

## Perspective

## Recent developments in one-pot stepwise synthesis (OPSS) of small molecules

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## SUMMARY

One-pot synthesis is an active topic in organic chemistry due to its intrinsic advantages of simple operation, high mass efficiency, low cost, and less amount of waste disposal. Among three kinds of one-pot syntheses, 1) cascade reactions, 2) multi-component reactions (MCRs), and 3) one-pot stepwise synthesis (OPSS), OPSS could be more flexible and practical since it is carried out stepwisely and have variable reaction conditions for different steps. This perspective article uses selected examples to highlight the recent development in OPSS involving cyclization, cyclo-addition, rearrangement, and catalytic reactions for the synthesis of heterocyclic scaffolds, asymmetric molecules, natural products, and bioactive compounds.

## INTRODUCTION

Synthetic chemistry poses constant demands on the development of more efficient and greener techniques to make the reaction processes to be high mass efficiency, minimal effort on intermediates isolation, less energy consumption, and with reduced amount of waste (Clark and Macquarrie, 2002; Anastas and Eghbali, 2010; Zhang and Cue, 2018). Performing organic reactions in single vessel (one-pot) is a good approach for high pot, atom, and step economy (PASE) (Trost, 2002; Wender, 2013; Clarke et al., 2007; Hayashi, 2016) and favorable in green metrics analysis such as E-factor and C factor (Constable and Jiménez-González, 2018; Sheldon, 2018; McElroy et al. 2015). The one-pot synthesis can be carried in three different ways: domino or cascade reactions (Tietze et al., 2006), multicomponent reactions (MCRs) (Zhu et al., 2014), and one-pot stepwise synthesis (OPSS) (Zhang and Yi, 2019). Examples on quantitative green metrics analysis could be found for MCR (Abou-Shehada et al., 2017) and OPSS (Climent et al., 2010).

Three one-pot reactions are different from their operation procedures (Scheme 1). A cascade reaction (also known as domino or tandem reaction) is a single-operation reaction but involving sequential chemical transformations. Once the reaction started, no additional reactants, reagents, or catalysts are introduced to the reaction system (Snyder and Schaumann, 2016; Pellissier 2020a). Total synthesis of (+/-) hirsutene via cascade radical cyclization is a good example (Curran and Rakiewicz, 1985). An MCR is also a single-operation reaction but has three or more reactants. The Ugi, Biginelli, Petasis, and Groebke-Blackburn-Bienayme are the well-known MCRs (Heravi and Zadsirjan, 2020). An OPSS has multi-operation steps, which allows reactants, reagents, and catalysts introduced stepwisely. The reaction conditions could be changed at each step. Solid-phase peptide synthesis (Merrifield, 1986), organic synthesis using solid-supported reagents and scavengers (Ley et al., 2000), polymer synthesis (Espeel and Du Prez, 2015), and synthesis of some biomolecules (Sui et al., 2021) are good examples of OPSS. Many biocatalysis-based OPSS have been reported in literature (Bruggink et al., 2003; Riva and Fessner, 2014; Groger and Hummel, 2014; Denard et al., 2013). This paper only covers solution-phase OPSS of heterocyclic small molecules with biological interests.

It is worth noting that “multistep” in this paper refers to *operation step*, not the *chemical transformation step* (Broadwater et al., 2005). Mislabeling of these three different kinds of one-pot reactions could be found in literature, which are caused by lack of clear differentiation on the operation step and the chemical transformation step. Defining the one-pot reactions based on the operation procedure shown in Scheme 1 could avoid following potential misnomers:

- 1) a single-operation reaction involving one reactant (intramolecular) or two reactants (intermolecular) with sequential chemical transformations should be called a cascade reaction instead of a multistep reaction;
- 2) a single-operation reaction with three or more components should be called MCR instead of a one-pot reaction;

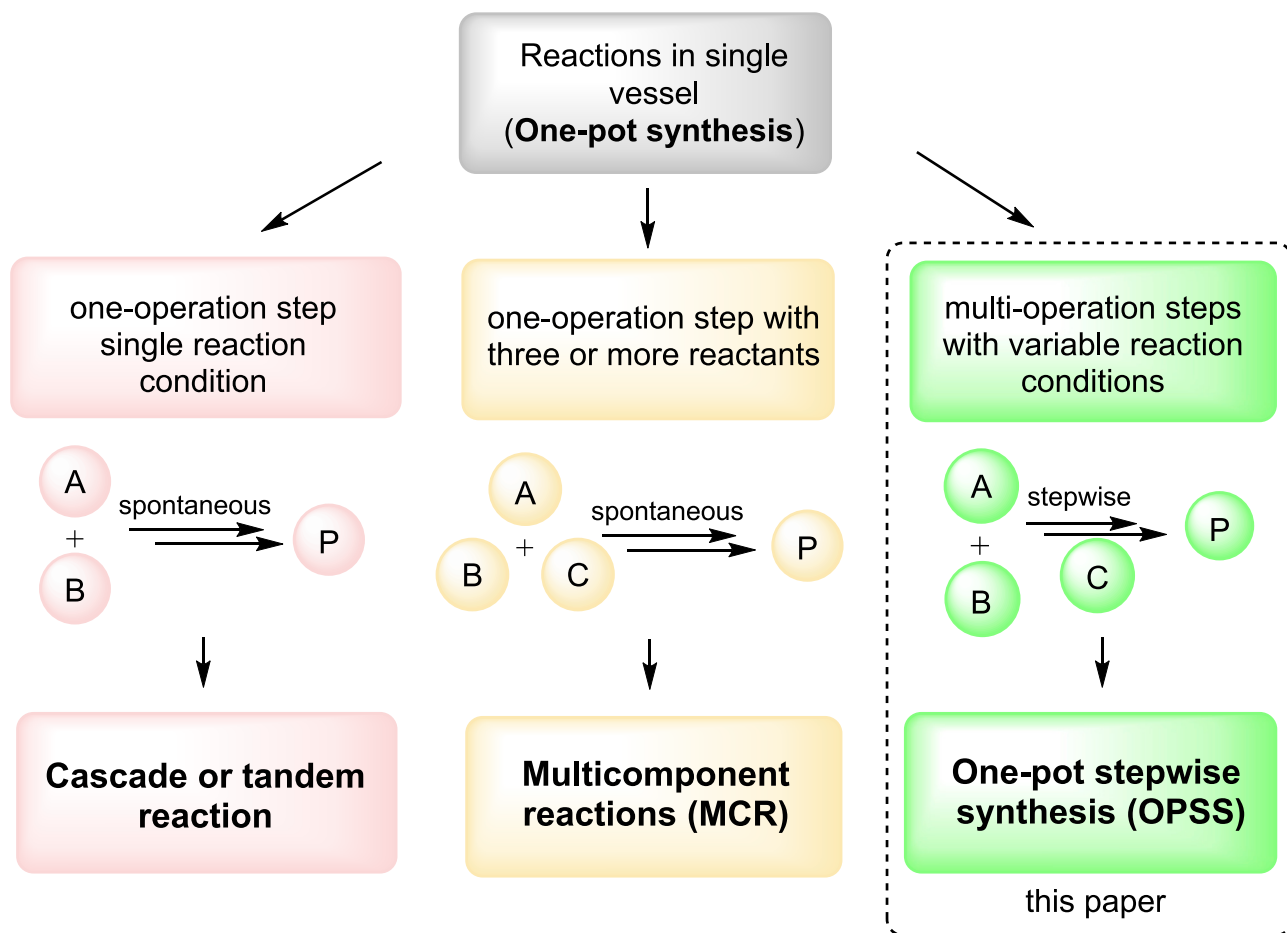
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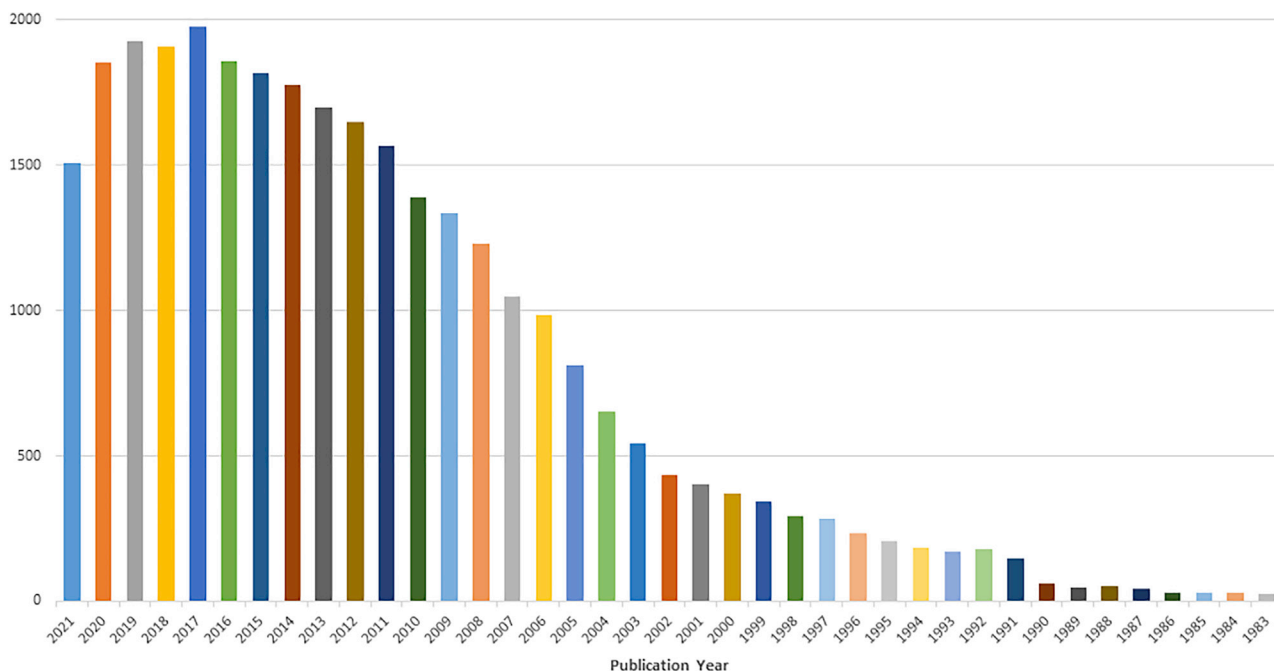


**Scheme 1. Conceptual figure of three one-pot reactions**

- 3) a one-pot reaction with multi-operation steps should be called OPSS instead of a cascade reaction;
- 4) a one-pot synthesis with three or more components in multistep should be called OPSS instead of MCR.

One-pot synthesis has been an active topic for two decades. A Web of Science search on “one-pot synthesis” (for chemistry organic) gave 31,195 hits (available at: <https://clarivate.libguides.com/webofscienceplatform/alldb>, accessed on Jan. 17, 2022). As shown in Figure 1, there was a steady increase on the number of papers from early 1990s and peaked at 2017. In last ten years, more than 1,500 papers on this topic published each year. The concept and practice of one-pot synthesis have been well integrated to different organic transformations such as cyclization, cycloaddition, rearrangement, catalysis, radical, click, microwave, electrochemical and photoredox reactions in the synthesis of heterocyclic compounds, drug molecules, biomolecules, and natural products (Figure 2). The number of publications on these three kinds of one-pot synthesis is quite different, MCRs 3,907, cascade reactions 2,287, but only 254 for stepwise reactions (173 if search on multistep reactions). MCRs (Cioc et al., 2014; Domling et al., 2012) and cascade reactions (Ardkhean et al., 2016), especially the radical cascade reactions (Huang et al., 2019; Zhang and Studer, 2015), have been well documented. However, other than a conceptual paper (Broadwater et al., 2005), no dedicated review articles on OPSS of small molecules could be found in literature. Some OPSS appeared in the review articles which are mainly for cascade-type synthesis (Zheng and Hua 2020; Martinez et al., 2021; Hayashi, 2021).

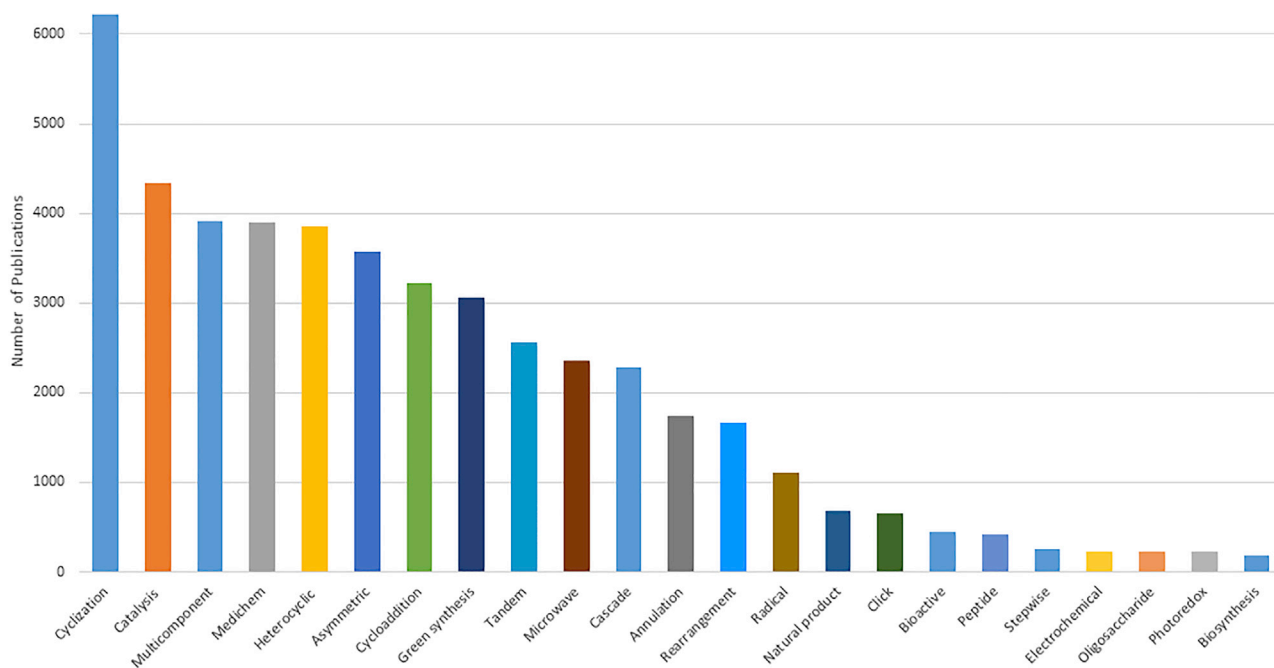
The numbers of MCRs are limited and not so easy to discover new MCRs. The cascade reactions are generally good for carrying out similar kind of transformations (such as radical reactions) in one-pot fashion. OPSS is more flexible and practical because the reactions are stepwise and conditions are variable. OPSS has more parameters for reaction condition optimization, good for exploring the scope of substrates, suitable for scale-up



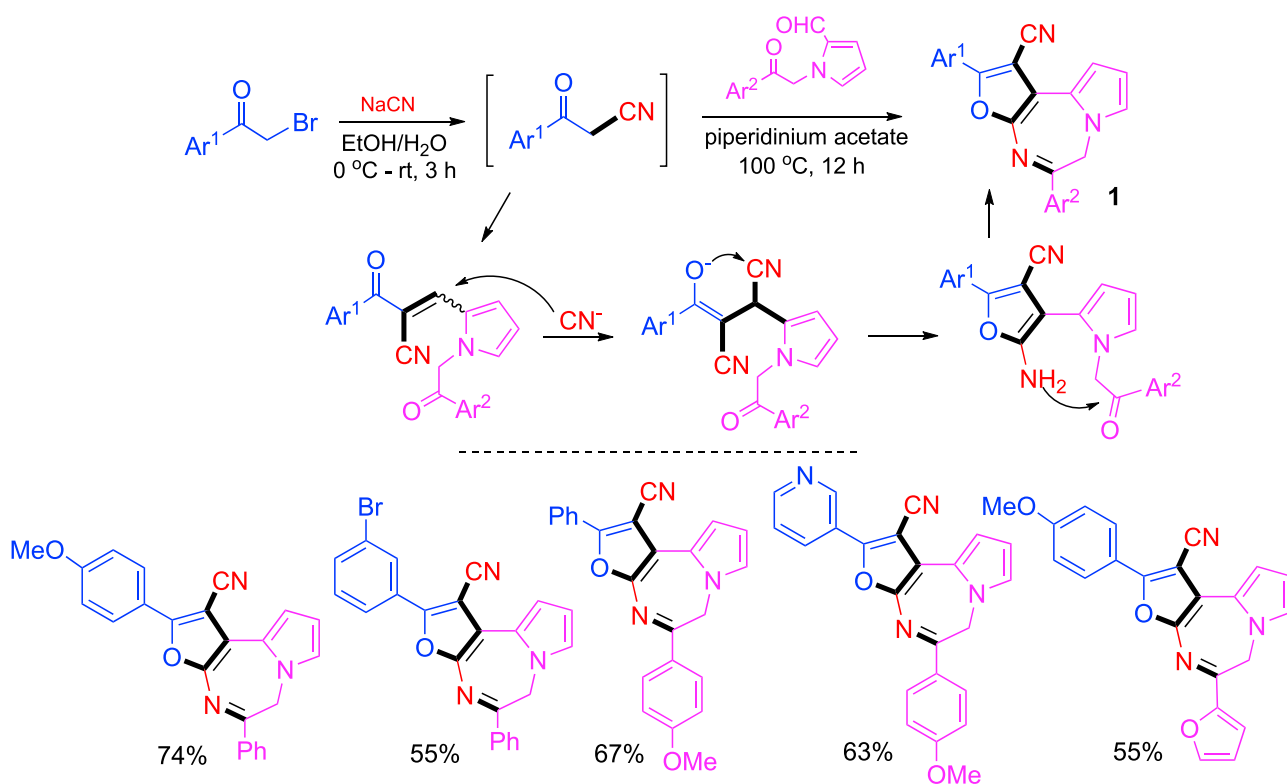
**Figure 1.** Distribution of "one-pot synthesis" papers by year

reactions, and capable to integrate different kinds of reactions. Other than developing new OPSS, there is a significant amount of recent effort on reengineering the known multistep synthesis to be one-pot synthesis. There are several general practices in the development of OPSS:

- 1) maximizing the conversion of the initial reaction to minimize the impact of side-products to the later reactions;

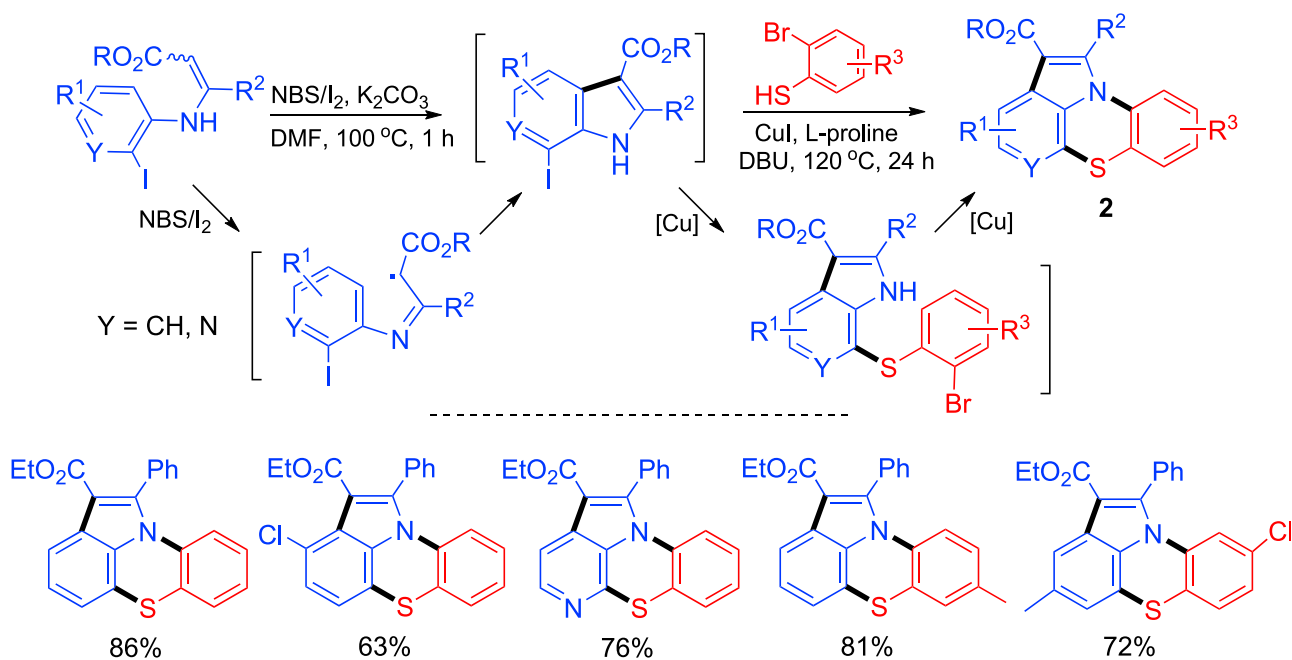


**Figure 2.** Distribution of "one-pot synthesis" papers by topic

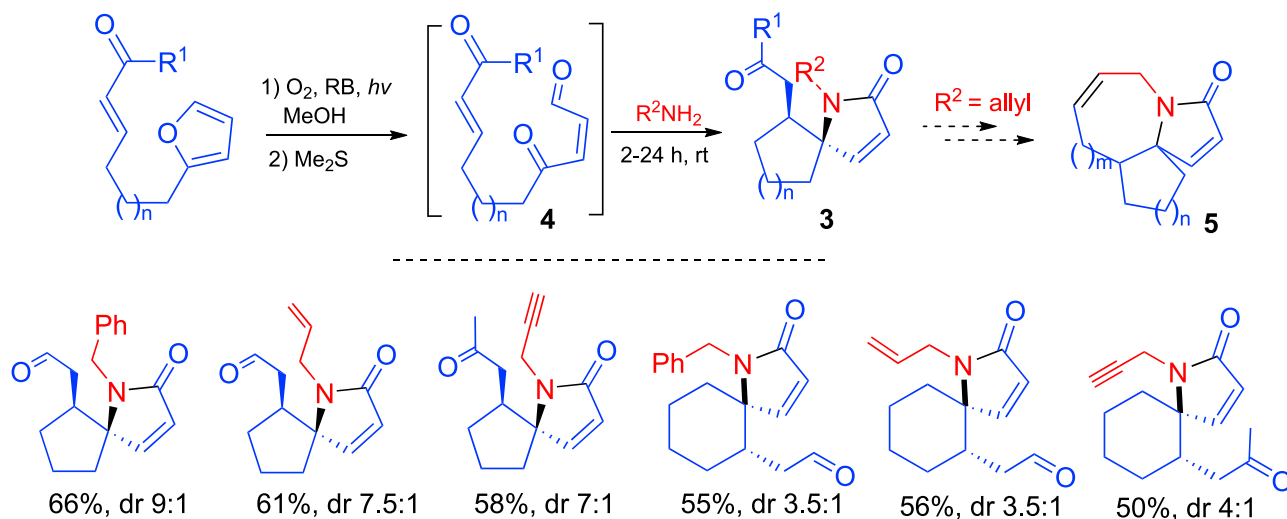


**Scheme 2. A two-step synthesis of diazepine-fused tricyclic compounds**

- 2) avoiding harsh reaction conditions such as using strong acid/base which may not be compatible to other transformations;



**Scheme 3. A two-step synthesis of thiazino[2,3,4-*h*]indoles**



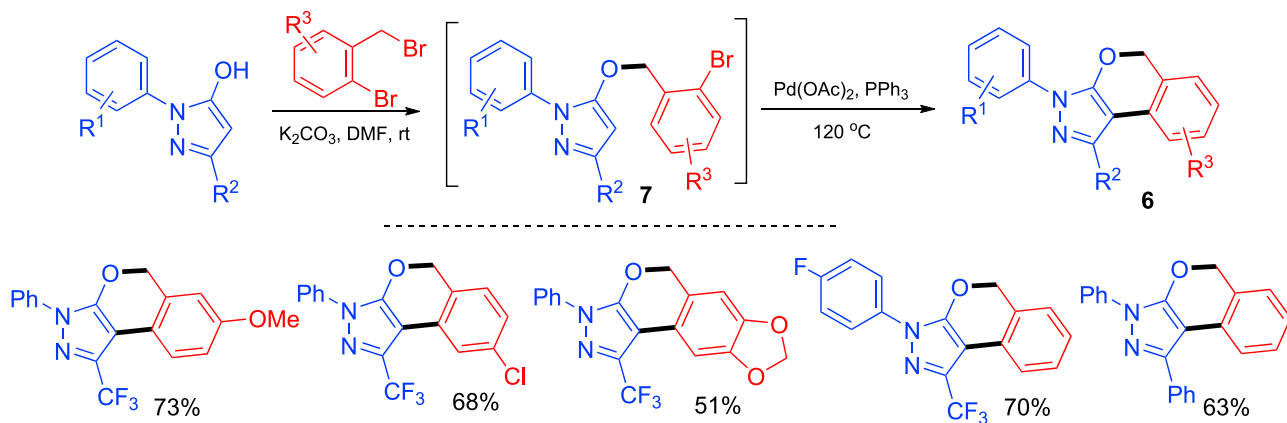
**Scheme 4.** A three-step synthesis of 1-azaspirocyclic scaffolds **3**

- switching solvents and changing reaction temperature at different steps to address reactant solubility and reactivity issues;
- balancing functional group tolerance, substrate scope, and reaction selectivity throughout the whole reaction process;
- generating unstable and highly reactive reactants *in situ* and integrating to the reaction sequence;
- performing complicated and/or sensitive reactions (such as MCR or transition metal-catalyzed reactions) at the beginning of the synthesis to minimize the impact of side-products from the previous steps.

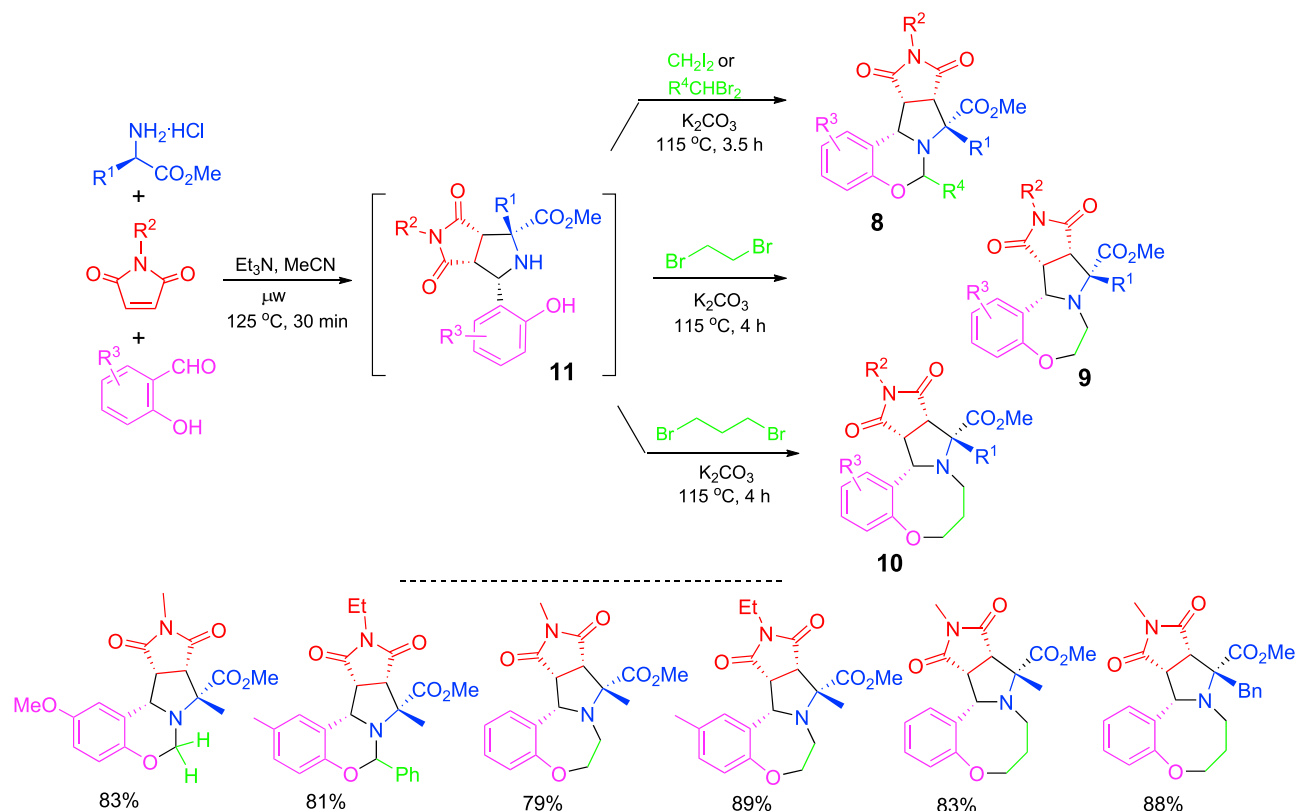
This perspective article highlights the recent development of solution-phase OPSS of small molecules. Examples are selected from the synthesis of heterocyclic molecules, privileged structures, and natural products with biological interests. They are presented in this paper based on the chemical transformations including cyclization, cycloaddition, rearrangement, multicomponent reactions, and metal-catalysis or organocatalysis. Solid-phase or solid-supported OPSS (Ley et al., 2000), biocatalytic OPSS (Bruggink et al., 2003; Riva and Fessner, 2014), and flow chemistry-based OPSS (Vaccaro, 2017) are not covered in his paper.

### Cyclization reactions

As shown in Figure 2, even cyclization reactions, including ionic, radical, and metal-catalyzed coupling have more than 6000 papers in one-pot synthesis. However, OPSS-related cyclization reactions are much less



**Scheme 5.** A two-step synthesis of isochromene-fused pyrazoles



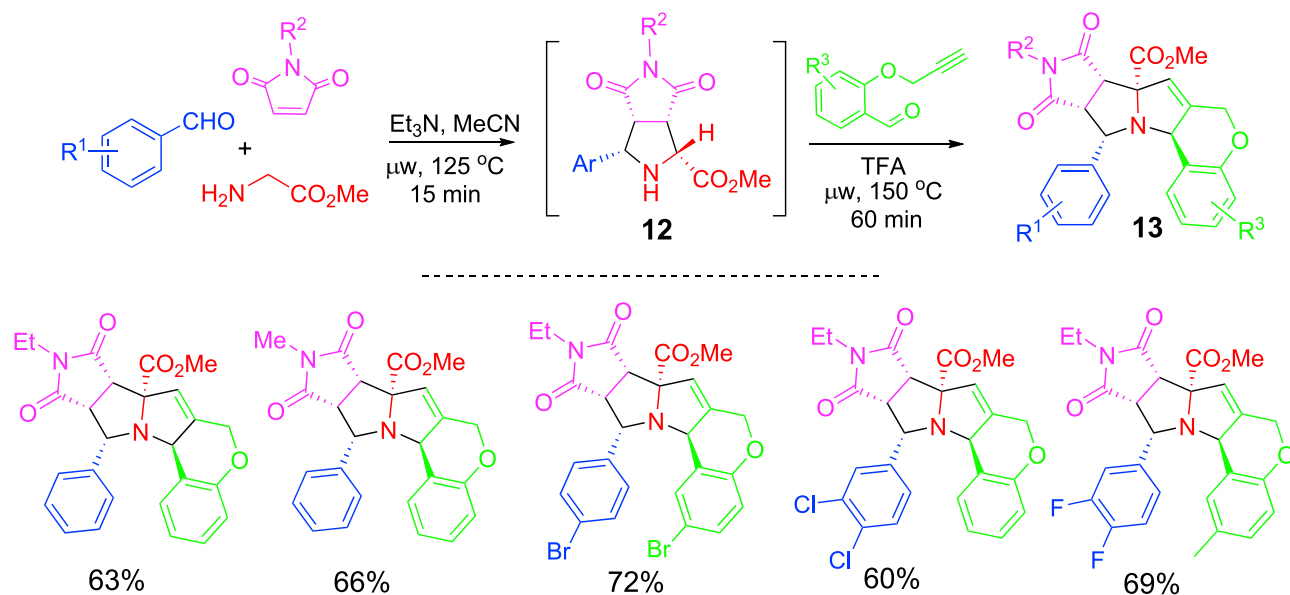
**Scheme 6. A two-step modular synthesis of three different ring scaffolds**

(<70) which means most one-pot cyclization reactions are cascade or tandem reactions instead of MCRs or OPSS (Tietze et al., 2006; Zhang and Yi, 2019).

Shown in Scheme 2 is a one-pot two operation-step sequence involving cyano substitution of  $\alpha$ -bromo ketones, aldol condensation, furan formation, and intramolecular amination for the synthesis of tricyclic compounds **1** (Yoon et al., 2020). The phenacyl bromide was first reacted with NaCN at 0°C to room temp for 3 h, then a pyrrolyl aldehyde and piperidinium acetate were added and the reaction mixture was heated at 100°C for 12 h to afford diazepine-fused tricyclic compounds. In this synthesis, the first step is only for Br/CN exchange, the remaining transformations including double nucleophilic cyclization were completed in the second step of introducing aldehydes.

A one-pot two-step synthesis of thiazino[2,3,4-*h*]indoles **2** from *o*-haloaryl enamines and *o*-bromothiophenols is shown in Scheme 3 (Mao et al., 2017). In this reaction sequence, NBS/I<sub>2</sub>-promoted radical cyclization of enamines produced 7-iodoindole-type intermediates which then reacted with bromothiophenols for Cu-catalyzed intermolecular C-S coupling and intramolecular C-N coupling to afford the tetracyclic products. The iodo group is more reactive than the bromo group, so the C-S coupling occurred prior to the C-N coupling. This project is a good example of integration radical cyclization and metal-catalyzed inter- and intramolecular coupling reactions in one-pot for making a novel heterocyclic scaffold.

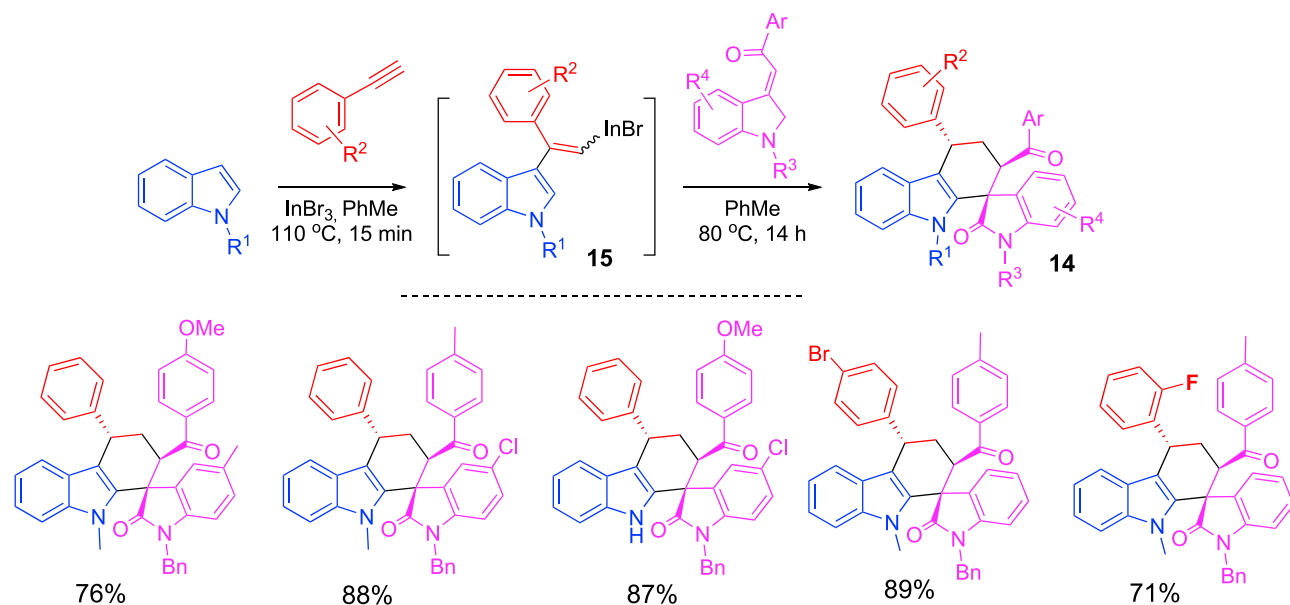
A stepwise synthesis of 1-azaspirocyclic scaffolds **3** has been developed from the reaction of furyl aldehydes (Scheme 4) (Hoxha et al., 2021). The furyl aldehydes with different length of linkers ( $n = 1$  or 2) underwent photooxygenation on the furan ring with O<sub>2</sub> and then Me<sub>2</sub>S. The resulted tricarbonyl compounds **4** reacted with primary amines for [5 + 1] annulation to afford 1-azaspiro[4.4]nonanes or 1-azaspiro[4.5]decanes **3**. The products could be converted to dienes for ring-close metathesis in the synthesis of tricyclic scaffolds **5** of natural alkaloid compounds. This is a good example of integration green techniques (one-pot, O<sub>2</sub>, photoreaction, and MeOH solvent) for organic synthesis.



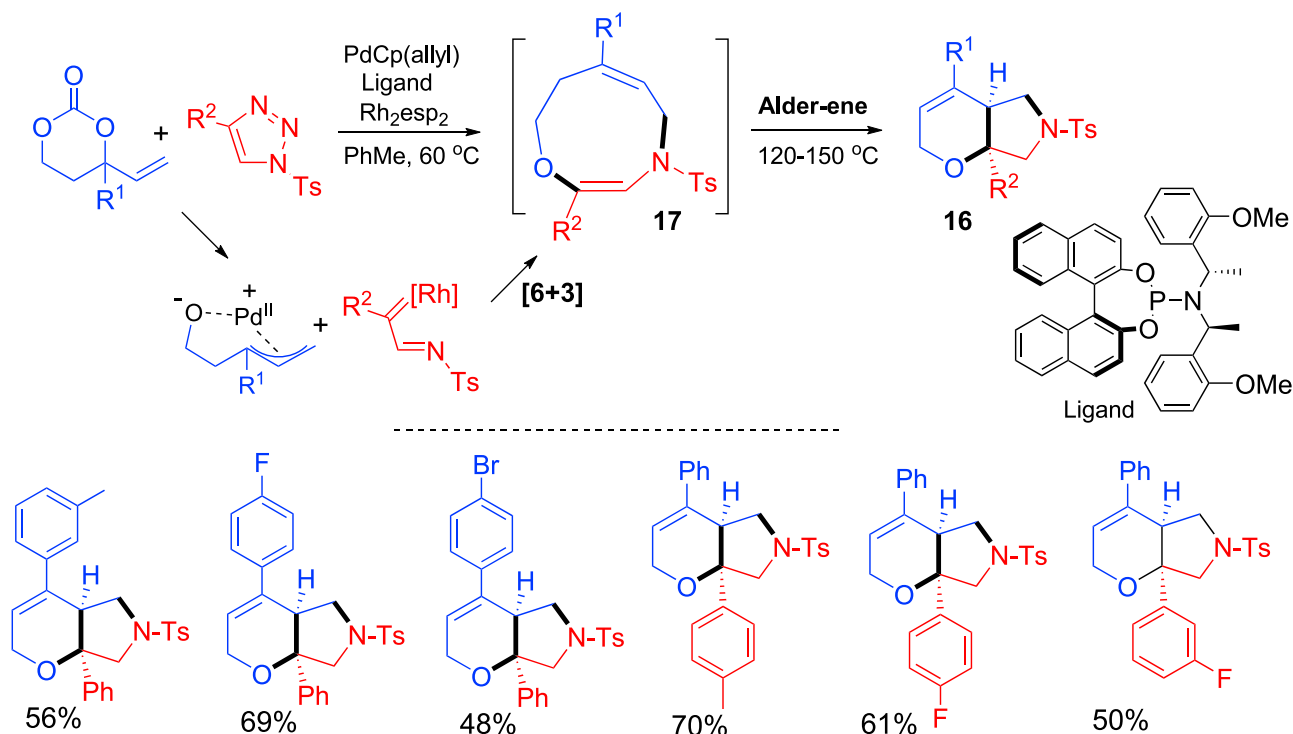
**Scheme 7.** One-pot inter- and intramolecular [3 + 2] cycloaddition for condensed ring system

A stepwise nucleophilic substitution and Pd-catalyzed  $\text{C}_{\text{sp}^2}$ - $\text{C}_{\text{sp}^2}$  biaryl coupling reaction sequence has been developed in the synthesis of isochromene-fused pyrazoles **6** (Scheme 5) (Nikolić et al., 2020). The reaction of hydroxypyrazoles and benzyl bromides gave intermediate **7** which were used for Pd-catalyzed C–H arylation to assemble the 6-membered ring of the tricyclic products. Same solvent (DMF) and base ( $\text{K}_2\text{CO}_3$ ) were used for the two reaction steps. The second step was performed by simply adding Pd-catalyst to the reaction mixture and increases the reaction temperature.

Other than above mentioned cases, more examples could be found in the synthesis of heterocycles such as indazol-3-ones (Liu et al., 2019), benzonaphthyridines (Kumar et al., 2017), pyrazolones (Howard et al., 2017), and pyrazolines (Ganesan et al., 2020).



**Scheme 8.** Two-step Diels-Alder reaction for spiro heterocyclic compounds

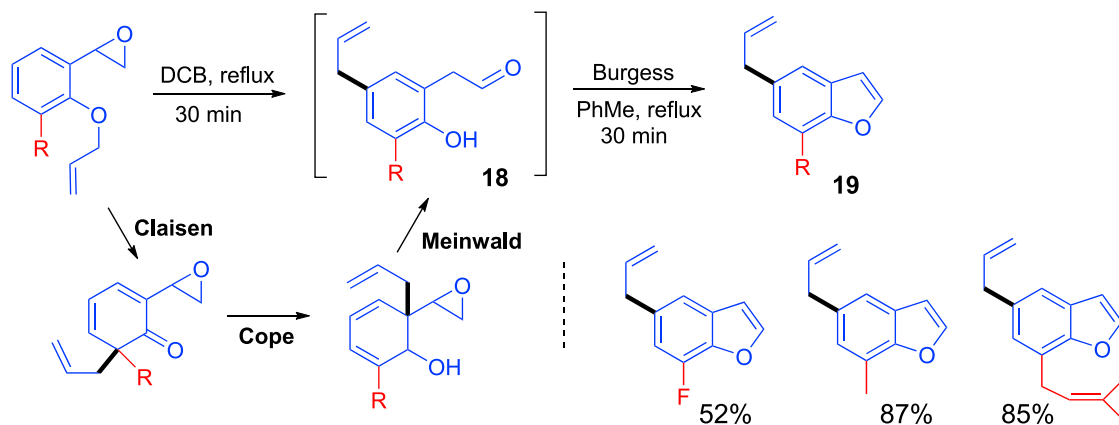


**Scheme 9.** One-pot synthesis involving transannular Alder-ene rearrangement

### Cycloaddition reactions

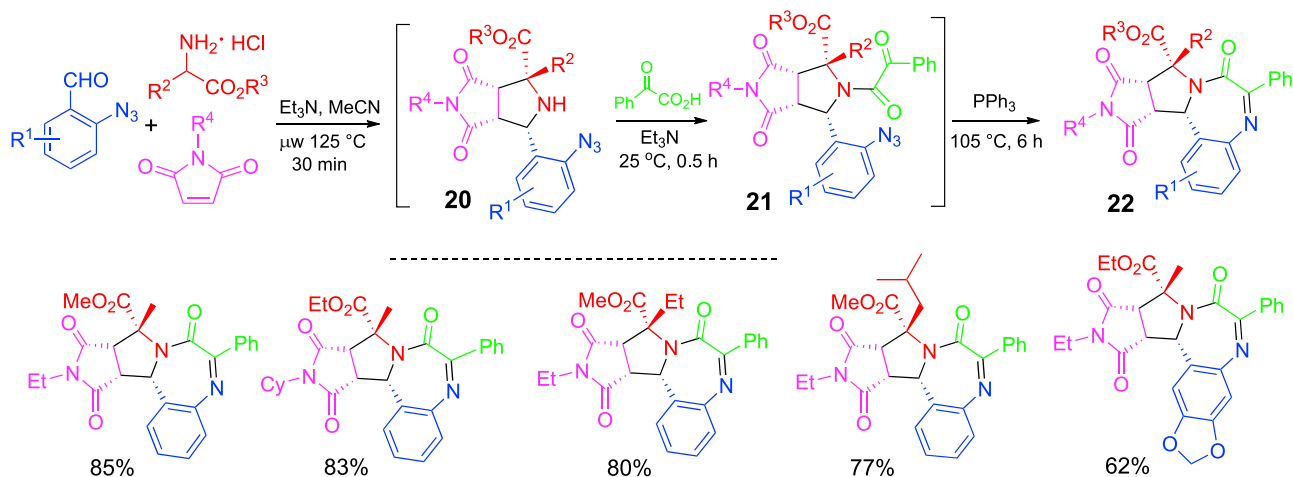
A cycloaddition is more powerful than a cyclization in the building up of molecular diversity and complexity (Gabriele et al., 2019). Because it involves multiple reaction centers and with high stereochemistry requirements, integration of cycloadditions in one-pot reactions could be more complicated than cyclizations, especially in the performing of consecutive cycloadditions (Sears and Boger, 2016).

A two-step protocol involving [3 + 2] cycloaddition and nucleophilic annulation has been developed for modular synthesis dihydrobenzoxazines **8**, tetrahydrobenzoxazepines **9**, and tetrahydrobenzoxazocines **10** (Scheme 6) (Muthengi et al., 2018). Azomethine ylides generated *in situ* from aminoesters and benzaldehydes underwent 1,3-dipolar cycloaddition with maleimides to give [3 + 2] adducts **11** which were used as common intermediates for three different nucleophilic [4 + n] annulation reactions to form 6-, 7-, and 8-membered ring-fused tetracyclic compounds, respectively. Et<sub>3</sub>N was used as a base for the first step



**Scheme 10.** One-pot sigmatropic rearrangement and dehydrative benzofuran formation reactions



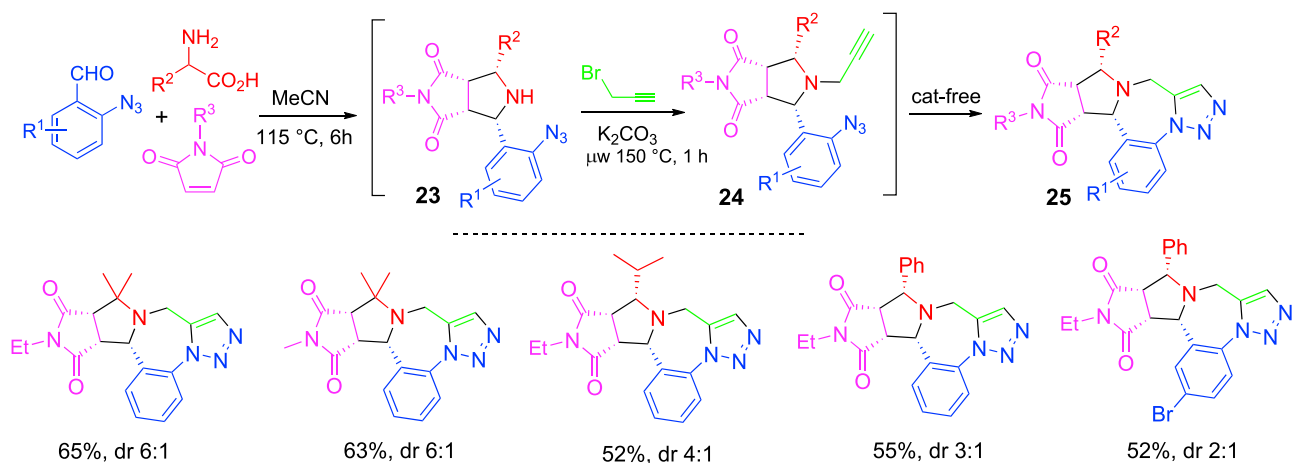


**Scheme 11. MCR-initiated one-pot synthesis of tetrahydro-pyrrolobenzodiazepinones**

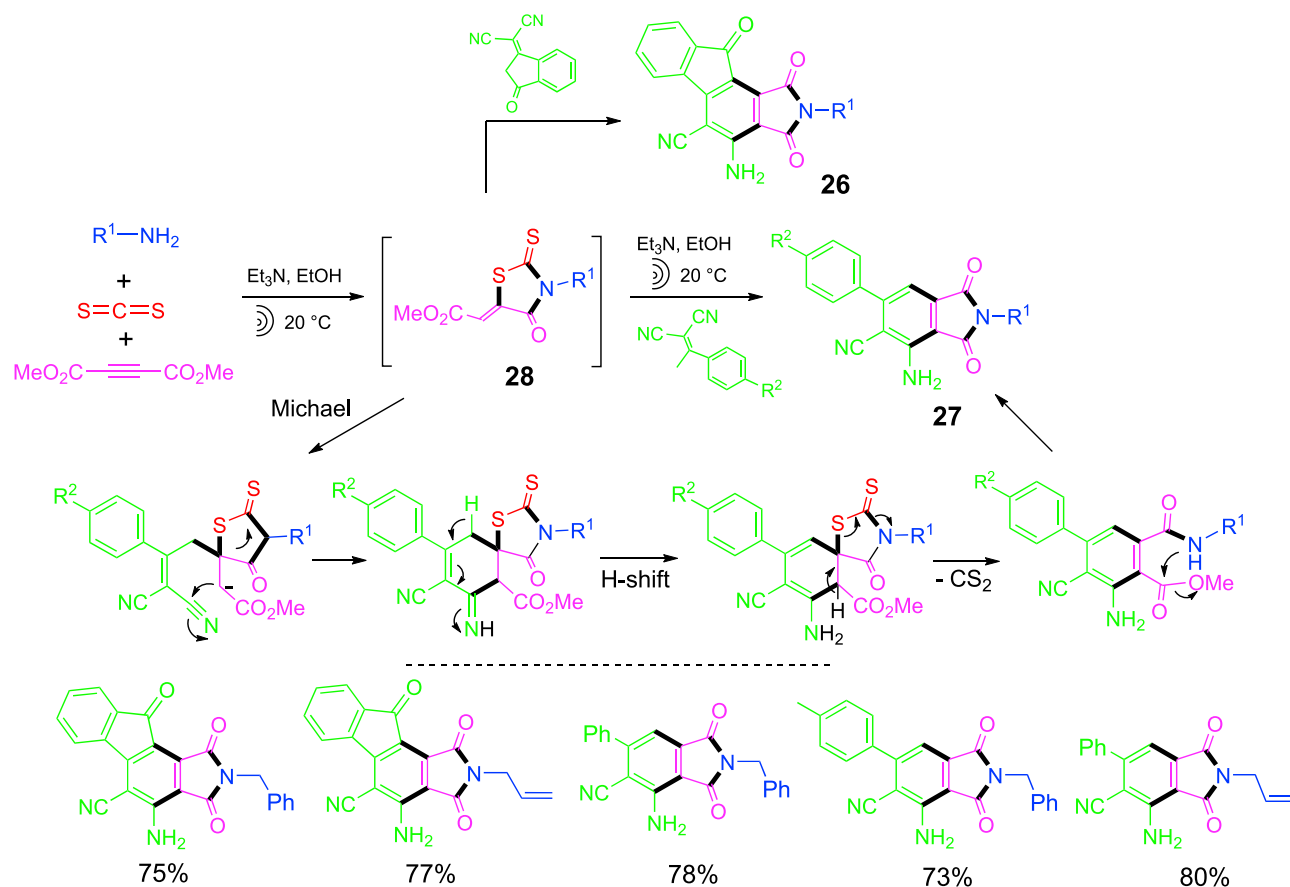
cycloaddition under microwave heating at 125°C for 30 min  $K_2CO_3$  was added to the reaction mixture to promote the nucleophilic [4 + n] annulation under conventional heating at 125°C for 3.5–4 h.

Another [3 + 2] cycloaddition-initiated one-pot synthesis is shown in [Scheme 7 \(Zhang et al., 2018\)](#). In this case,  $\alpha$ -unsubstituted amino esters were used in the initial [3 + 2] cycloadditions with benzaldehydes and maleimides. The resulted proline ester derivatives **12** which have  $\alpha$ -proton could be used for intramolecular [3 + 2] cycloadditions with propargyl benzaldehydes to assemble a condensed ring system **13** in a diastereoselective manner. Both reaction steps were performed under microwave heating.  $Et_3N$  was used to promote the first cycloaddition, while TFA was added to improve the conversion for the second cycloaddition. It is a highly operational efficient and mass efficient synthesis, only 2 equiv of water was generated as a byproduct.

The Diels-Alder reaction is one of the most popular cycloaddition reactions. It has been integrated into a one-pot process involving the formation of dienes and sequential [4 + 2] cycloaddition in the synthesis of a spiro heterocyclic scaffold **14** containing indolinone and indoline moieties ([Scheme 8](#)) ([Wang et al., 2021](#)). The first step reaction was  $InBr_3$ -catalyzed coupling of indoles with phenylacetylenes to form 2-alkenylindoles **15** which then served as dienes to react with olefinic isatin for [4 + 2] cycloaddition to form spiro compounds **14** diastereoselectively. Lewis acid  $InBr_3$  catalyzed both reactions and also contributed to the transition states to control the diastereoselectivity, which is a key factor to the success of this one-pot synthesis.



**Scheme 12. MCR-initiated one-pot synthesis of triazole-fused polycyclic compounds**



**Scheme 13. One-pot synthesis of phthalimide-containing scaffolds**

### Rearrangement reactions

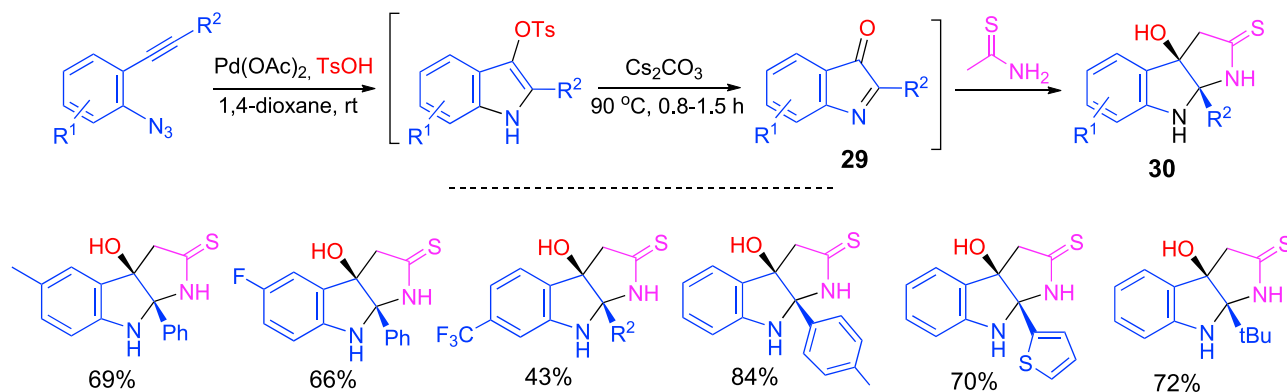
As a mass efficient chemical transformation, the rearrangement reaction reorganizes the molecular structure without releasing byproducts (Jones et al., 2014). The reactions are commonly performed under relatively simple catalytic or heating conditions.

Highlighted in Scheme 9 is a transition metal-catalyzed [6 + 3] cycloaddition followed by transannular Alder-ene rearrangement to form bicyclic hexahydropyranopyrroles **16** (Lee et al., 2021). The [6 + 3] cycloaddition of vinylpropylene carbonates with *N*-sulfonyl-1,2,3-triazoles was catalyzed by Pd(0) and Rh(III) at 60°C to form 9-membered monocyclic *N,O*-heterocycle compounds **17**. Heating of the reaction mixture at 120°C–150°C promoted the Alder-ene rearrangement to form bicyclic hexahydropyranopyrroles **16**.

Shown in Scheme 10 is an innovative one-pot and two-step synthesis involving thermal Claisen, Cope, and Meinwald rearrangement reactions followed by a Burgess reagent-promoted dehydrative benzofuran formation reaction (Song et al., 2020). Special starting materials bearing epoxide and allyl ether moiety were refluxed in 1,2-dichlorobenzene (DCB) for cascade sigmatropic rearrangement reactions to form intermediate **18**. Switch reaction solvent to toluene and addition of the Burgess reagent for the dehydration reaction afforded substituted benzofurans **19**.

### Multicomponent reaction-involved OPSS

A single-step MCR reaction is easy to perform. However, reported numbers of MCRs are limited. Performing post-MCR is a good strategy to increase the structural diversity and also generate new scaffolds (Zhi et al., 2019; Ghashghaei et al., 2019). A one-pot synthesis involving a three-component [3 + 2] cycloaddition followed by amide coupling and aza-Wittig reactions is shown in Scheme 11 (Ma et al., 2019a). In this three-step synthesis,



**Scheme 14.** Pd-catalyzed one-pot synthesis of pyrroloindolines

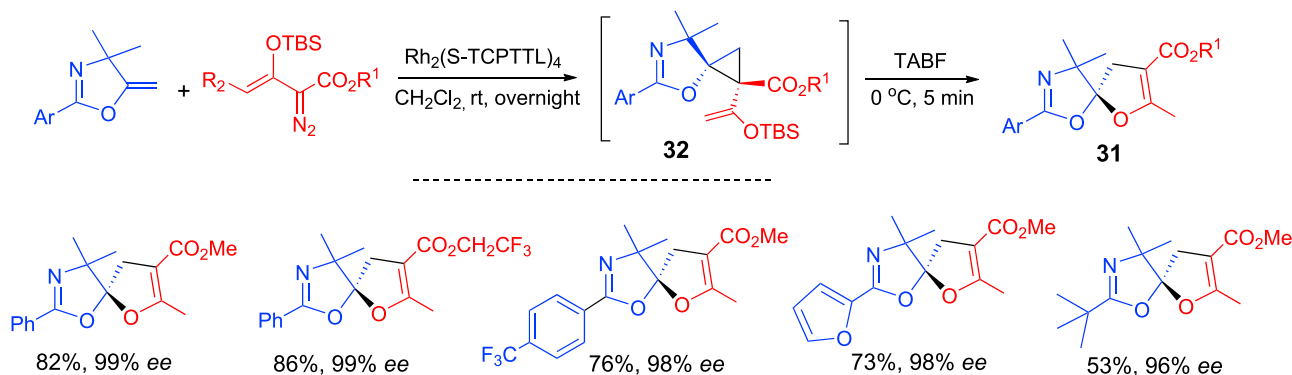
the [3 + 2] cycloaddition was performed as a three-component reaction of 2-azidobenzaldehydes, amino esters, and maleimides under microwave heating to give adducts **20** diastereoselectively. The reaction mixtures were subjected to amide coupling with phenylglyoxylic acid at room temp for **21** and then cyclative aza-Wittig reaction with PPh<sub>3</sub> at 105°C to afford tetrahydro-pyrrolobenzodiazepinones **22**. Green chemistry metrics analysis indicated that this one-pot synthesis has favorable atom economy, carbon efficiency, mass productivity, and solvent and water intensity.

In another three-component [3 + 2] cycloaddition-initiated synthesis using 2-azidobenzaldehydes, the adducts were used for *N*-propargylation and click reaction to form triazole-fused polycyclic compounds (Scheme 12) (Ma et al., 2019b). Amino acids were used for decarboxylative [3 + 2] cycloaddition with 2-azidobenzaldehydes and maleimides by heating in a sealed tube at 110°C for 6 h. Adducts **23** were used for K<sub>2</sub>CO<sub>3</sub>-promoted *N*-propargylation for **24** and intramolecular triazole formation reactions to give products **25**. It is worth noting that the last step click reaction was spontaneous, no Cu-catalyst was required.

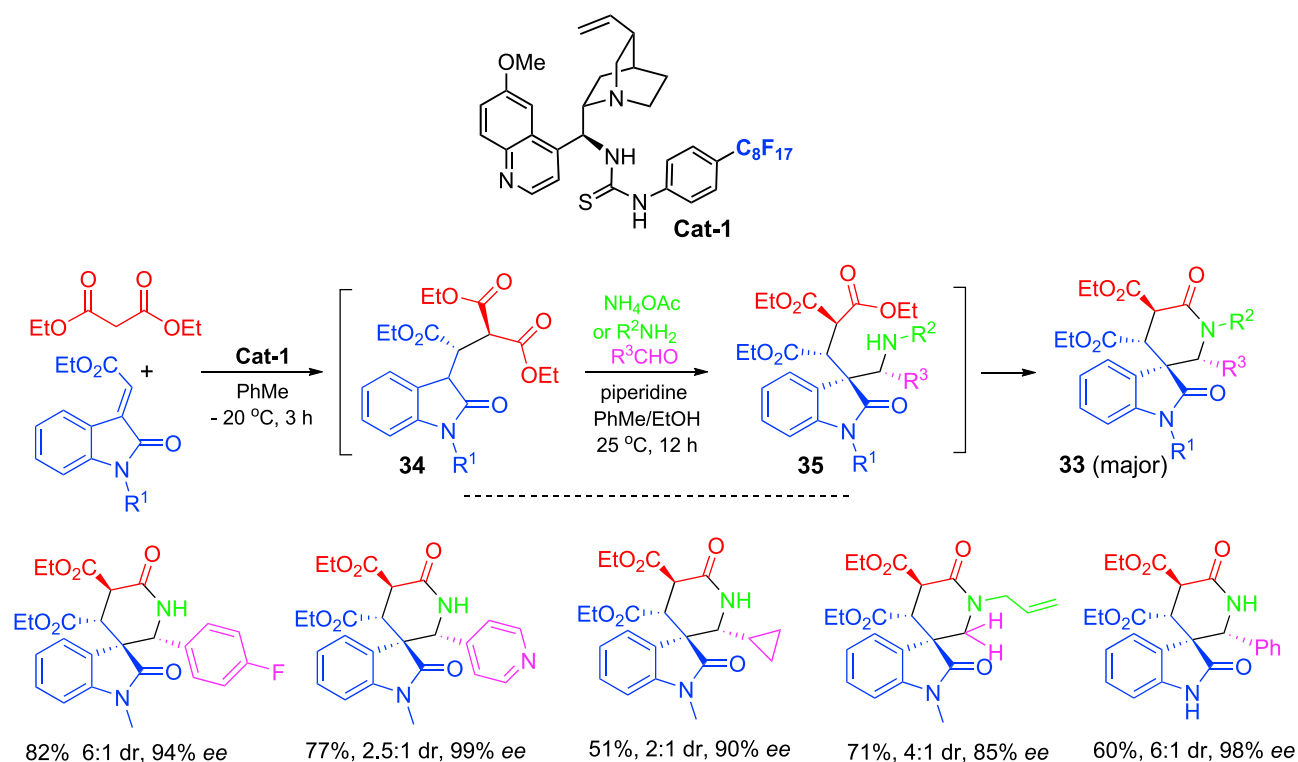
An MCR-initiated one-pot synthesis of two phthalimide-containing scaffolds **26** and **27** is shown in Scheme 13 (Alizadeh et al., 2021). A three-component reaction of benzylamine, CS<sub>2</sub>, and dimethyl acetylenedicarboxylate afforded 2-thioxothiazolidin-4-one intermediates **28** which were treated with two different malononitriles to afford products **26** and **27**, respectively. Both the MCR and phthalimide formation reactions were conducted under sonication. The second step reaction has a series of transformations including Michael addition, cyclization, elimination of carbon disulfide, and acyl substitution to afford product scaffold.

### Transition metal-catalyzed reactions

Transition metal (TM)-catalyzed reactions are well established and probably still more popular than that of under organocatalysis and biocatalysis. There are many reviews on catalytic one-pot reactions (Vlaar et al.,



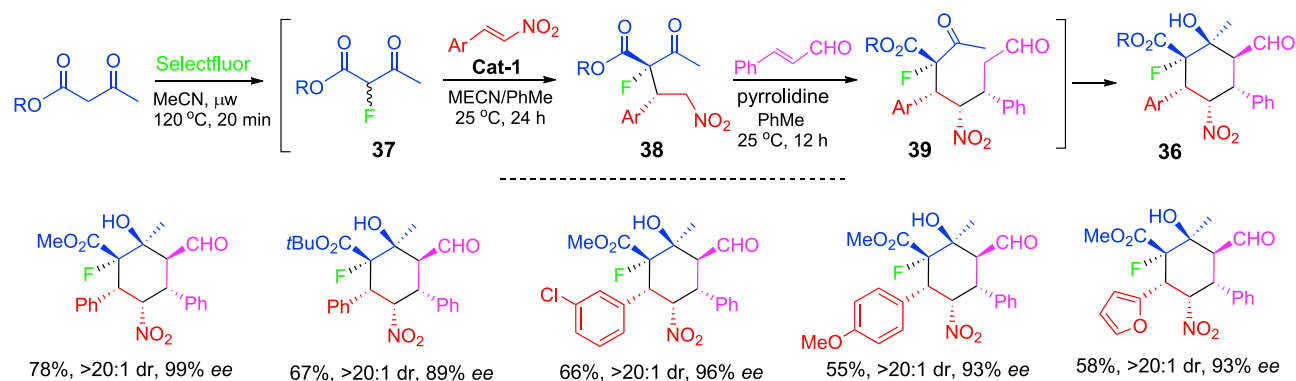
**Scheme 15.** Rh-Catalyzed one-pot asymmetric synthesis of spiroketals



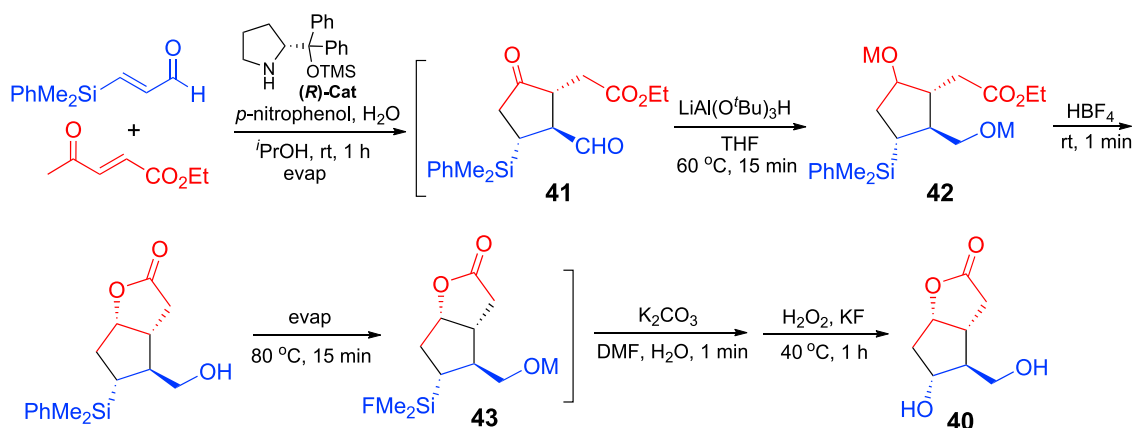
**Scheme 16. One-pot two-step organocatalytic synthesis of spirooxindoles**

2011; Afewerki and Cordova, 2016; Szöllösi, 2018) and mult catalysis (Pellissier, 2020b; Martínez et al., 2021). However, the number on catalytic OPSS is very limited, especially for TM-catalyzed reactions due to the catalysts are general sensitive to moisture and air, and with limited scope on substrates. The systems are more complicated in the cases of asymmetric synthesis involving specially designed ligands. A general practice in the development of a TM-catalyzed OPSS is to carry the catalytic reaction prior to other reactions.

Shown in Scheme 14 is a one-pot synthesis involving Pd-catalyzed formation of indolones followed by second annulation to form pyrroloindoline ring system (Li et al., 2021). The reaction of 1-azido-2-(phenylethynyl)benzenes with TsOH under the catalysis of Pd(OAc)<sub>2</sub> at room temperature followed by the treatment with CsCO<sub>3</sub> at 90 °C gave **29**. The synthesis was finished by the addition of ethanethioamide for annulation to give pyrroloindoline products **30**.



**Scheme 17. One-pot three-step asymmetric synthesis of substituted cyclohexanols**



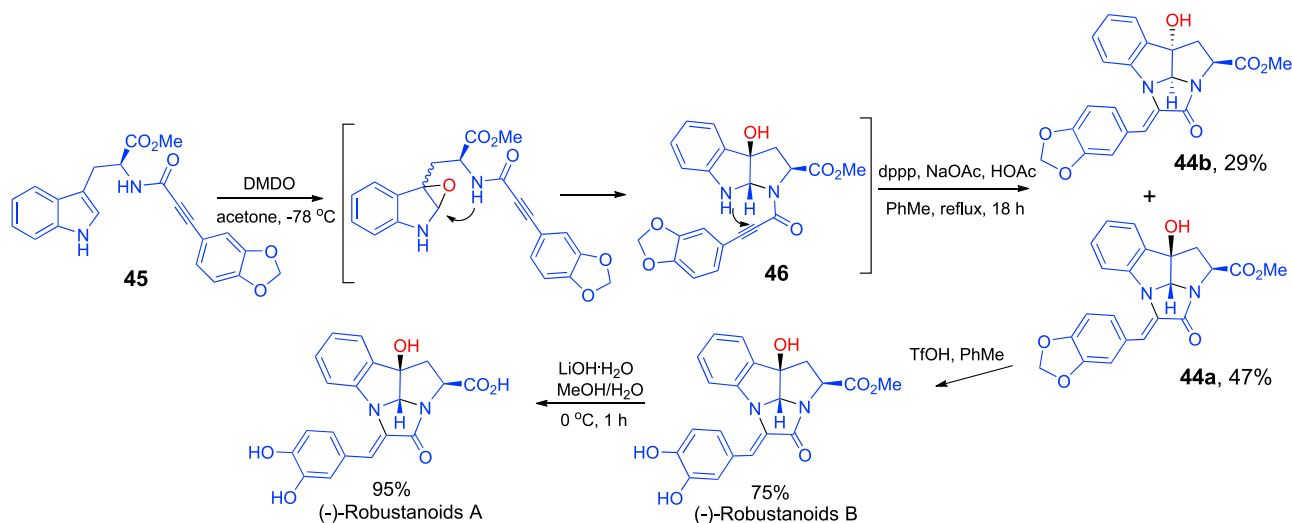
**Scheme 18. Organocatalysis-initiated one-pot asymmetric synthesis of Corey lactone**

One-pot asymmetric synthesis of spiroketals **31** has been accomplished through Rh-catalyzed cyclopropanation and TABF-promoted ring expansion reactions (Scheme 15) (Dong et al., 2021). A variety of 4,4-dimethyl-methylenedihydrooxazoles and enoldiazoacetates were used for an asymmetric cyclopropanation reaction under the catalysis of  $\text{Rh}_2(\text{S-TCPTTL})_4$  at room temp for overnight. Intermediates **32** were treated with TABF at  $0^\circ\text{C}$  for 5 min for a quick rearrangement reaction to form chiral heterobicyclic spiroketals with high enantioselectivity.

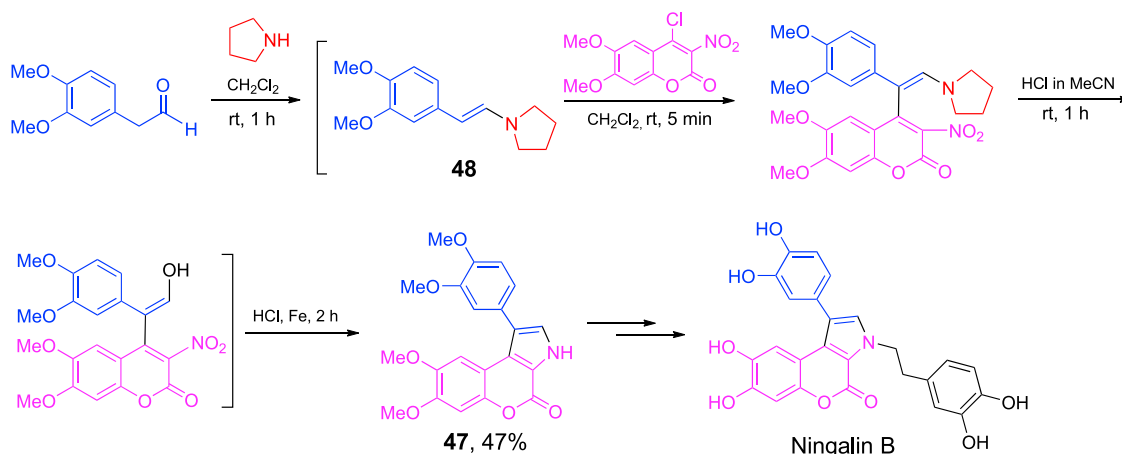
### Organocatalytic asymmetric synthesis

Organocatalytic reactions could be performed under mild conditions which make them easier to be developed as OPSS (Chanda and Zhao, 2018; Albrecht et al., 2011). A one-pot and two-step synthesis involving Michael/Mannich/cyclization reactions has been developed for the synthesis of spirooxindoles **33** bearing multiple stereogenic centers (Scheme 16) (Huang et al., 2015). The Michael addition of 1,3-diester to olefinic oxindoles under the catalysis of recoverable cinchona-based catalyst **Cat-1** for **34** followed by the Mannich reaction with aldehydes and  $\text{NH}_4\text{OAc}$  or secondary amines for **35** and sequential lactamization afforded spiro-oxindole/ $\delta$ -lactam products **33** with four contiguous stereogenic centers on the newly formed lactam ring. Products have high ee values, but the dr are more substrate dependent.

Recyclable **Cat-1** was used in another one-pot asymmetrical synthesis of biologically interesting cyclohexanols **36**. It involves sequential fluorination/Michael/Michael/aldol reactions (Scheme 17) (Huang et al., 2017). The fluorination of  $\beta$ -ketoesters with Selectfluor gave racemic-fluorinated  $\beta$ -ketoesters which were



**Scheme 19. One-pot synthesis of intermediate X for (-)-robustanoids B and A**



**Scheme 20.** One-pot synthesis of intermediate **47** for ningalin **B**

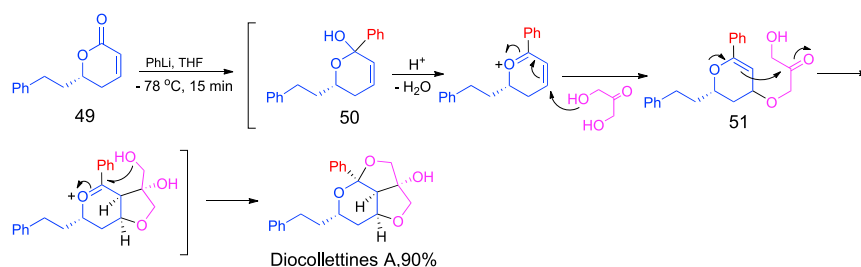
used for Michael addition for **37** under the catalysis of **Cat-1** for **38** followed by second Michael addition for **39**, and finally intramolecular aldol reaction to give the products **36** bearing six contiguous stereogenic centers including a fluorinated tertiary carbon. The Michael addition of racemic-fluorinated  $\beta$ -ketoesters **37** afforded **38** as the major diastereomers which underwent second Michael addition to form **39** followed by cyclative aldol addition to give products **36** which were stabilized by the intramolecular H-bonding to avoid dehydration.

Corey lactone is an asymmetric bicyclic compound which is a versatile intermediate for the synthesis of prostaglandin hormones. A multistep synthesis initiated with the diphenylprolinol silyl ether-catalyzed Michael/Michael reactions of 3-(dimethylphenylsilyl) propenal and ethyl 4-oxo-2-pentenoate is shown in [Scheme 18](#) (Umekubo et al., 2020). Intermediate **40** was treated with 3.5 equiv of  $\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$  to reduce ketone and aldehyde carbonyls for **41** followed by addition of  $\text{HBF}_4$  to form dihydroxy ester which immediately cyclized to give lactone **42** and then **43** after evaporation of THF solvent. Neutralization of the reaction mixture with  $\text{K}_2\text{CO}_3$  followed by oxidative alkyl silyl removal with  $\text{H}_2\text{O}_2$  and  $\text{KF}$  afforded the Corey lactone. This one-pot six-operation-step synthesis could be done in 152 min to give the product in 99% ee.

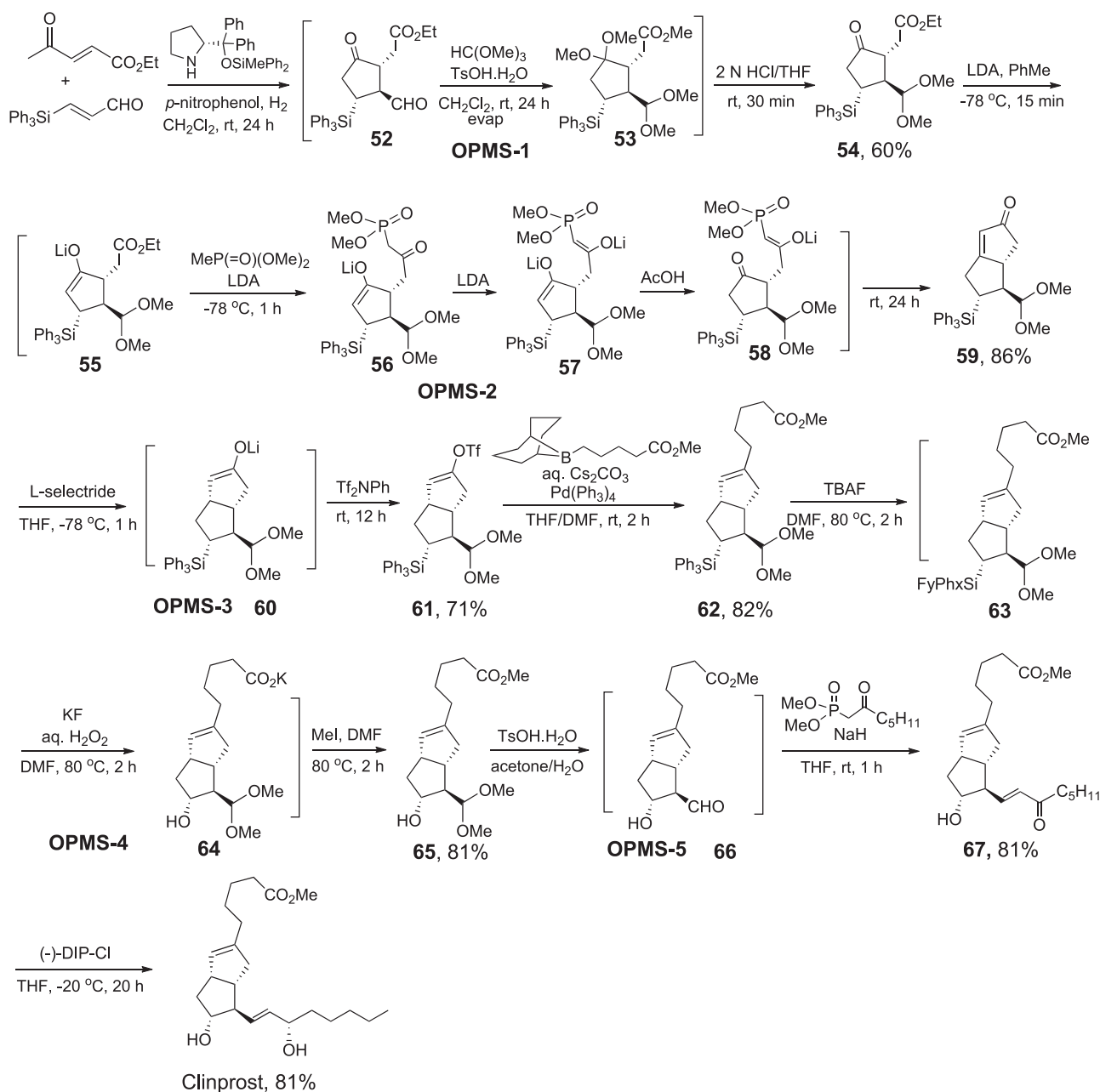
### Synthesis of natural products and bioactive molecules

Mother nature is a master of performing highly efficient and yet selective enzymatic multistep synthesis for making complicated molecules in living organisms. Synthetic chemists have accomplished numerous natural product synthesis with the assistance of newly developed techniques (Dückert et al., 2012; Ard-khean et al., 2016; Nicolaou et al., 2003) including biosynthesis (Riva and Fessner, 2014). But non-bio-catalytic OPSS for total synthesis is still a dream to be fully realized. Some successes have been achieved on the synthesis of key intermediates in natural product total synthesis (Pellissier, 2020b).

Highlighted in [Scheme 19](#) is a one-pot synthesis triggered by 3,3-dimethyldioxirane (DMDO) epoxidation in the synthesis of **44a** which is an intermediate for (–)-robusanoids B and A ([Scheme 18](#)) (Liu and Huang,



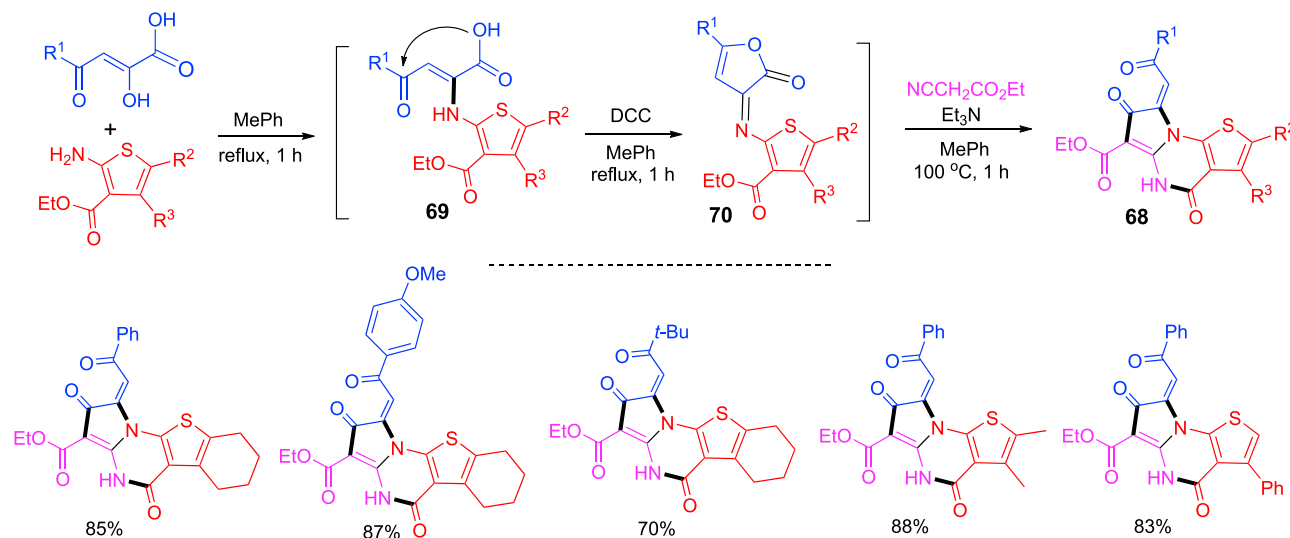
**Scheme 21.** One-pot synthesis in the preparation of diocollettines **A**



**Scheme 22. Total synthesis of clinprost involving five steps of OPSS**

2019). DMDO epoxidation of **45** in acetone at  $-78^{\circ}\text{C}$  was followed by bis(1-3-diphenylphosphino)propane (dppp)-promoted cyclization to form **44a** and **44b** as a mixture of diastereomers. Isolated diastereomer **5** was readily converted to for (–)-robustanoids **B** and **A**.

A one-pot three-step synthesis of intermediates **47** in the total synthesis ningalin B is shown in [Scheme 20](#) (Wu et al., 2019). Condensation of 2-(3,4-dimethoxyphenyl) acetaldehyde and pyrrolidine afforded enamine **48** which was reacted with 4-chloro-3-nitrocoumarin followed by enamine hydrolysis and  $\text{NO}_2$  reduction with Fe under acidic condition to form chromenopyrrol-4-one **47**. Additional two-step reactions from **47** finished the total synthesis of ningalin B. In the one-pot synthesis, the solvent was switched from  $\text{CH}_2\text{Cl}_2$  for the first two steps to MeCN at the third step.



**Scheme 23. One-pot synthesis of bioactive thieno[3,2-e]pyrrolo[1,2-a]pyrimidines**

Diocollettines A has a unique oxygen-containing tricyclic core. One-pot synthesis was applied to the last steps of the total synthesis of diocollettines A (Scheme 21) (Kawamoto et al., 2019). Enantiopure compound **49** was treated with PhLi at  $-78^{\circ}\text{C}$  to form transient intermediate **50** which then reacted with 1,3-dihydroxyacetone (DHA) under basic conditions to give the tricyclic product diastereoselectively through the processes of *trans*-selective oxa-Michael addition for **51**, aldol-type cyclization, and intramolecular acetalization.

Clinprost is a bicyclo[3.3.0]octenone core with four stereogenic centers. Extensive effort on the integration of one-pot synthesis was invested in a recently reported total synthesis of clinprost (Scheme 22) (Umekubo and Hayashi, 2020). Five OPSS were incorporated into a 17-step synthesis. The first OPSS was initiated with the organocatalyst-promoted asymmetric [3 + 2] cycloaddition of ethyl 4-oxo-2-pentenoate with 3-(triphenylsilyl) propenal to form **52** which was subjected to double carbonyl group acetalization to form **53** and then selective hydrolysis to finish the one-pot synthesis of **54** in 60%. This intermediate was used for a new one-pot synthesis treated with LDA to form enolate **55** for Claisen reaction with dimethylmethylphosphonate to afford  $\beta$ -keto phosphonate **56** which was quickly converted to dianion **57**. Addition of AcOH selectively regenerated a keto group in **58** to afford bicyclo[3.3.0]octenone **59** as a Horner–Wadsworth–Emmons reaction product in 86%. In the third one-pot two-step synthesis, **59** was treated with L-selectride to generate enolate **60** which was trapped with  $\text{TiF}_2\text{NPh}$  to afford **61** in 82%. After the Suzuki–Miyaura coupling reaction to convert **61** to **62**, the fourth OPSS took place by treated **62** with TBAF for **63** and then with KF for **64** followed by addition of MI to form methyl ester **24** in 81%. The last OPSS was to treat **65** with TsOH hydrolysis the acetal to form **66** for Horner–Wadsworth–Emmons reaction to afford **67** in 81%. Asymmetric reduction of keto group with (–)-DIP-Cl afforded clinprost in 85% yield. This is an excellent example of implement OPSS strategy in the total synthesis. If all the reaction steps were conducted in one-pot, this could be a dream sequence in asymmetric total synthesis of a natural product.

Thieno[3,2-e]pyrrolo[1,2-a]pyrimidines **68** highlighted in Scheme 23 are biologically interesting compounds with potential poly(ADP-ribose) polymerase-1 (PARP-1) inhibitory activity (Shipilovskikh and Rubtsov, 2019). An OPSS protocol has been developed start from the reaction of Gevald's aminothiophene and 2-hydroxy-4-oxobut-2-enoic acid to form 2-(2-(thienyl)amino)-4-oxobut-2-enoic acid **69** which underwent dicyclohexylcarbodiimide (DCC)-promoted dehydrative cyclization to yield furanone **70**. It was treated with cyanoacetic ester and  $\text{Et}_3\text{N}$  under heating the reaction mixture at  $100^{\circ}\text{C}$  for 1 h to afford products **68**. Toluene was the only solvent used in this one-pot three-step synthesis.

## Summary

One of the aims of this perspective article is to define the one-pot stepwise synthesis (OPSS) and to differentiate it from the cascade reaction and multicomponent reaction (MCR). Even these three one-pot



reactions share some common green chemistry advantages such as low cost, high efficiency, resource saving, and minimal waste disposal. The OPSS could be operational more flexible and transformational more feasible than other two methods. Since there is no focused review on OPSS, this paper uses selected examples to demonstrate the recent development of OPSS in the synthesis of biologically interesting heterocyclic compounds, asymmetric molecules, and natural products through cyclization, cycloaddition, and rearrangement reactions.

I like to offer my personal perspective on the future development of OPSS. Design and discovery of new OPSS could have great potential in the areas such as catalytic reactions involving dual or multiple catalysts. The catalysts could be transition metals, enzymes, and organic molecules, or a mixture use of these three classes of catalysts. Conducting an MCR followed by post-condensation modifications is a good direction for OPSS for making complicated structures. In addition to the development of new OPSS, reengineer reported multistep synthesis could be important, especially in the synthetic optimization for drug molecules and natural products. More success on OPSS could be achieved by performing following practices: 1) streamlining the synthetic process and maximizing the conversion for each step, 2) balancing substrate scope, functional group tolerance, and reaction selectivity, 3) incorporating more reaction steps for higher efficiency in making complicated structures, and 4) integrating different kind of reactions (such as ionic and radical reactions) or using different catalysts (such as organo, metal, and photoredox catalysts) which are hard to achieve in MCRs and cascade reactions. The introduction of new software and programs for AI-assisted synthesis and computational molding is increasingly important for the designing of new OPSS. Interdisciplinary effort and systematic approach to incorporate new synthetic techniques such as flow chemistry, mechanochemistry, and photoredox and biocatalysis could set up new platforms for the development of OPSS (Constable, 2021). Promoting the reactions in green solvents such as water, ionic liquids, and supercritical fluid (Horváth, 2008) and using alternative energy such as microwave, light, sonication, and electricity (Robertson et al., 2019) also provides new avenues for OPSS in the synthesis of small molecules with biological interests.

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## AUTHOR CONTRIBUTIONS

X.M. and W.Z. wrote the manuscript. X.M. draws the Figures and arranged the references based on the comments of W.Z. who supervised the overall project.

## DECLARATION OF INTERESTS

The authors declare no competing interests.

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