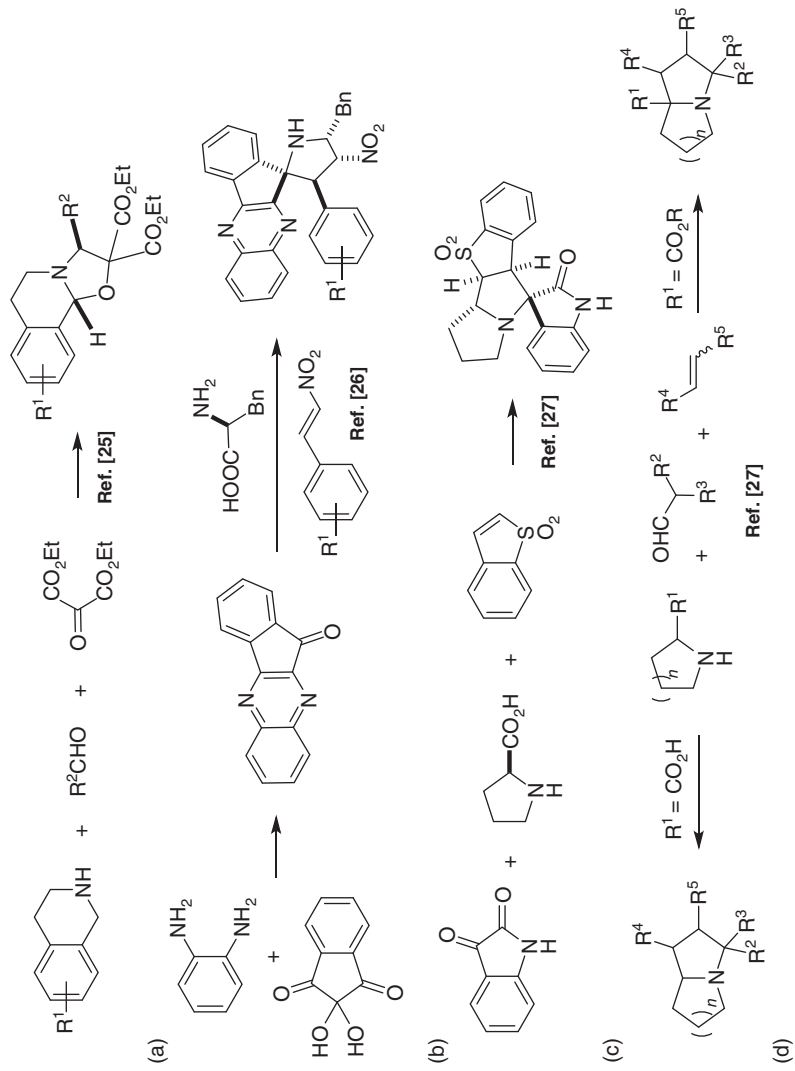(Alkynes: through A^3 coupling pathway)
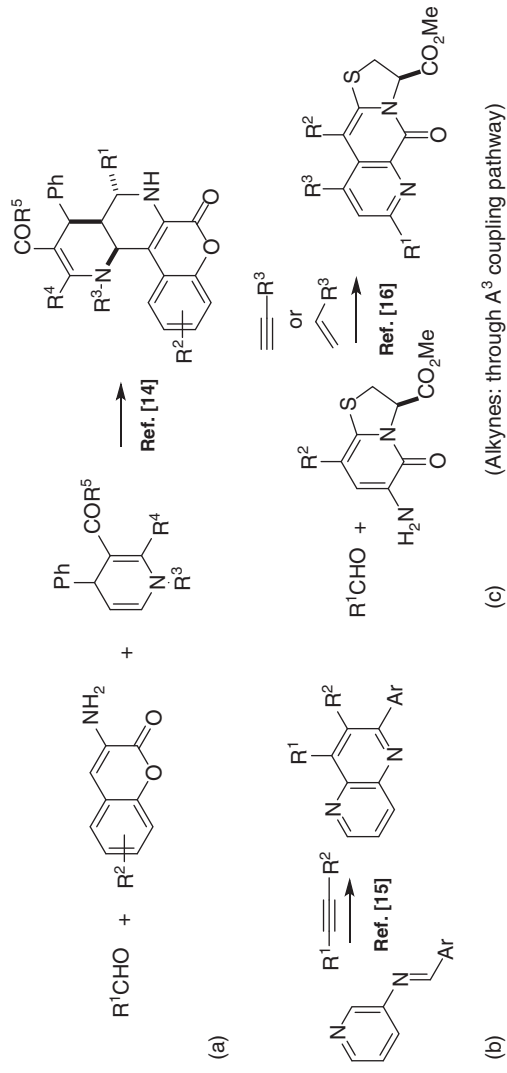
Scheme 1.4 Aminoheterocycles in Povarov MCRs.
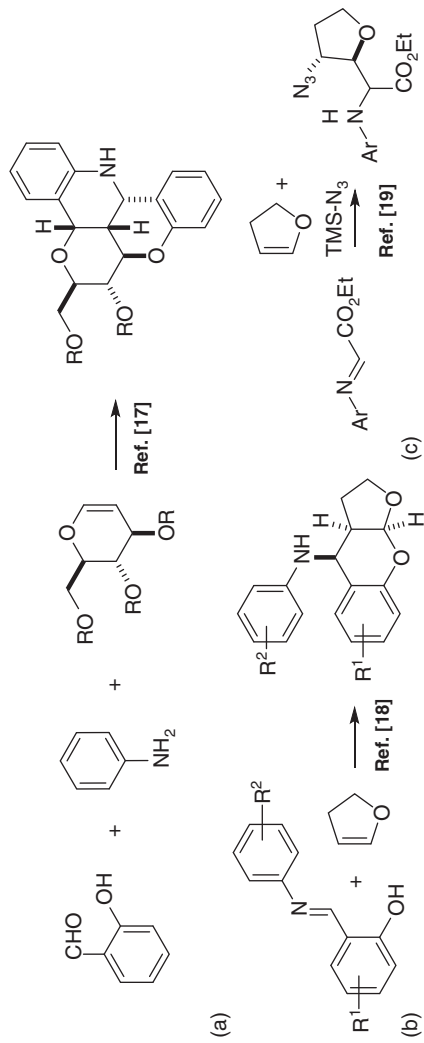
Scheme 1.5 Mechanistic variations of the Povarov-type processes.
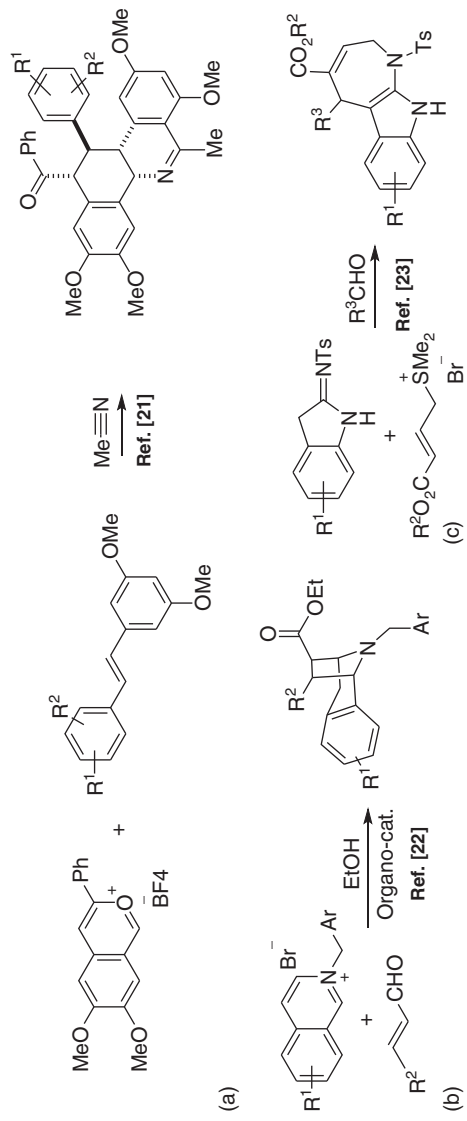
Scheme 1.6 Cycloaddition-type MCRs.

Scheme 1.7 [3 + 2] Dipolar cycloaddition MCRs.

(e)

NH.HCl
CO₂Me

$+$ OHC

Ph

$+$

R^1

R^2

$\xrightarrow[\textbf{Ref. [27]}]{Et_3N}$

Ph

R^1

R_2

N

MeO₂C

(f)

R^1CHO $+$

R^2

H₂N

CO₂H

$+$

O

N–R^3

O

$\xrightarrow{\textbf{Ref. [28]}}$

R^1

R^1

N

R^2

R^1

N–R^3

O

O

O

N

R^3

O

Scheme 1.7 (*Continued*)

(a)

(i) R^{2}CHO, Δ

(ii) R^3———CO$_2$R^4

Ref. [29]

(b)

Ref. [30]

(c)

R^2 = Bn

R^2 = Bn

Ref. [31]

R^2 = H

H$^+$ cat.
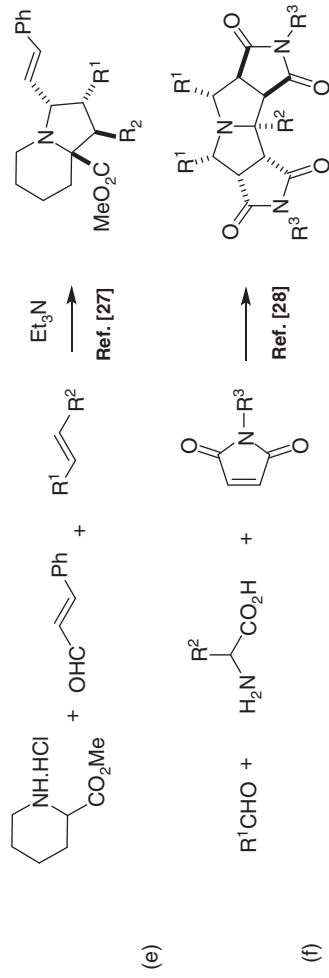
Scheme 1.8 Azines and isatins in dipolar MCRs.

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].
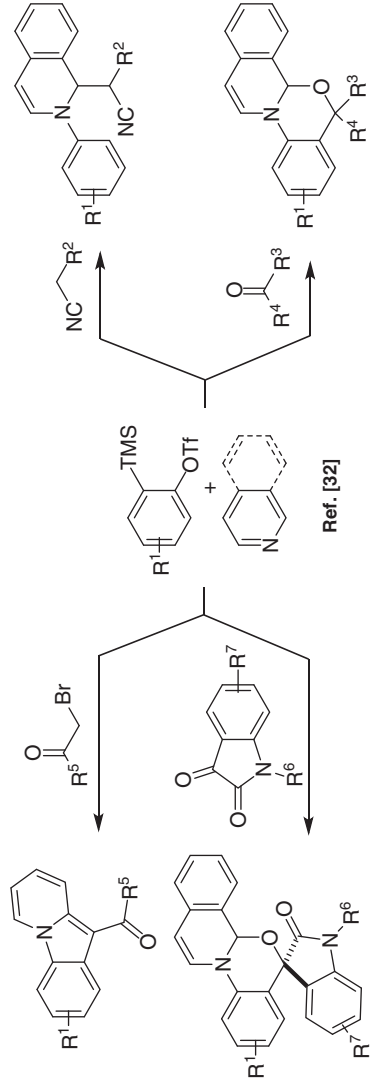
1.3 Radical MCRs

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].

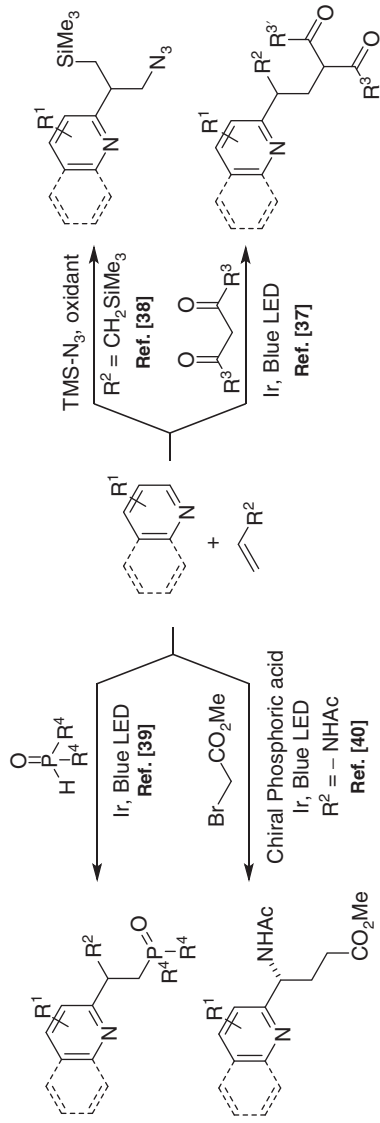Dearomatization of indoles and related heterocycles has also been achieved through radical MCRs. In a remarkable approach, C3-spiro trifluoromethylindolines have been assembled in a copper-catalyzed radical MCR with β-aminomethylindoles,
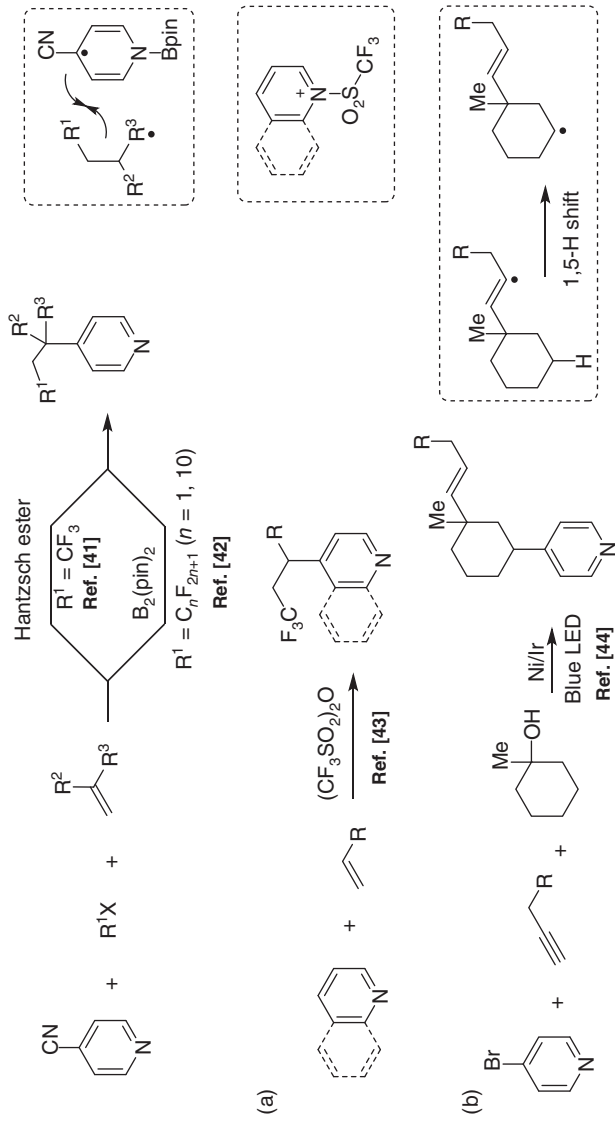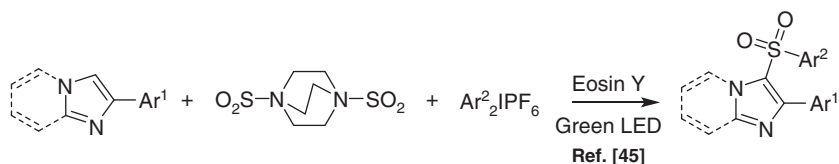
Scheme 1.9 Azine-aryne MCRs.
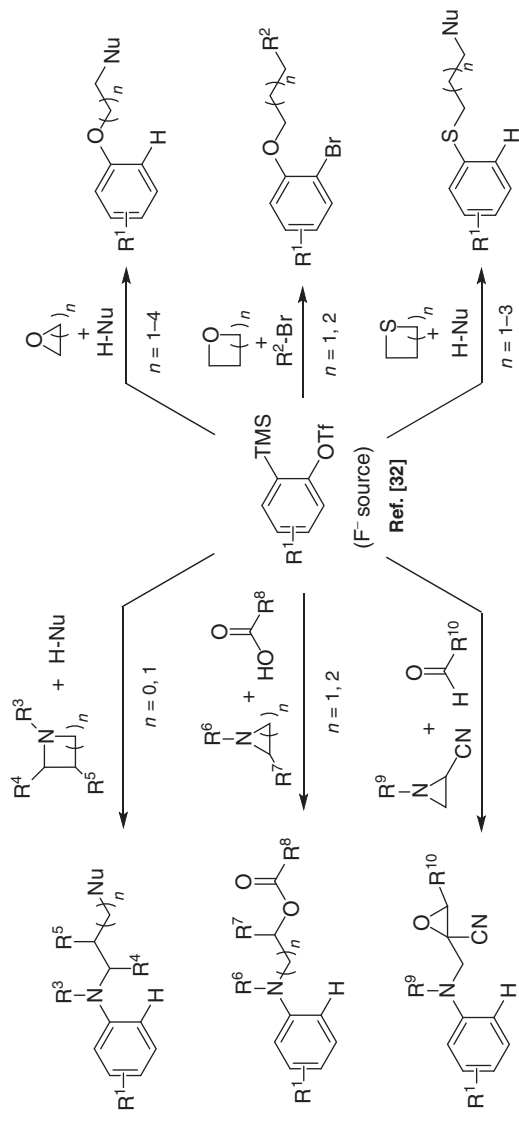
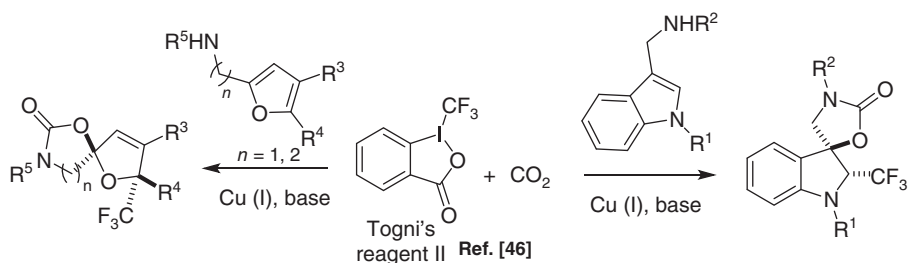**Scheme 1.10** 3/4-Membered heterocycles in aryne MCRs.

Scheme 1.11 Minisci-type radical MCRs.

Scheme 1.12 Site-selective azine-based radical MCRs .
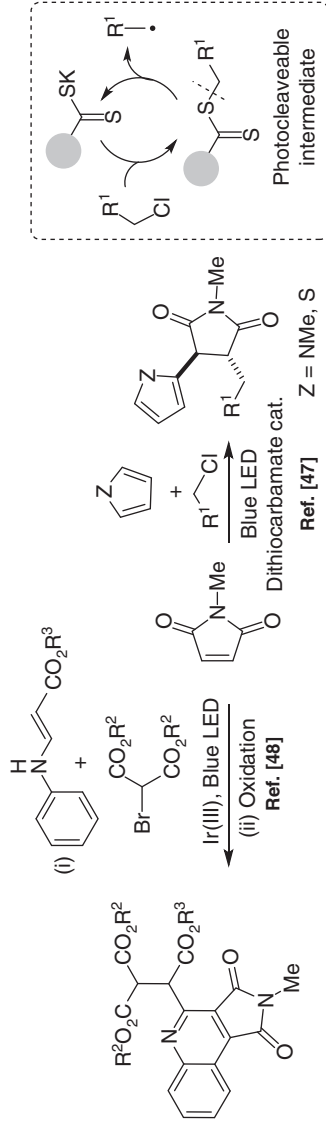
Scheme 1.13 SO_2 photoredox MCR.

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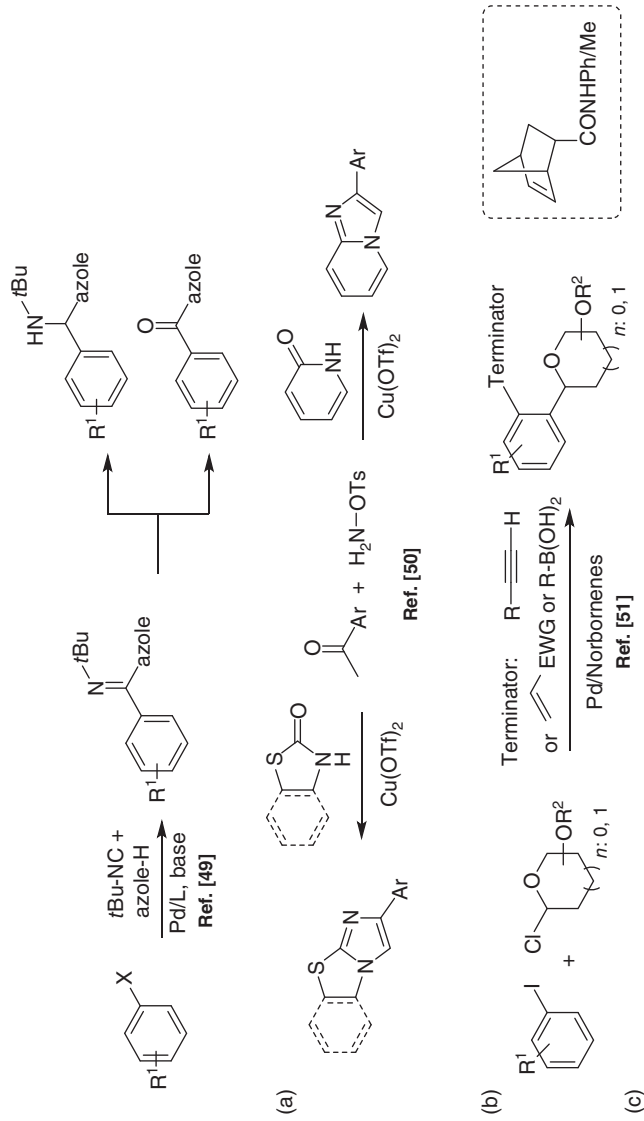
Finally, maleimides have been involved in a remarkable Minisci-type MCR, in which the initiating alkyl radical was generated through a novel mild process [47]. Moreover, the assembly of fused quinolines through the condensation of 3-arylaminoacrylates, maleimides, and an electrophilic radical source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

Scheme 1.15 Maleamides as inputs in radical MCRs.

(a)

R^1—X

tBu-NC +
azole-H
Pd/L, base
Ref. [49]

R^1

N—tBu
azole

HN—tBu
azole
R^1

O
azole
R^1

(b)

Ar
N
S
N

O
S
N
H

Cu(OTf)$_2$

O
Ar + H$_2$N—OTs

Ref. [50]

Cu(OTf)$_2$

O
NH

N
N
Ar

R^1
I
+
Cl
O
OR^2
n: 0, 1

Terminator: R———H
or   ⟨=   EWG or R-B(OH)$_2$
Pd/Norbornenes
Ref. [51]

R^1
Terminator
O
OR^2
n: 0, 1

(c)

CONHPh/Me

Scheme 1.16 C–H activation MCRs.

Progress in the A3-related MCRs, the interaction of aldehydes, amines, and alkynes, includes the use of isoquinolines, suitably activated by a chloroformate as amine inputs through an enantioselective copper-catalyzed protocol [52]. Remarkably, the interaction of azine-2-carbaldehydes with secondary amines and terminal alkynes starts via the A3 MCR, and the adduct undergoes a formal Cu-catalyzed hydroamination to yield indolizines [53, 54]. Terminal alkynes are also useful inputs in the MCR coupling of *N*-heteroaromatics (quinolines) with alkyl halides. The tandem process is catalyzed by CuI and allows the formation of 1,2-difunctionalized quinoline-type derivatives (Scheme 1.17) [55].

Some carbonylative MCR processes dealing with heterocyclic inputs have also been disclosed: a Pd-catalyzed four-component coupling involving tryptamine leads to alkaloid-like compounds featuring the quinazolinone core [56]. Divergent PdI_2/KI-catalyzed aminocarbonylation-cyclization pathways starting from alkynylthioimidazoles yield functionalized imidazo-thiazinones and -thiazoles (Scheme 1.18) [57].

Although not strictly belonging to this section, metal-catalyzed post-modifications of MCR adducts constitute a powerful and versatile synthetic tool. For instance, Au/Ag-catalysis on phenol-alkynyl Ugi adducts efficiently promotes an intramolecular dearomative cyclization, followed by an aza-Michael addition yielding the tetracyclic scaffold [58]. Similarly, a concerted $[4 + 2]$ cyclization on an indole substrate terminates the assembly of complex bridged polycyclic alkaloid arrangements [59]. In this approach, the key step involves the alkyne hydroarylation. A related process involving a furane-alkyne Ugi adduct, undergoes the Au-domino process ending with a ring fragmentation to yield unsaturated 2-pyridones (Scheme 1.19) [60].

1.5 Carbonyl/Imine Polar MCRs

In this section a variety of multicomponent transformations involving carbonyl and/or imine substrates (not specifically related to the rest of the sections) is analyzed. For instance, a Mannich-type MCR of indoles, amines, and substituted aldehydes followed by a lactamization leads to a bicyclic a adduct [61]. A cascade three-component reaction of 6-aminouracil, aldehydes and tetrahydroisoquinolines allows the formation of a new pyrimidine ring through the functionalization of the C–H adjacent to the nitrogen by a 1,5-hydride transfer and concomitant oxidation [62]. A domino process involving heterocyclic *N*-acylenamines, formaldehyde, and primary amines builds conjugated pyrimidine rings in a stepwise Mannich-aminal MCR [63]. A mechanistically related process connects tryptamines, alkyl propiolates, and nitroalkenes, yielding indolizino-indoles or chromeno-indolizinoindoles (Scheme 1.20) [64].

The Petasis MCR, the interaction of *in situ* generated imines and boronic acids has been reviewed [65]. A highly diastereoselective three-component Petasis/intramolecular Diels–Alder tandem reaction involving allyl amines,
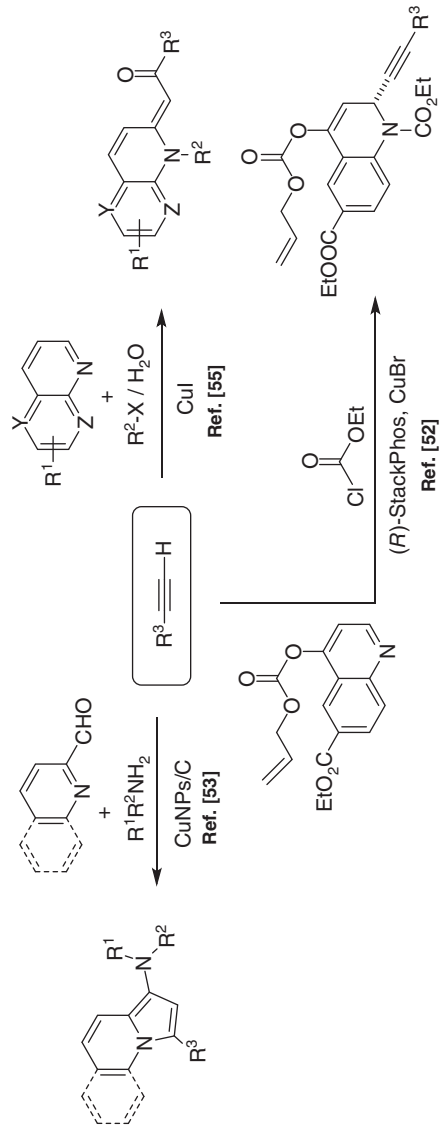
Scheme 1.17 A3-type MCRs.

(a)

(b)
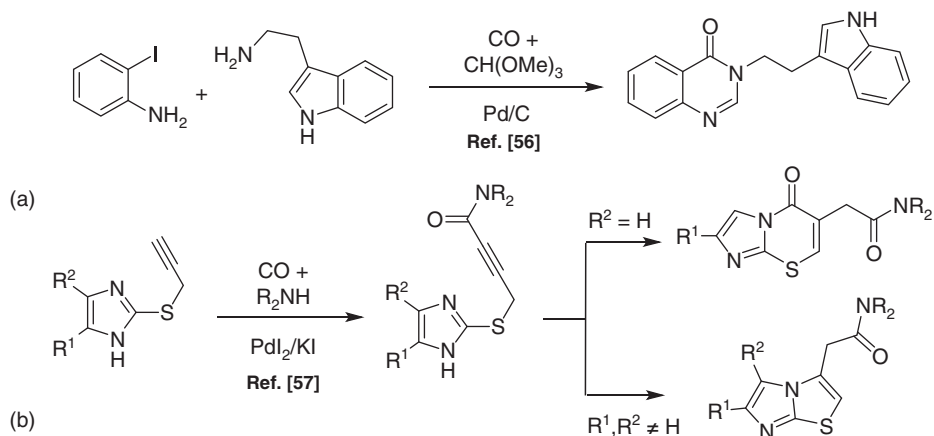
Scheme 1.18 Carbonylative transition-metal catalyzed MCRs.

furylboronic acid, and α-hydroxylated aldehydes led to a compact functionalized tricyclic system (Scheme 1.21) [66].

The Biginelli-type MCRs stand for the interaction of urea or urea-like compounds, aldehydes, and dicarbonyl derivatives. In this way, thiazolo-quinazolinones are generated from aminothiazoles [67]. Diversely substituted aminotriazoles [68] and aminopyrazoles [69] are active in Bigineli MCRs leading to the corresponding pyrimidine adducts (Scheme 1.22).

In a Hantzsch-type MCR, fused-tricyclic pyrans, and dihydropyridines were prepared by an indium (III)-catalyzed protocol involving a Knoevenagel adduct that cyclized to the final *N*- or *O*-tricyclic core (Scheme 1.22) [70]. Similarly, coumarin-fused pyrimidines were prepared by Biginelli-type MCRs (Scheme 1.23) [71, 72].

The Yonemitsu MCR has been employed for the synthesis of indole-based triarylmethanes. As an example, coumarines, diversely substituted indoles and quinoline-aldehydes led to highly crowded adducts [73]. Cyclic thio-substituted β-enaminoesters reacted in a diastereoselective manner with isatins cyclic β-diketones or 4-hydroxychromen-2-one to furnish complex polycyclic spiroindolines (Scheme 1.23) [74].

In a variation of this reactivity pattern, a nitro-Michael acceptor is introduced, and azolopyrimidines were synthetized by a BF$_3$-catalyzed MCR involving aminoazoles, aldehydes, and morpholinonitroalkenes, through the *in situ* generation of the reactive nitroalkynes (Scheme 1.24) [75].

The Reissert-type reactions involve the addition of nucleophiles to *in situ* *N*-activated azines to yield covalent adducts, usually at the α-position. Progress in the area deals with the regioselective phosphonylation of quinolines upon activation with chloroformates. Thus, reaction of the intermediate with differently substituted *N*-heterocyclic phosphines, where the substituent at the oxygen atom determines the α- or γ-attack (Scheme 1.25) [76].
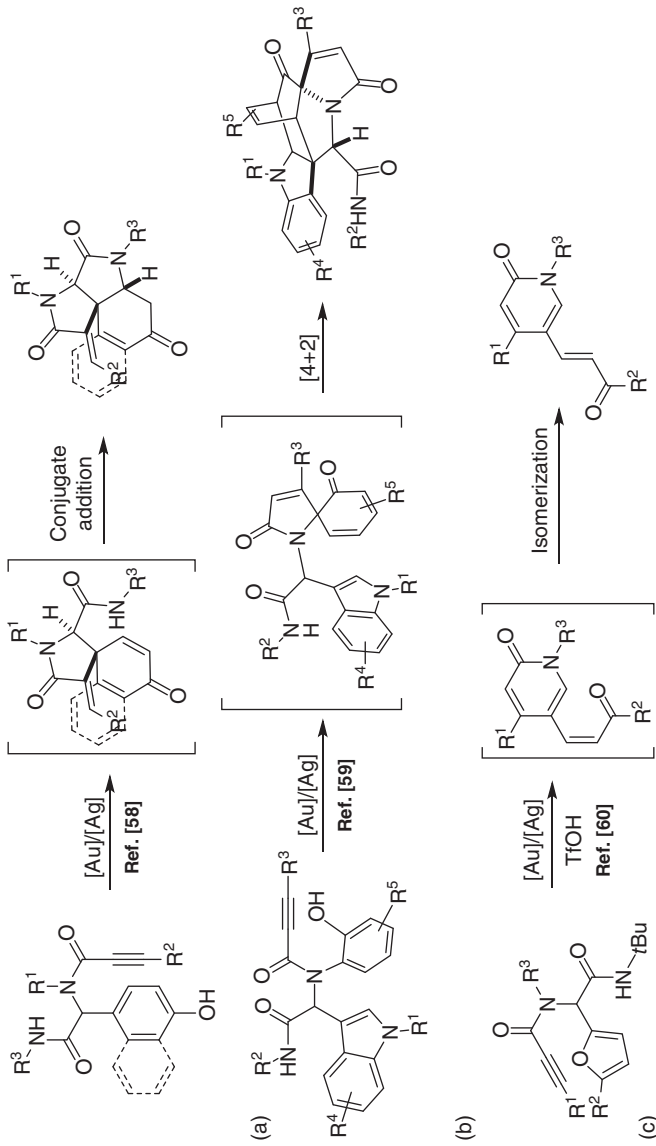
Scheme 1.19 Au(Ag)-catalyzed MCR post-transformations.

Scheme 1.20 Mannich-type MCRs.
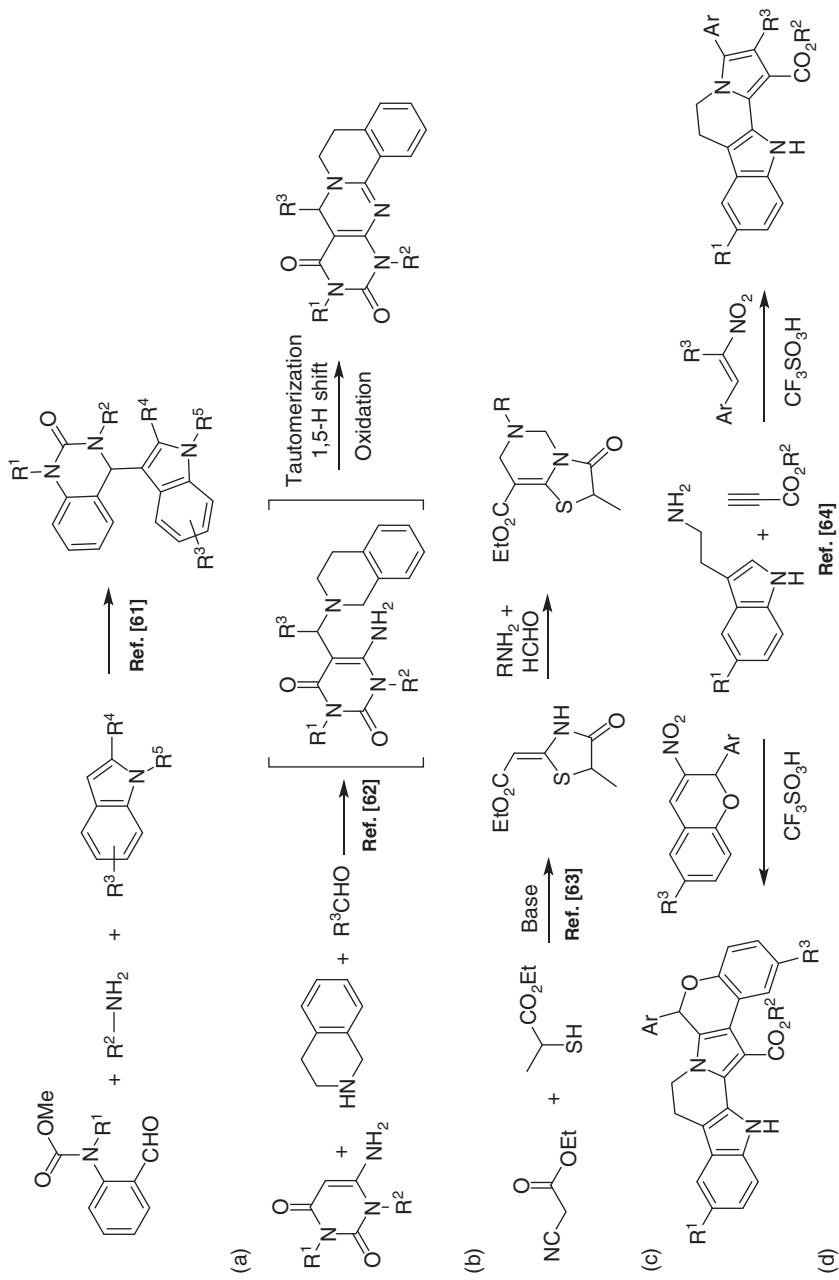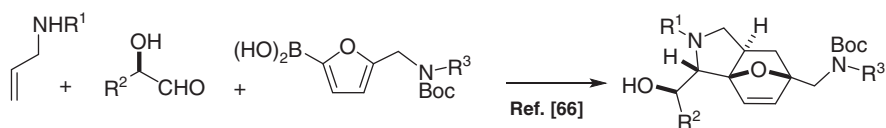
Scheme 1.21 Petasis MCR.

New enantioselective catalytic methods have been disclosed for this transformation. Chiral phosphoric acid promotes the *N*-addition of indoles upon *in situ* generated *N*-Boc-isoquinolinium ions [77]. Also, chloroformate promoted silyl ketene acetal additions to isoquinolines and other azines catalyzed by chiral anion-binding triazoles (Scheme 1.25) [78].

1.6 Isocyanide-based MCRs

Isocyanides stay as the most fruitful functional group in the MCR field. The classic Ugi and Passerini processes are still matter of active research, mainly dealing with mechanistic modifications and novel substrates. With respect to the Ugi-type MCRs, relevant results have appeared in this period. Regarding novelties in the reaction modes, interrupted processes have gained much importance. In these transformations, the usual trapping of the intermediate nitrilium ion by carboxylates and the subsequent Mumm rearrangement are replaced by a variety of nucleophilic additions affording structural diversity [79]. For instance, indole can efficiently trap the nitrilium, leading to spiroindolines, which continue a domino process to complex alkaloid-like compounds (Scheme 1.26) [80].

Heterocyclic amines have provided a series of oxidative [81] and redox neutral [82, 83] processes, involving the *in situ* formation of the active imine/iminium species, which subsequently react in an Ugi fashion. The Ugi–Smiles approach has been extended to functionalize thiouracil derivatives [84]. The interaction of an *in situ* generated Knoevenagel adduct with isocyanides and maleimides leads to a convenient preparation of a polycyclic adduct, which spontaneously evolves into a variety of isoindolocarbazoles (Scheme 1.26) [85].

Oxochromones react in a similar manner, upon the interaction with isocyanides and alkenes, through a series of [4 + 1]/[4 + 2] cycloadditions [86]. Interestingly, the closely related formylchromones can react with amines and isocyanides in a different way, leading to adducts arising from the initial conjugate addition of the isocyanide or the amine input to the conjugate carbonyl (Scheme 1.27) [87, 88].

Activated aziridines have produced polysubstituted tetrahydropyridines upon the interaction with cyanomalonates and isocyanides [89]. Finally, 2-bromo-6-isocyanopyridine is a general and affordable convertible isocyanide, since it suitably participates in Ugi processes, and the resulting aminopyridine unit can be replaced by a variety of nucleophiles in the adduct (Scheme 1.27) [90].

The Joullié MCR involves the interaction of imines with carboxylic acids and isocyanides [91]. From a synthetic point of view, this process is not just a simplification of the Ugi MCR, but rather a way to promote novel reactivity pathways. For

Scheme 1.22 Dicarbonyl derivatives in Biginelli- and Hantzsch-type MCRs.
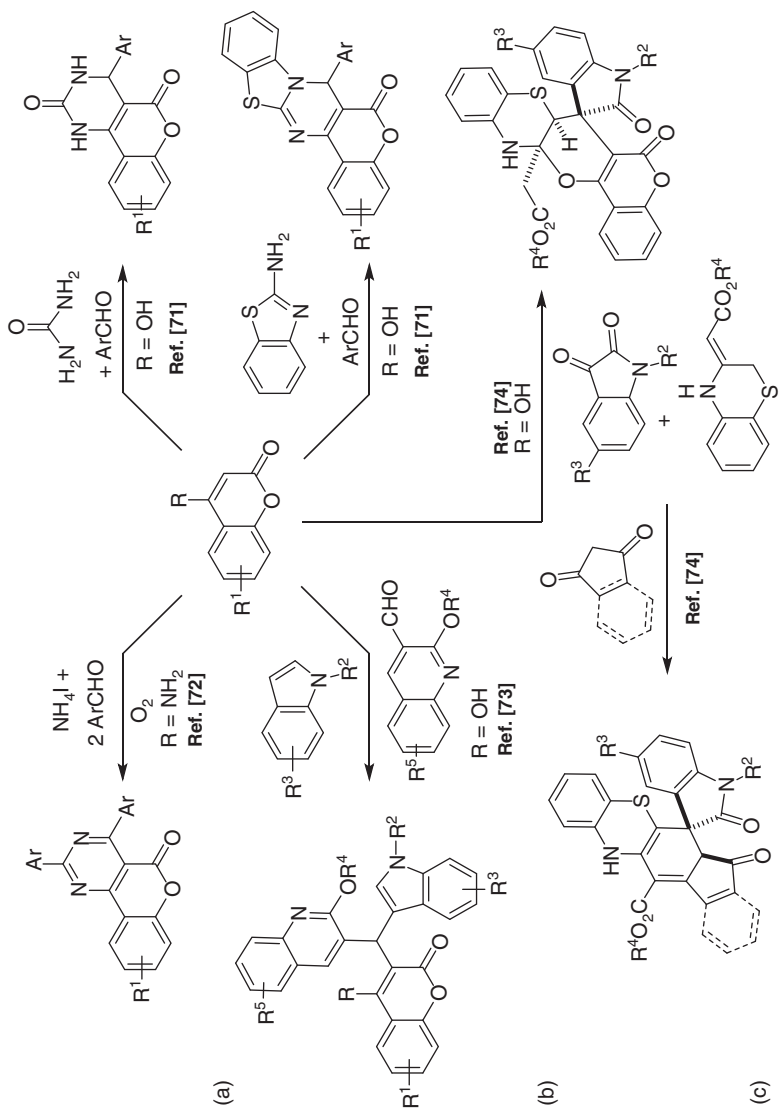
Scheme 1.23 Coumarins and isatins in MCRs.
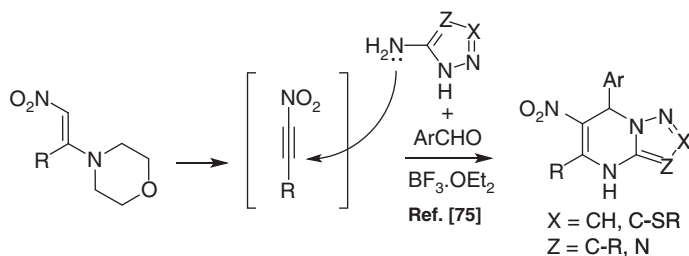
Scheme 1.24 Aminoazoles in conjugated addition-type MCRs.

instance, the *in situ* generation of cyclic imines from the (electro) chemical oxidation of secondary amines and their subsequent transformation has been described [92].
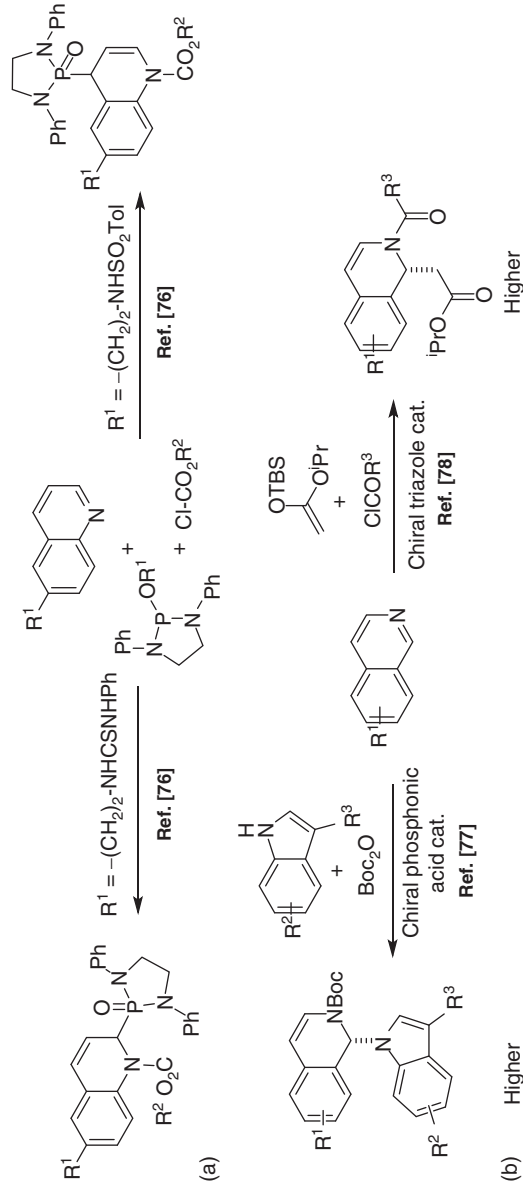
With respect to the different substrates engaged in the Joullié MCR, it is worth mentioning the spiroindolenines, which have suitably reacted to yield fused diketopiperazines, linked diamides, and tetrazoles [93, 94]. A remarkable approach to bicyclic hydantoines from *in situ* generated iminium salts resulting from the trifluoroacetic acid (TFA) treatment of *N*-Boc protected dihydropyrazines and β-aminoketones has been disclosed [95]. Azirines have recently been brought into this chemistry through Lewis acid activation, allowing a stereoselective access to functionalized *N*-acyl-aziridinecarboxamides (Scheme 1.28) [96].

The Groebke–Bienaymé–Blackburn (GBB) MCR, the interaction of α-aminoazines, aldehydes, and isocyanides, yield fused aminoimidazoles, a highly privileged scaffold in medicinal chemistry [97]. Mainly nonconventional examples of these transformations are mentioned here. Regarding aminoazines, GBBs with *N*-Boc-3-aminoindole followed by an oxidative cascade have resulted in the one-pot access to pyridodindoles [98]. The reaction mechanism features an interesting azirine intermediate, which evolves into the final adduct through a radical Neber-type rearrangement followed by a [1,2]-hydrogen shift/cyclization (Scheme 1.29).

Tetrahydroquinolin-8-amine, aldehydes, and isocyanides react to afford fused tricyclic quinoxaline adducts in a homoGBB transformation, in the presence of DMAP. The mechanism relies on the condensation of the aldehyde with the aniline to form the initial iminium ion, followed by the attack of the isocyanide [99].

Polyaminopolyazines have also been reported to afford multiple GBB adducts. The innate selectivity [100] observed in the case of 2,4-diaminopyrimindine results in the exclusive formation of a single monoadduct, enabling a selective second GBB upon the former product [101]. Incidentally, the monoadduct with the alternative regioselectivity was prepared through a protection strategy [102]. In a similar manner, triple-GBB transformations upon melamine yield unprecedented tripodal scaffolds, amenable to further diversification via suitable post-modifications (Scheme 1.29) [101].

Carbonyl components further diversify the reach of these transformations. GBBs with isatine and aminopyridines result in the one-pot formation of fused imidazopyrimidone salts through the expected spiroimidazole GBB adduct that

Scheme 1.25 Reissert-type reactions.

(a)

$R^1 = -(CH_2)_2-NHCSNHPh$

Ref. [76]

R^2O_2C

R^1

$+$ Cl-CO$_2$R^2

$R^1 = -(CH_2)_2-NHSO_2Tol$

Ref. [76]

CO$_2$R^2

R^1

(b)

R^1

Higher

$+$ Boc$_2$O R^3

Chiral phosphonic acid cat.

Ref. [77]

NBoc

R^1

R^3

R^2

R^1

OTBS

$+$ O^{i}Pr

ClCOR^3

Chiral triazole cat.

Ref. [78]

R^3

R^1

^{i}PrO

Higher
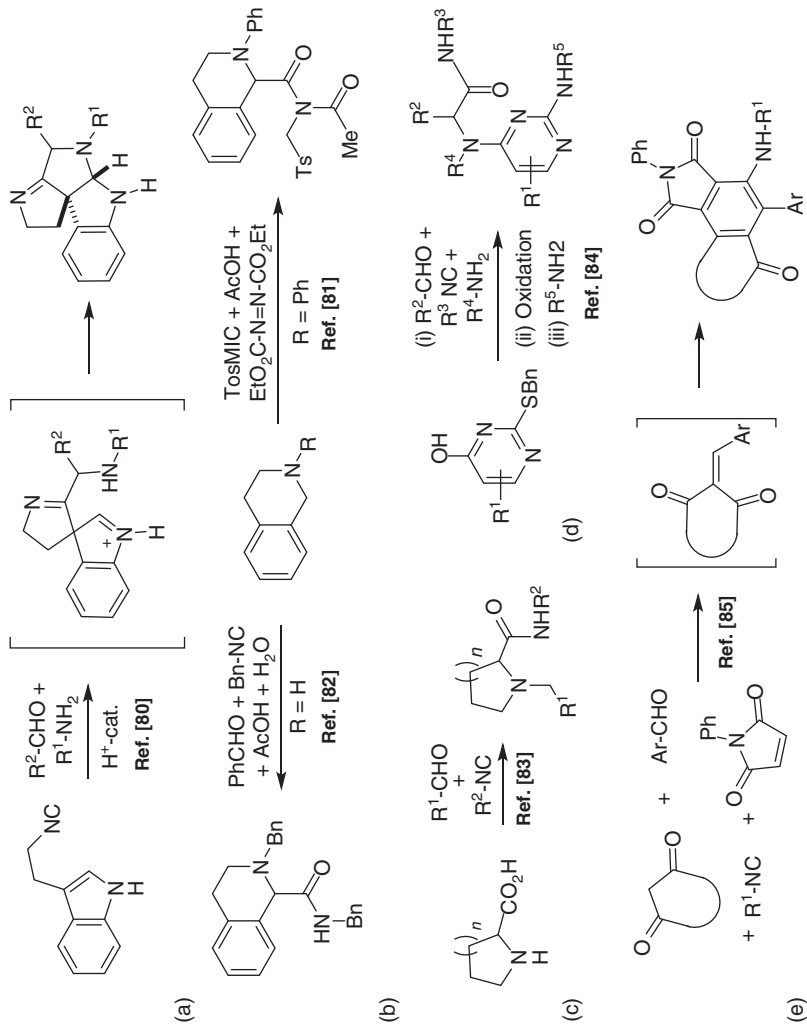
Scheme 1.26 Ugi-type MCRs. Mechanistic variations.
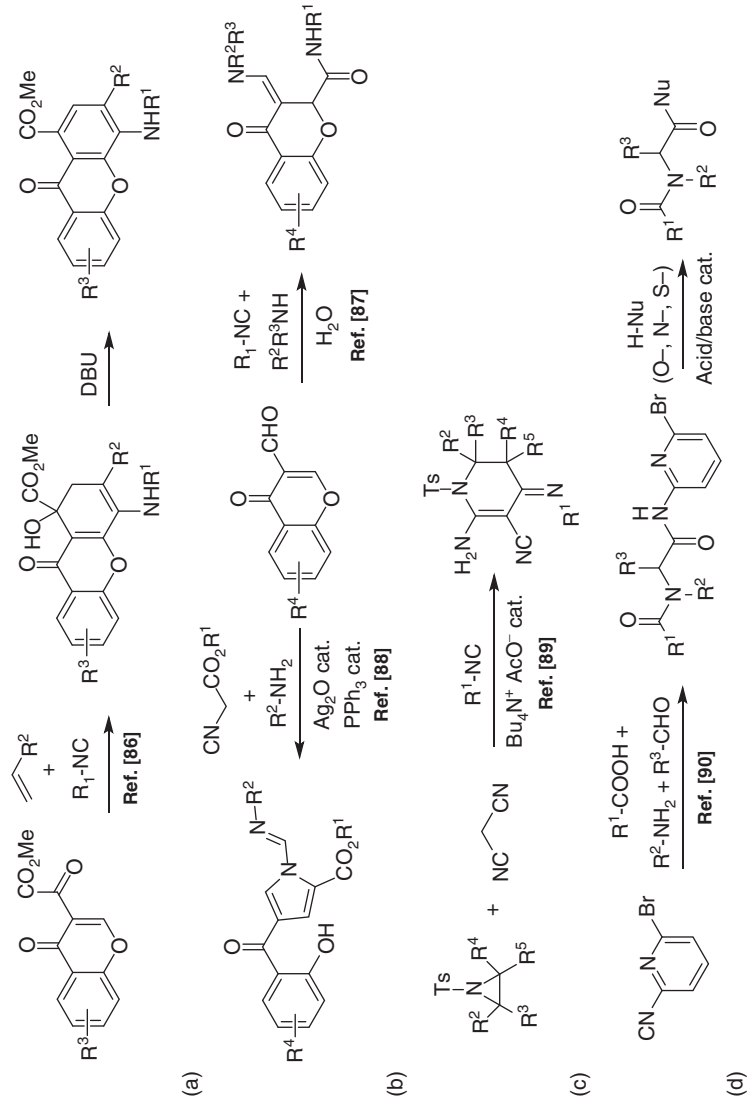
Scheme 1.27 Ugi-type MCRs. Substrate variations.
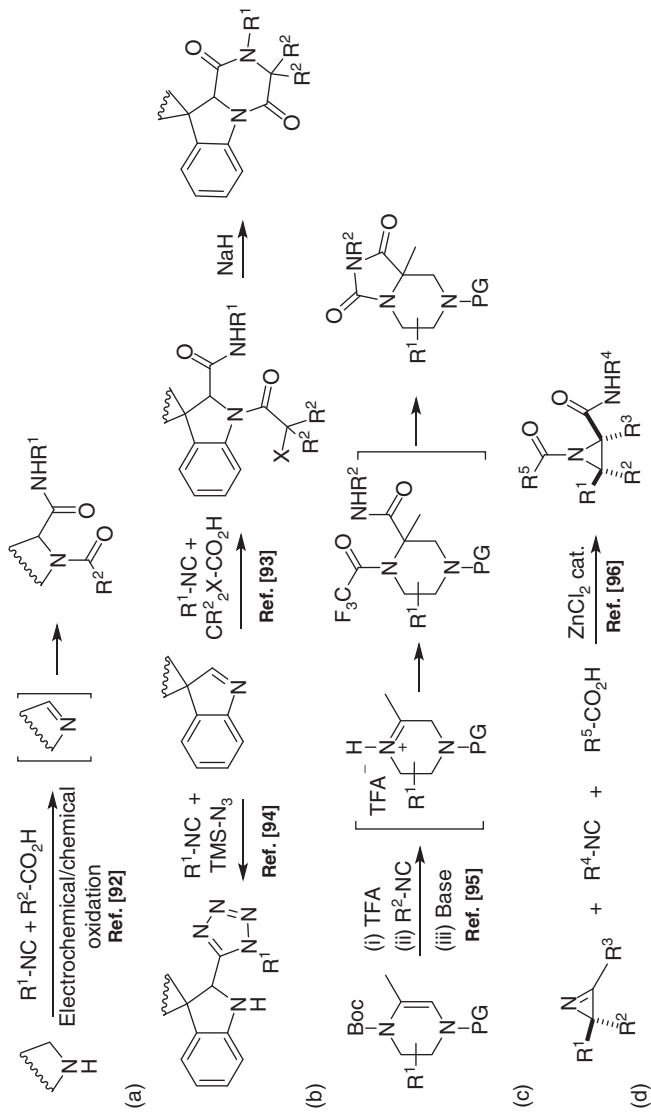
Scheme 1.28 Joullié-type MCRs. Substrate variations.

(a)

(b)

(c)

(d)

R¹-CHO + Ph-CH₂-NC
H⁺ cat. **Ref. [98]**

R¹-CHO + R²-NC
Sc(OTf)₃
DMAP
TMSOTf cat. **Ref. [99]**

R¹-CHO + R²-NC
Yb(OTf)₃ cat. **Ref. [100]**

R³-CHO + R⁴-NC
p-TsOH cat.

(i) R¹-CHO + R²-NC
Sc(OTf)₃ cat.
(i) TFA **Ref. [101]**

R¹-CHO + R²-NC
p-TsOH **Ref. [100]**

R¹-NC
HX **Ref. [102]**

p-TsOH **Ref. [103]**
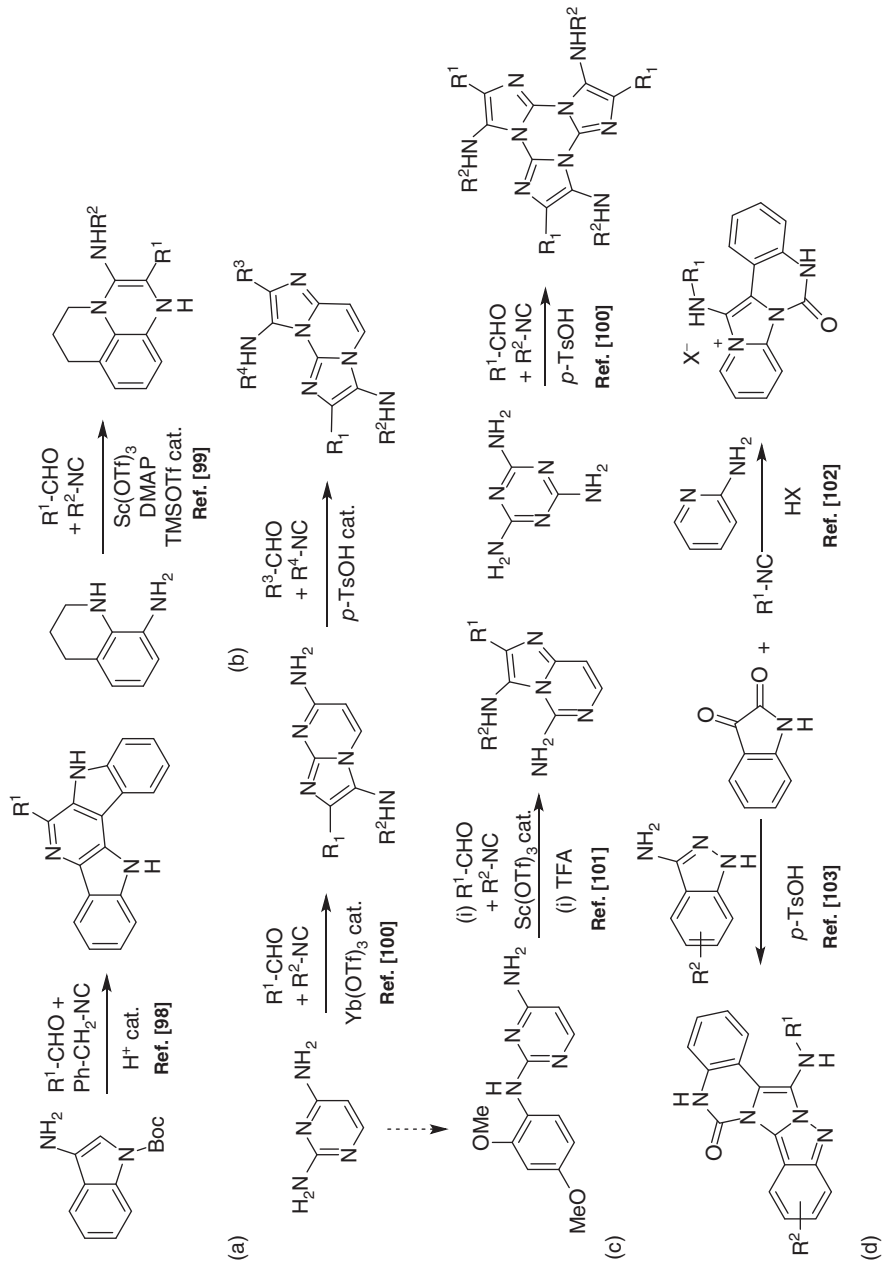
Scheme 1.29 GBB-type MCRs. Mechanistic variations.

suffers a [1,5]-H shift, followed by the intramolecular trapping of the isocyanate intermediate [103]. Aminoindazoles give the corresponding adduct in a similar manner (Scheme 1.29) [104].

The combination of 2-(2-bromoethyl)benzaldehyde and aminopyridines yields a dihydroquinolinium ion that continues the GBB reaction upon the attack of the isocyanide and the cyclization/aromatization step to afford the corresponding adduct [105]. Similar transformations have been reported with aminoindazole [106].

GBB reactions with propynals afford interesting post-condensation modifications exploiting the triple bond transformations, to yield iodo-substituted fused imidazopyrroles upon the cyclization with iodine [107]. In a recent report, however, the participation of benzyl isocyanide in GBB MCRs with propynals activates an alternative route: upon the *in situ* oxidation of the benzyl residue to give an imine, and the TBAB-mediated activation of the triple bond, the cyclization affords imidazo-dipyridines instead (Scheme 1.30) [108].
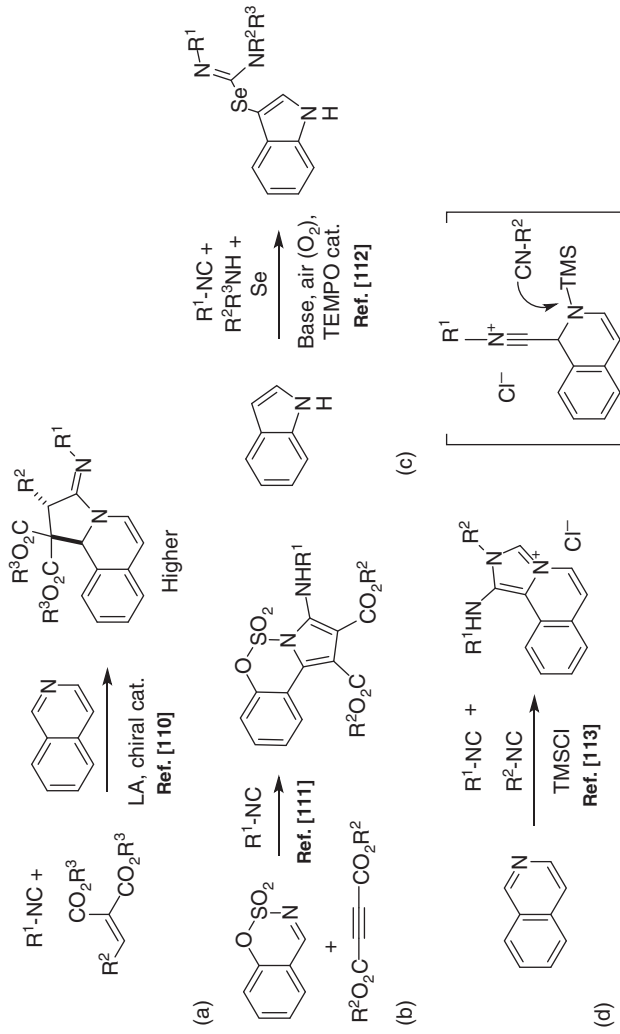
The incorporation of indole carbaldehydes enables GBB adducts to undergo a variety of domino processes, due to a key polarity inversion of the indole residue after the MCR. In this way, indole 3-carbaldehyde GBB adducts suffer a spontaneous oxidative Pictet–Spengler transformation to afford a variety of fused polyheterocyclic systems. However, indole 2-carbaldehyde GBB adducts yield indolocabazoles in an AB_3C fashion, and a striking bicyclic scaffold at higher temperature (Scheme 1.30) [109].

A variety of formal [3 + 2] cycloadditions involve novel interactions of isocyanides with heterocyclic substrates, forming part of the either dipole or the dipolarophile. For instance, the interaction of dipoles, *in situ* generated through the addition of isocyanides to unsaturated carbonyls, with isoquinolines leads to single adducts with high stereoselectivity, under chiral organocatalysis [110]. Similarly, the participation of acetylenedicarboxylate and sulfamate-derived cyclic imines leads to fused pyrroles in a regioselective manner via the corresponding isocyanide-dipole (Scheme 1.31) [111].

Insertion processes, not included in previous sections, account for meaningful transformations. For instance, indole, selenium, isocyanides, and secondary amines lead to a four-component adduct through a selenourea radical intermediate, under oxidative conditions [112]. Another mechanistic variation involves the insertion of isocyanides upon N—Si bonds, in a TMSCl-promoted interaction. In this way, azines and two equivalents of isocyanides, which can be differentiated because of having different roles in the process, lead to fused isoquinoline-imidazolium salts (Scheme 1.31) [113].

1.7 Miscellany Processes

Among the processes that do not fit in the precedent sections, we may mention the productive research in the chemistry of the BODIPY derivatives as a source of smart fluorophores. Formyl-BODIPYs have been prepared and reacted in Passerini MCR [114]. Interesting contributions to the synthesis of BODIPYs through MCRs

Scheme 1.30 GBB-type MCRs: post-transformations.

(a)

R^1-NC +

R^2 CO$_2$R^3 / CO$_2$R^3

LA, chiral cat.
Ref. [110]

R^{3}O$_2$C R^2 N–R^1
R^{3}O$_2$C N

Higher

(b)

O–SO$_2$ N

+

R^{2}O$_2$C CO$_2$R^2

R^1-NC
Ref. [111]

O–SO$_2$ N NHR^1
CO$_2$R^2
R^{2}O$_2$C

(c)

R^1-NC +
R^{2}R^{3}NH +
Se

Base, air (O$_2$),
TEMPO cat.
Ref. [112]

N–R^1
Se NR^{2}R^3
N H

N H

[R^1–N$^+$≡ Cl$^-$ CN-R^2 N–TMS]

(d)

N

R^1-NC +
R^2-NC

TMSCl
Ref. [113]

R^{1}HN N–R^2
N$^+$ Cl$^-$

Scheme 1.31 Isocyanide MCRs based on cycloadditions and insertions.

have also appeared: the Lewis acid–catalyzed condensation of lactones with pyrrole [115] and the interaction of a phenol-substituted pyrrole with boronic acids and another pyrrole unit to yield the dye in one step [116]. The known interaction of isocyanides, azines, and trifluoroacetic anhydride leading to dipolar acid fluorides has been performed on a fluorophore-linked isoquinoline to afford a probe capable of selectively labeling amines, allowing its direct visualization in cell environments (Scheme 1.32) [117].

Fused imidazoazines have been prepared through aldol-type condensation followed by a SNAr (or Ullmann coupling) and a click reaction to yield complex MCR adducts [118]. Also, the interaction of aminopyridines with ketones and thiols yields thio-substituted imidazopyridines via a remarkable coupled I_2-Flavin catalysis (Scheme 1.33) [119]. Some MCR processes are based on a series of nucleophilic displacements: the interaction of azines with indoles and dichloroethane triggers a domino process, which is oxidatively terminated to yield cationic azahelicenes [120]. Furthermore, the participation of DABCO, α-chloroazines, and sulfide anions promotes an orchestrated sequence of SNAr-SN2-SNAr processes leading to a four-component scaffold (Scheme 1.33) [121].

Unsaturated nitro derivatives display a rich chemistry, enabling new MCRs based on conjugated additions and subsequent Henry or NO_2 elimination processes. For instance, their interaction with cyclohexanone and aminopyrazole leads to heterocyclic spiroadducts [122]. Furthermore, 3-nitro-indole or -benzothiazole reacts with *in situ* generated cyclic ketimines leading to indole-fused heteroacenes (Scheme 1.34) [123].

To finish this section, we mention an impressive contribution to the field of reaction discovery where, among other transformations, novel MCRs were described using a high-throughput autonomous organic synthesis robot fitted with analytical tools and controlled by a machine learning algorithm (Scheme 1.34) [124].

1.8 Conclusion

Merging the synthetic power of MCRs with the particular reactivity of heterocycles leads to an impressive array of new transformations and unprecedented connectivity patterns. These new scaffolds are produced in a straightforward manner, often by simply mixing the reactants and, due to their combinatorial nature, are amenable to parallelization. Furthermore, the highlighted processes show high levels of structural variability. The reaction discovery based on these heterocycle-based MCRs is already very fruitful and, although in its infancy, the description of this uncharted reactivity is paving the way to a systematic use of these processes in synthetic chemistry.
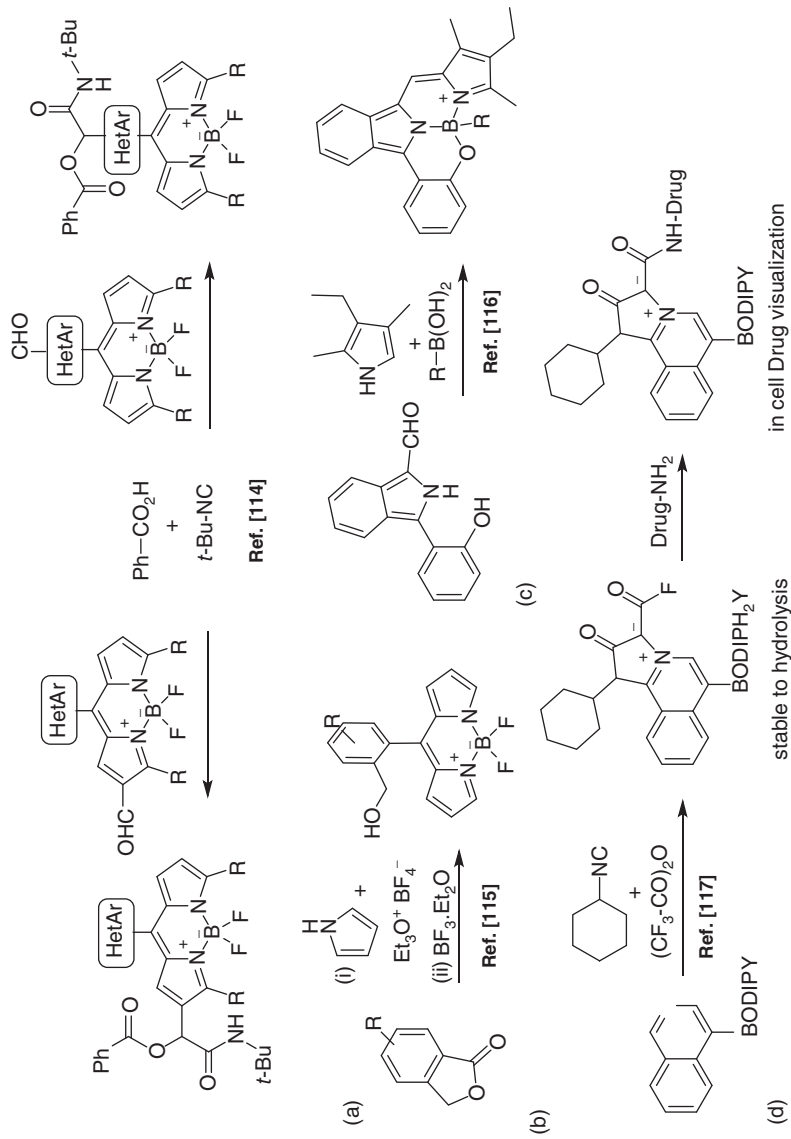
Scheme 1.32 MCRs featuring BODIPYs.
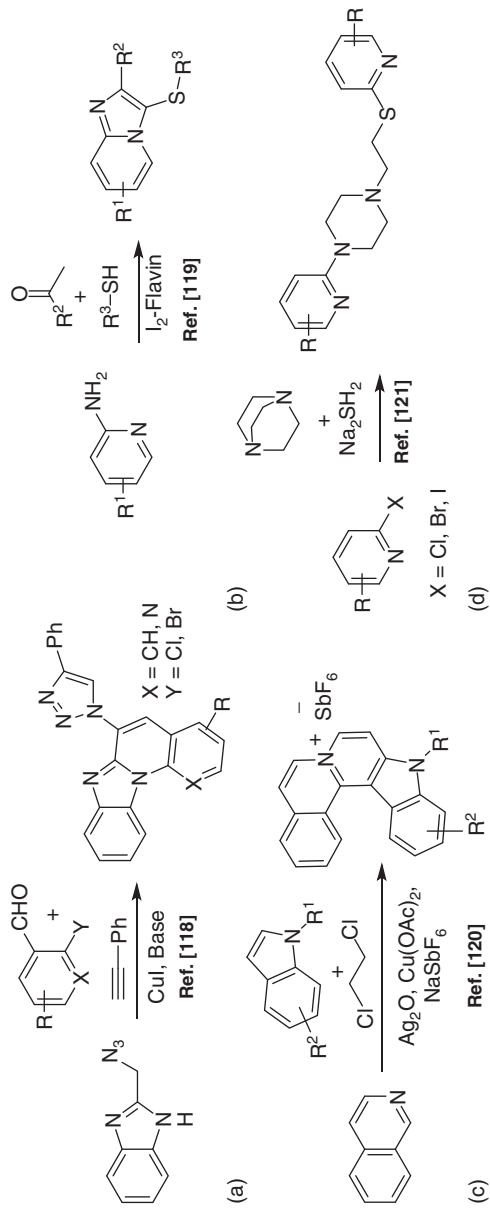
Scheme 1.33 Azole and azine nucleophilic MCRs.
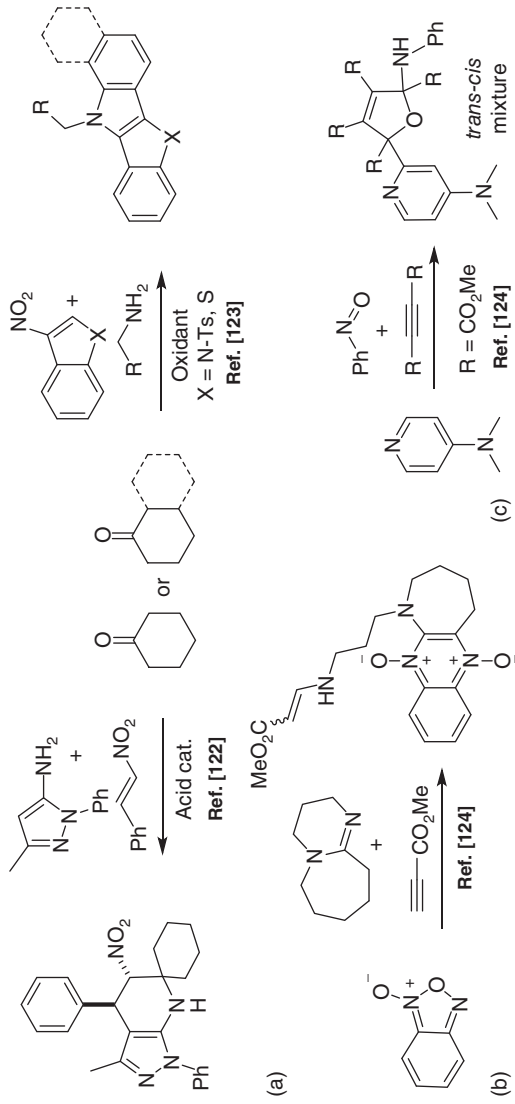
Scheme 1.34 MCRs based on nitro derivatives and AI reaction discovery.

Acknowledgment

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