Recent advances on diversity oriented heterocycle synthesis via multicomponent tandem reactions based on A³ coupling

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Abstract
A³ coupling reactions are the reactions between aldehydes, amines and alkynes, which yield propargylamine derivatives under various catalyst conditions. By making use of the versatile reactivity of propargylamines, tandem reactions initiated by the functional group(s) in the \textit{in situ} generated propargylamines constitute one of the most important applications of A³ couplings. These tandem reactions are especially useful for the synthesis of heterocyclic compounds. In this review, the progress on multicomponent tandem reactions based on A³ coupling is summarized.

Keywords: A³ Coupling, tandem, multicomponent reactions, heterocyclic compounds

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1. Introduction

The A³ coupling reactions are known as the three-component reactions of aldehydes, amines and alkynes yielding propargylamines as products. The earliest example of this kind of
transformation can be dated back to 1953, when Guermont employed terminal alkynes, secondary amines and formaldehyde for the synthesis of propargylic amino ethers. During the past several decades, the group of Li has conducted seminar work in exploring these reactions and named these reactions as A³ coupling based on the three characteristic reactants involved in the reactions (Scheme 1).

![Scheme 1](image)

Owing to the important and broad applications A³ coupling has exhibited, worldwide attention has been drawn to this research field. The advantages of A³ coupling reactions, such as excellent functional group tolerance and the broad utilities of propargylamine products in organic synthesis, account mainly for the prevalent interests afforded to these reactions. Among the numerous synthetic examples associated with A³ coupling chemistry, tandem reactions involving A³ coupling as key transformation has evolved as versatile tools for the synthesis of structurally diverse heterocyclic products. These syntheses were usually achieved via the transformations on the *in situ* generated propargylamines in the presence of a second functional group located in the propargylamine intermediates or provided by other additional component. These tandem reactions involved at least the formation of three new chemical bonds and shown widespread application in the synthesis of heterocyclic products. In this present review, we comprehensively summarized the progress on A³ coupling-based tandem reactions for heterocycle synthesis. The reactions were classified based on the location of second functional group that initiates the tandem annulation after A³ coupling.

2. Heterocycle Synthesis via Tandem Multicomponent Reactions via A³ Coupling

2.1. Reactions based on functional amine participated tandem A³ coupling transformation

Among the three reactants of A³ coupling reactions, amines possessed the most versatile structural variability and flexibility since they could participate in the reactions not only in the form of aromatic and aliphatic substrates, but also in the form of primary amine, secondary amine or even ammonia. Therefore, it was convenient to devise A³ coupling-based tandem reaction to access heterocyclic scaffolds by using the functional amines. In 2002, Iqbal and co-workers reported the first CuCl-catalyzed three-component reactions of aromatic amines, alkynes and aldehydes for direct synthesis of quinolines. The reactions were performed in refluxing THF and provide quinolines in 31-48 % yield while propargylamine products occurred as side or only products in some entries. During the reaction process forming, A³ coupling products.
were the key intermediates, the tautomeration of 6 to intermediates 7 with copper catalysis led to transition state 8, and the nucleophilic carbon site in amines initiated the intramolecular annulation to provide the other key intermediates 9 which underwent aromatization to give products 5 (Scheme 2).

![Scheme 2]

Wang\textsuperscript{11} et al. employed AuCl\textsubscript{3} and CuBr as mixed catalysts in methanol solvent to carry out the same multicomponent reactions, which remarkably enhanced the product yields (Scheme 3). Later on, Tu\textsuperscript{12} and coworkers developed a new atom economical protocol for quinolines synthesis wherein FeCl\textsubscript{3} was used as catalyst, and the reactions were performed in toluene at 110 °C with moderate to excellent yield of products (Scheme 3). Similar results has also later been reported by Wang and coworkers.\textsuperscript{13} Recently, iron species Fe(CF\textsubscript{3}COO)\textsubscript{3}\textsuperscript{14} and Fe(OTf)\textsubscript{3}\textsuperscript{15} were respectively reported as efficient catalysts for quinolines synthesis via the same multicomponent reactions. On other othe hand, Kumar\textsuperscript{16} and coworkers developed a rapid catalytic method for the reaction using Yb(OTf)\textsubscript{3} catalyst in ionic liquid medium with the promotion of microwave, advantages of broad application scope as well as excellent product yield have been demonstrated (Scheme 3). Following this work, Wang\textsuperscript{17} et al. devised recyclable Ytterbium catalyst Yb(Pfb)\textsubscript{3} (Pfb = pentafluorobenzoates) to enable the this transformation under solvent-free condition with good to excellent yields of quinolines. Mohammadpoor-Baltork\textsuperscript{18} et al. synthesized a series of similar quinolines using this three-component assembly employing K\textsubscript{2}CoW\textsubscript{12}O\textsubscript{40}·3H\textsubscript{2}O as catalyst under microwave irradiation, products were obtained with generally excellent yields with solvent-free operation (Scheme 3).
Besides quinolines 5, many other heterocyclic products bearing quinoline backbone have been found readily accessible through the same kind of tandem reactions, for example, Nagarajan\(^1\) and co-workers developed the three-component reactions of aminocarbazoles 11, aldehydes and terminal alkynes for the synthesis of polycyclic scaffolds 12 with excellent application scope. The reactions were performed in ionic liquid [Bmim]BF\(_4\) at 100 °C in the presence of CuI/La(OTf)\(_3\) co-catalysts (Scheme 4).

On the other hand, Zhang\(^\text{20}\) et al. investigated similar three-component reactions using fluorine functionalized aldehydes 13, the reactions conditions of CuCl catalysis and microwave assistance enabled the synthesis of various fluorine containing quinoline derivatives 14. Based on the difference in reactions conditions, reactions could proceed to the stage of conventional A\(^3\) coupling products or products 14, the selectivity of the reactions were mainly determined by
oxidative conditions, the air atmosphere mainly led to the production of quinoline products (Scheme 5).

Scheme 5

As another frequently utilized N-nucleophiles, hydrazines could be used as alternatives of amines for three-component coupling reactions with aldehydes and terminal alkynes. After A³ coupling, tandem annulation/aromatization transformation could be initialized to provide pyrazole products. Pan and co-workers²¹ employed PTSA catalyst and achieved the three-component reactions of hydrazines 15, aldehyde and terminal alkynes for tandem synthesis of pyrazoles 16, the key intermediates 17 in the reactions were generated from the hydrazine-based A³ coupling (Scheme 6).

Scheme 6

Imidazo[1,2-a]pyridine is another useful heterocyclic backbone that can be easily constructed through functional amine initiated, A³ coupling-based tandem reactions. Gevorgyan²² and co-workers employed 2-aminopyridine 18 as amine component for A³ coupling tandem reactions, and the coupled intermediates 20 have been directly transformed to
imidazo[1,2-a]pyridines 19 as products through 5-exo-dig annulation in the presence of CuCl/Cu(OTf)2 co-catalysts (Scheme 7).

Scheme 7

Later on, various other different catalysis conditions have been developed to smoothly perform the same reactions. Ghosh et al.23 employed CuI catalyst to carry out the three-component assembly in reflux toluene in the presence of NaHSO4·SiO2 additive, and corresponding products were obtained with good to excellent yield (Equation 1, Scheme 8), while Guchhait group devised an interesting protocol of D-glucose/CuSO4·5H2O catalysis to performed this three-component heterocycle synthesis wherein Cu(I) species has been generated in situ via reduction of partial CuSO4·5H2O to serve as cocatalyst of Cu(II). The application
scope of reactions in this work has been extended to other heteroaryl amines from 2-aminopyridine (Equation 2, Scheme 8).

\[
\begin{align*}
\text{R}^1\text{N}^\text{NH}_2 + \text{O} + \text{R}_2^3\text{C} & \rightarrow \text{R}^1\text{N}^\text{N}_2\text{R}_2^3\text{R}_3^3 \\
\text{CuI, 5 mol % NaHSO}_4\cdot\text{SiO}_2 & \text{Toluene, reflux} \\
\end{align*}
\]

28 examples 60-91 % yield

\[
\begin{align*}
\text{Het}^\text{N}^\text{NH}_2 + \text{O} + \text{R}_2^3\text{C} & \rightarrow \text{Het}^\text{N}^\text{N}_2\text{R}_2^3\text{R}_3^3 \\
\text{CuSO}_4\cdot5\text{H}_2\text{O}, 15 \text{ mol}\% & \text{D-Glucose, 30 mol}\% \\
\text{EtOH, reflux} & \text{Cu(II)-Cu(I)} \\
\end{align*}
\]

24 examples 20-82 % yield

**Scheme 8**

### 2.2. Reactions based on functional aldehyde participated tandem A³ coupling transformation

As the electrophilic component in A³ coupling reaction, aldehyde has exhibited excellent tolerance to catalytic conditions and functional groups, meanwhile, aldehydes containing many other reaction functional groups were usually of easy access, employing functional aldehydes for the design of A³ coupling based tandem reactions for heterocycle synthesis is also important content in A³ coupling reactions. For example, Liu²⁵ and co-workers achieved the three-component synthesis of indolizine 21 through the reactions of pyridinly-2-aldehydes, terminal alkynes and amines. The loading of 1 mol % NaAuCl₄·2H₂O catalyst and 60 °C heating efficiently promoted the synthesis of different indolizines under solvent-free operation. The key transformation of the reaction was also A³ coupling of three components yielding corresponding propargylamine intermediates 22, and the insertion of Au catalyst to C-C triple bond on 22 initiated further tandem annulation to provide final products 21 with moderate to excellent yield (Scheme 9).
Successful synthesis of indolizine derivatives via this kind of reactions triggered considerable research efforts in improving the reactions through a number of other catalytic methods. For example, the AgBF$_4$/toluene$^{26}$, Fe(acac)$_3$/TBAOH$^{27}$ and CuI/PEG$^{28}$ system etc. have all been reported as good methods for this three-component synthesis (Scheme 10).

Batra$^{29}$ et al. utilized polycyclic compounds 23 which contain a pyridinyl-2-aldehyde fragment to incorporate amine and terminal alkynes for similar reaction, and a series of polycyclic scaffolds 24 have been synthesized with excellent application scope on substrates (Scheme 11).
Among the various available functional aromatic aldehydes, salicaldehyde is one of the most frequently utilized species in the synthesis of heterocyclic products. Reasonably, salicaldehyde was also useful building block in the synthesis of heterocyclic compounds via A3 coupling based tandem reactions. Li30 and co-workers reported CuI (some examples with AgCl)-catalyzed three-component synthesis of dihydrobenzofuran derivatives 27 by making use of salicaldehydes 25, terminal alkynes 26 and cyclic secondary amines as starting materials. A3 coupled products 28 were key intermediates in the reactions, and the hydroxyl or amino functional group has been found to be key factor determining the chemo-selectivity of the reaction since these functional groups were able to interact with Au catalyst via hydrogen bond and promote the activation of gold catalyst on C-C triple bonds to trigger subsequent transformation, while alkynes containing no hydroxyl or amine group led to the formation of only tradition A3 coupling products (Scheme 12).

Sakai31 and co-workers discovered that trimethylsilyl substituted alkynes 29 in stead of terminal alkynes could proceed directly to benzofuran derivatives 30 via 5-exo-dig annulation,
these reactions were performed in reflux MeCN using Cu(OTf)₂ as catalyst and DMAP as additive (Scheme 13).

Scheme 13

Interestingly, Li³² and co-workers found that employing terminal alkynes containing no silyl group, salicaldehydes and secondary amines was also able to afford benzofurans 30 through three-component tandem reactions. Products were provided with generally good yields in the presence of CuI catalyst, and K₂CO₃ as well as Bu₄NBr additives in toluene at 110 °C (Scheme 14).

Scheme 14

Li and Yao³³ reported another interesting three-component reactions of o-alkynyl benzaldehydes 31, terminal alkynes and aryl amines for facile synthesis of dihydroisoquinolines 32 with the catalysis of CuOTf and the assistance of Pybox ligand, corresponding heterocyclic products were provided with up to >99 % yield. The key intermediates were also propargylamines 33 which underwent intramolecular addition annulation to yield products 32 (Scheme 15). Ts-protected o-amino benzaldehydes 34 were similar with salicaldehydes in term of reactivity for many transformations, they also participate in similar three-component transformations with secondary amines and terminal alkynes to yield corresponding N-containing heterocycles, dihydroindoles 35. Reactions were performed in the presence of CuCl/Cu(OTf)₂ co-catalysts and DMAP additive, and excellent application scope has been demonstrated (Scheme 16).³⁴
Using hydrolyzed formyl carboxylic acid 36, Ji et al. reported an unprecedented three-component selective furanone synthesis, in the presence of secondary amines and terminal alkynes, the three-component reactions proceed under the catalysis of AuBr₃ to selectively generate different furanone products 37 and 38 at different temperature. The reactions proceed via propargylamines 39 as key intermediates, the intermediates could be activated by gold catalyst to give transition state 40, and 40 coupled with electrophiles to provide products 37 or 39 while releasing catalyst for further recycling process. Besides temperature, the reaction selectivity was also affected by the property of terminal alkynes, aryl alkynes mainly led to the
productions of 38, while main products obtained from entries using alkyl alkynes were 37 (Scheme 17).

Scheme 17

Another interesting three-component tandem synthesis of heterocycle initiated by A³ coupling has been reported by Li et al in 2012. By employing methyl 2-formylbenzoate 42 as functional aldehyde component to react with amines and terminal alkynes in the presence of Cu(OTf)₂ catalyst. A class of isoindolinones 43 have been provided via tandem intramolecular amidation cyclization on A³ coupling intermediate 44. This method afforded products only in moderate to good yields (Scheme 18)³⁶
Scheme 18

Besides the direct tandem cyclization transformation on propargylamines, there was also another kind of $A^3$ coupling-based tandem reactions wherein a fragment in propargylamine intermediates dissociated during transformation. The example was the synthesis of coumarins 47 via copper-catalyzed reactions of salicylaldehydes and terminal alkynes 45 in the presence of pyrrolidine. During the reaction process, the intermediates 46 which were generated via tandem $A^3$ coupling and 6-endo-dig cyclization underwent a subsequent hydrolysis transformation to provide 47. It should be noted that products 47 were constructed only by salicylaldehydes and terminal alkynes, this tandem process was not MCRs (Scheme 19).

Scheme 19

2.3. Reactions based on functional alkyne participated tandem $A^3$ coupling transformation
Owing to the high reactivity of alkynes, these compounds, especially terminal alkynes are usually unstable, and corresponding alkynes bearing other reactive functional groups are accordingly of less availability compared with amines or aldehydes. Therefore, less examples on
functional alkynes participated A³ coupling-based tandem reactions are available in literature. A typical example based on functional alkynes was the three-component synthesis of indole derivatives using o-aminophenylacetylene 48, formaldehyde and secondary amines. In the presence of 1 Mol % CuBr catalyst, the three-component reactions performed in dioxane at 80 °C and provided directly indoles 49. The process of the reactions involved in the CuBr-catalyzed A³ coupling giving intermediates 50 and further copper-catalyzed intramolecular anulation (Scheme 20).³⁸ The application scope of this three-component synthetic approach has later been extended and more indole products have been synthesized as building blocks for the construction of more complex products. More interestingly, it has been found that aliphatic aldehyde such as butyraldehyde could react with secondary amine and aminophenylacetylens 48 to provide 49 with moderate enantioselectivity with the assistance of chiral phosphine ligand (Scheme 21).³⁹
2.4. Reactions of more than three components based on A³ coupling tandem transformation

Based on the above introduced contents, it could be easily conclude that those heterocycle synthesis were all designed by making use of a reactant containing two reactive functional groups, these reactions could be classified as intramolecular tandem transformation of propargylamine intermediates, reactions correspond these reactions were the intermolecular transformations of propargylamines, which mean the utilization of additional reactant. The intermolecular tandem transformations were achieved in the fashion of multicomponent assembly by directly employing more than three components based on A³ coupling. Through this strategy some heterocyclic products could be easily accessed. For example, Li⁴⁰ and co-workers developed an useful method for the synthesis of isoindolines ⁵¹ by employing amine, 2 equiv mole of formaldehyde and 3 equiv mole of terminal alkynes. During the reactions, intermediates ⁵⁰ which were generated by double A³ coupling reactions underwent [2+2+2] cycloaddition in the presence of additional terminal alkynes to afford target products (Scheme 22).

![Scheme 22](image)

In addition, Li⁴¹ group also developed the A³ Coupling-based four-component reactions using A³ substrates and carbon dioxide. CuBr catalyzed the reactions at 70 °C heating in the atmosphere of 1 atm CO₂ to give oxazolinone products ⁵². The reactions were achieved through the incorporation of propargylamine intermediates to CO₂ as shown in Scheme 23.
3. Conclusions and Outlook

During the last decade, A$^3$ coupling reaction has evolved to a classical three-component protocol for accessing various propargylicamines. Numerous papers have been published on the investigation of this synthetic method and spectacular advances on A$^3$ coupling reactions have been witnessed in terms of green catalyst system, asymmetric catalysis etc. which also promoted this coupling protocol as the most preferred option for propargylicamine synthesis. From the perspective of application, the propargylicamines possessed broad spectrum of diversity and
reactivity, and these compounds could serve as main building blocks in the synthesis of many organic small molecules. From the perspective of atom economics, devising tandem reactions based on key transformation of $A^3$ coupling for the synthesis of more complex and structurally diverse heterocyclic products in one-pot represent a promising direction in modern organic synthesis. As introduced in the contents, many elegant results have already been reported on this area. On the other hand, at current state, this kind of tandem reactions were mainly performed by using the second functional group in aldehyde, amine or alkyne to initiate subsequent transformations on propargylamine intermediates, although some reactions using additional components such as carbon dioxide to design tandem synthesis of heterocyclic products have also been reported, this kind of examples are still rather rare. Thus, deeper and broader explore is still demanding since using additional substrates for reactions is theoretically able to provide considerably higher diversity both in reactions and corresponding products. In addition, versions of asymmetric catalysis on traditional $A^3$ coupling have already been accomplished with nice results, while asymmetric catalysis protocols of $A^3$ coupling-based tandem synthesis of heterocycles kept unexplored, more systematic and advanced approaches of asymmetrical catalysis on these tandem reactions are expected in future.

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