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# Recent advances in asymmetric multicomponent reactions (AMCRs)

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ABSTRACT

Asymmetric multicomponent reactions (AMCRs) include the reaction of three or more reactants simultaneously to produce chiral products that they have some advantages containing simple procedures, saving time and energy, and being environmentally friendly processes. AMCRs have seen much development and their potent synthetic approaches are discussed in this review.



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## 1. Introduction

Multicomponent reactions (MCRs) allowed great progress in organic chemistry and were developed as a dominant method for the formation of new and complicated molecular structures because of their benefits over conventional multisteps reactions.[1,2] The main advantages of MCRs include diminished costs, quick reaction times, atom-economy, energy preservation, and prevention of time consuming product purification.[3,4] The improvement of catalytic asymmetric reactions has been one of the main approaches for the past two decades and nowadays, it remains a common chemical technique. Unimolecular or bimolecular syntheses can be achieved under catalytic conditions to give products in high yields and with excellent enantioselectivities, in the development of asymmetric multicomponent reactions (AMCRs).

AMCRs involve the reaction of three or more substrates in a single container, which have been added together to provide stereoselectively a new chiral derivative; the product contains all portions of the substrates, to afford one stereogenic component.[5,6] Although in some reactions, none of starting materials are chiral, a chiral catalyst, solvent or chiral auxiliary is used to obtain an optically active product.

So far, two inclusive review articles have been published about the whole scope of AMCRs in 2005[7] and in 2011.[8] In continuation

*Abbreviations:* AMCRs, asymmetric multicomponent reactions; BINOL, 1,1′-bi-2-naphthol; DCE, dichloroethane; de, diastereomeric excess; DIPEA, diisopropylethylamine; DMCHA, dimethylcyclohexylamine; dppe, (diphenylphosphino)ethane; d.r., diastereomeric ratio; ee, enantiomeric excess; *ent*, enantiomeric; HybCat, hybrid catalyst; JohnPhos, (2-biphenyl)di-*tert*-butylphosphine; Piv, pivaloyl; py-imine, 2,4,6-trimethylphenyl-*N*-(pyridin-2-ylmethylene)aniline; *m*CPBA, *meta*-chloroperoxybenzoic acid; MS, molecular sieves; MTBE, methyl *tert*-butyl ether; MW, microwave; TBAB, tetrabutylammonium bromide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMS, trimethylsilyl; TMSO, tetramethylorthosilicate.

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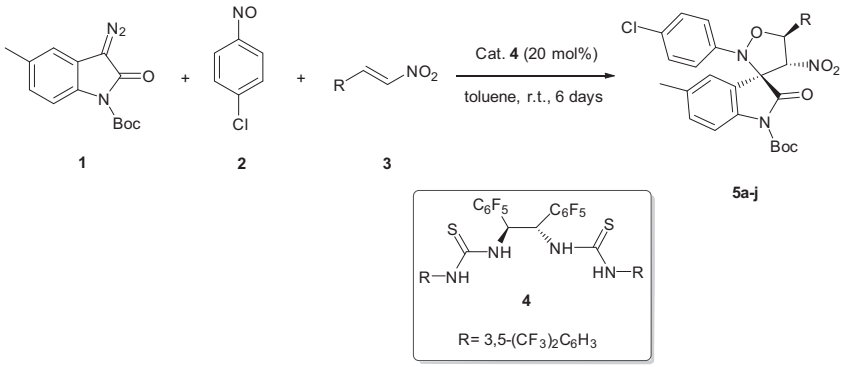
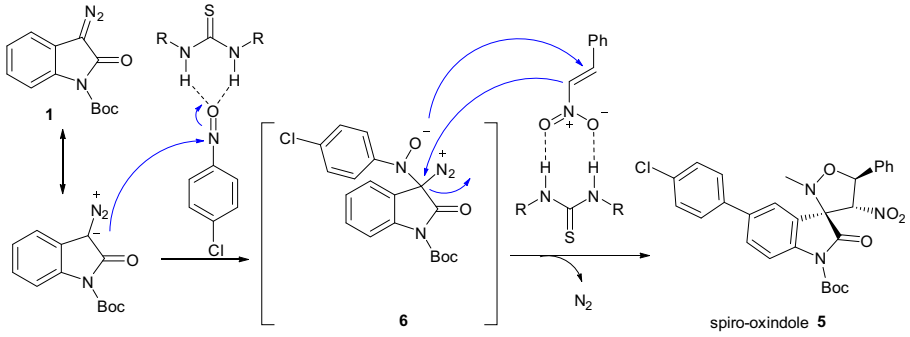



| 5 | R | Yield % | ee % | d.r. |
|---|---|---|---|---|
| **5a** | 4-$FC_6H_4$ | 99 | 99 | > 99:1 |
| **5b** | 4-$ClC_6H_4$ | 99 | 99 | > 99:1 |
| **5c** | 4-$BrC_6H_4$ | 99 | 99 | > 99:1 |
| **5d** | 4-$CF_3C_6H_4$ | 85 | 98 | > 99:1 |
| **5e** | 4-$MeC_6H_4$ | 98 | 99 | > 99:1 |
| **5f** | 2-$MeC_6H_4$ | 72 | 97 | > 99:1 |
| **5g** | 2-Thiophenyl | 73 | 98 | > 99:1 |
| **5h** | Et | 86 | 99 | > 99:1 |
| **5i** | *i*-Pr | 73 | 98 | > 99:1 |
| **5j** | Cyclohexyl | 90 | 97 | > 99:1 |
| **5k** | 1-Naphthyl | 84 | 99 | > 99:1 |

**Scheme 1.** Synthesis of spirooxindole derivatives **5**.




**Scheme 2.** Proposed mechanism for the synthesis of spirooxindole.

of our previous work on asymmetric synthesis,[9–13] we herein report the recent advances in AMCRs are reviewed since 2012.

## 2. Asymmetric synthesis

### 2.1. Spirooxindole compounds

The oxindole skeleton bearing a tetrasubstituted carbon stereocenter at the 3-position is a recognised structural backbone found in many biologically active alkaloids, natural products, and pharmacological agents.[14–16] In 2015, the advances in the use of isatin as a starting material have been highlighted in numerous asymmetric syntheses of 3,3-disubstituted oxindoles.[17] Wu et al. originated their studies via estimating the feasibility of the MCRs of the diazooxindole **1** with nitrosoarene **2** and nitroalkenes **3** in the presence of the bifunctional catalyst **4** to yield spirooxindoles **5** based on the organocatalytic asymmetric nucleophilic addition of imines and diazo derivatives. They tested the generality of this reaction by using various nitroalkenes **3a–j** as the reactant (Scheme 1). Furthermore, these reactions were completed within six days and provided the products in good to excellent yields (72–99%) and with high enantioselectivities (97–99% ee) and diastereoselectivities (>99:1 d.r.). In this way, both electron donating and withdrawing substituents on the aromatic ring of β-aryl nitroalkanes **3** have the same effect on the reaction rate and the stereoselectivity, as well. Significantly, alkyl nitroalkenes were likewise suitable substrates and the desired products were obtained with good results under the modified conditions. The absolute configuration of spirooxindole derivatives **5** was proved by X-ray crystallographic analysis. As depicted in the proposed mechanism (Scheme 2), intermediate **6** is created via the reaction of diazooxindole **1** and nirosoarene **2** activated by the chiral catalyst. During the removal of $N_2$ from intermediate **6**, nitroalkene **3** attacks it via an intramolecular cyclization, to give spirooxindole product **5**.[18]

Some optically active natural spirooxindoles are biologically active compounds.[19,20] Xie et al. reported the synthesis of chiral spirooxindole pyran derivatives[21,22] wherein the catalyst used is either a metal[23,24] or small organic molecules.[25] The reaction was accomplished with aldehydes **7**, nitro-olefins **8** and isatins **10**, and gave the desired product **11** in good yields (Scheme 3).[26] The Michael–aldol–acetalization cascade reaction was carried out in toluene in the presence of catalyst **8** at room temperature for about 3 h. The reaction proceeded smoothly to afford the corresponding spirooxindolelactone **11** in good yields up to 84%, with high diastereoselectivities up to 95:5 dr and excellent