

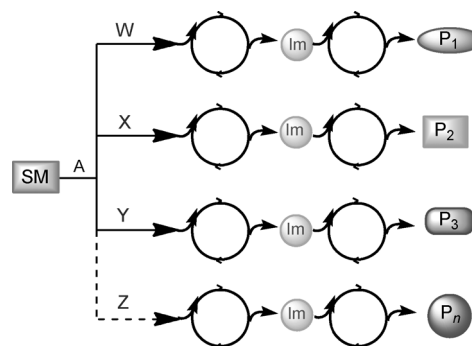
# Relay Catalytic Branching Cascade: A Technique to Access Diverse Molecular Scaffolds\*\*

Nitin T. Patil,\* Valmik S. Shinde, and Balasubramanian Sridhar

The screening of compound libraries to identify useful modulators of biological systems is fundamental to the drug discovery process and chemical biology studies.<sup>[1]</sup> Traditionally, the molecules in these libraries have come from nature, and there are many examples in which natural products and their derivatives and analogues are either new drug candidates or tools for chemical biology and medicinal chemistry research. However, some difficulties are associated with using natural products in screening experiments; for instance, their purification, the identification of biologically active components, and nature “fails” to provide several analogues, which are necessary for structure–activity relationship (SAR) studies. These restrictions make chemical synthesis the only alternative to obtain unambiguously characterized, diverse, multifunctional molecules that are similar to natural products.

Diversity-oriented synthesis (DOS), a terminology initially coined by Schreiber,<sup>[2]</sup> is a techniques to identify biologically relevant chemical space.<sup>[3]</sup> Several DOS strategies have been reported, such as the build-couple-pair strategy,<sup>[4]</sup> the click-click-cyclize strategy,<sup>[5]</sup> the fragment-based approach,<sup>[6]</sup> and others.<sup>[7]</sup> In recent years, the branching-cascade technique has gained much interest, because of its potential to transform a common type of substrate into diverse and distinct molecular frameworks under the influence of either different reagents or different reaction conditions.<sup>[8]</sup> The branching-cascade approach is appealing because it enables access to a library of thousands of compounds in an efficient manner through permutation and combination. Kumar and co-workers reported a cascade with twelve branches to access diverse and complex molecular frameworks from a chromone-based starting material.<sup>[9]</sup> Recently, O’Connell, Stockman, and co-workers reported a cascade with twelve branches to access a range of carbo-, aza-, and oxocycles with fused, bridged, and spiro-polycyclic structures from a keto diester.<sup>[10]</sup> Although there are quite

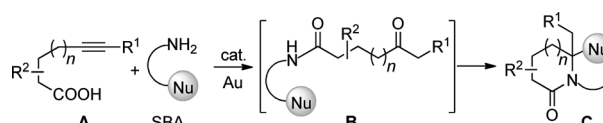
a few reports on branching cascades,<sup>[8–10]</sup> to the best of our knowledge, there is no precedence of a catalytic branching cascade that generates a large scaffold diversity.<sup>[11]</sup> Scaffold diversity is very important in DOS, because it is used to populate chemical space efficiently.<sup>[3,12]</sup> Therefore, we wondered whether it would be possible to develop a catalytic branching-cascade technique, a process that would allow the rapid synthesis of several multifunctional polyheterocyclic scaffolds (Figure 1).<sup>[13]</sup> More specifically, we expected that the



**Figure 1.** Concept of relay catalytic branching cascade (RCBC).

SM = easily available starting materials, A = catalysts or reagents, W–Z = various cascade-initiating molecules, Im = intermediates, P = diverse scaffolds.

alkynoic acid **A** (common type of substrate) would react with several scaffold-building agents (SBAs; variables) in the presence of suitable metal catalysts, thus leading to the formation of keto amides **B**. Compounds **B** would then undergo a metal-catalyzed cyclization cascade to produce various heterocyclic scaffolds **C** (Scheme 1).<sup>[14]</sup> Overall, the process can be termed relay catalytic branching cascade (RCBC) with regard to the classification of a one-pot catalysis proposed by us.<sup>[15]</sup> The main challenge and beauty of the methodology would be the access to a large scaffold diversity, as a result of the design of a large number of SBAs (Scheme 2) in an apparently simple manner.



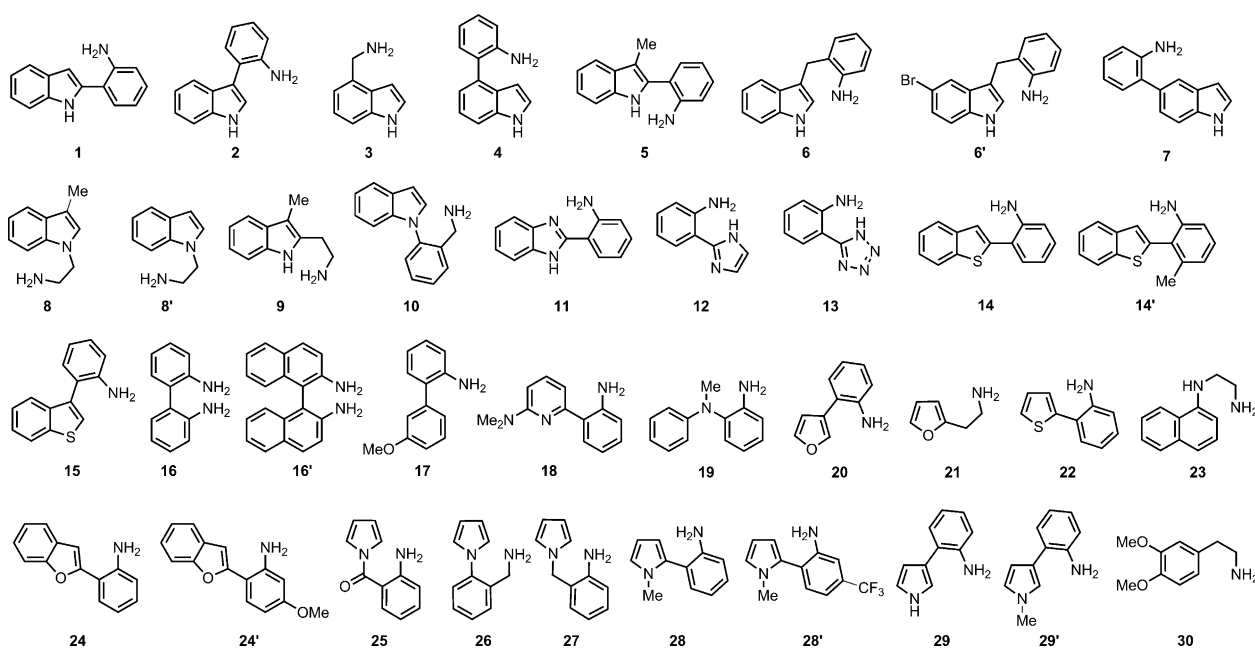
**Scheme 1.** Concept of RCBC employing alkynoic acids (common type of substrates) and SBAs (variables).

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**Scheme 2.** Structures of various scaffold-building agents (SBAs).

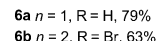
At the outset of this study, our efforts were directed toward finding appropriate reaction conditions that would work well for a broad range of SBAs, which were prepared from easily available starting materials (see the Supporting Information). Because it is known that the judicious choice of a  $\pi$ -acid<sup>[16]</sup> influences the outcome of the reaction, we opted to study these reactions in greater detail using a variety of catalysts and solvents, and different temperatures. The catalyst  $\text{Ph}_3\text{PAuOTf}$  in dichloroethane gave the best results with a large number of SBAs. An equimolar mixture of scaffold-building agents **1–30** and alkynoic acids **aa1–aa8** in dichloroethane was heated to 100 °C for 24–36 h in the presence of  $\text{Ph}_3\text{PAuOTf}$  (5 mol %; Scheme 3). In almost all cases, the starting materials were completely consumed and the products were produced in good to high yields.

We first focused our attention on indole-based SBAs, as this heterocycle occurs widely in nature and its derivatives have remarkable biological activities. Interestingly, the reaction proved to be very general, and the reaction of more than ten SBAs gave various indole-fused heterocyclic scaffolds in good to high yields. For instance, SBA **1** (2-aminophenylindole) afforded dihydroindolo[3,2-*c*]pyrrolo[1,2-*a*]quinolones **1a** and **1b** in 79 and 69% yield, respectively (Scheme 3, branch A). Likewise, SBAs **2** and **3** ((indol-4-yl)methanamines) reacted well with terminal and internal alkynoic acids to afford the corresponding pyrrolo quinolone **2a** (branch B) and pyrrolo isoquinolinones **3a** and **3b**, respectively (branch C), with moderate to high yields. Similarly, SBA **4** underwent cascade cyclization under the developed reaction conditions to afford indolo benzazepinones **4a** and **4b** in 76 and 63% yields, respectively (branch D). Interestingly, the 2-ethynyl benzoic acid **aa7** also reacted well, giving **4c** in 59% yield. This experiment confirms that additional aromatic rings can be introduced in SBAs to obtain functionalized polycyclic heteroaromatic

compounds. To further expand the scope of the RCBC, indolamines **5** and **9** were reacted with alkynoic acids to give indolo[1,2-*c*]pyrido[1,2-*a*]quinazolinones **5a/5b** (branch E) and **9a/9b** (branch I), which were probably formed through an intramolecular attack of the indole N–H group to the incipient iminium ions. The polycyclic benzazepinone indolones **6a** and **6b** were obtained in 79 and 63% yield from SBAs **6** and **6'**, respectively (branch F). Halo-substituted compounds, such as **6b**, can serve as versatile synthons, enabling the introduction of various functional groups and expanding the diversity of the targeted products. When indole-based amino-substituted aromatic compound **10** was employed as substrate, products with seven-membered rings were formed in moderate yields, although relatively longer reaction times were needed for complete substrate conversion (branch J).

Interestingly, when SBA **7** was used, an almost 1:1 mixture of two regioisomers was obtained (resulting from cyclization at C4 and C6; branch G). These regioisomers were easily separable by column chromatography. It should be noted that each of the regioisomers has a skeletally distinct pyrrolo phenanthridinone scaffold. Both terminal and internal alkynoic acids reacted similarly with **7**, although the reaction was somewhat sluggish and took 36 hours until completion. The SBAs **8** and **8'** also reacted well and afforded C2-cyclized polyheteroaromatic scaffolds in 78 and 63% yield (branch H).

To further explore the generality and scope of this approach, benzimidazole **11** (branch K), 2-(2-aminophenyl)imidazole **12**, and 2-(2-aminophenyl)tetrazole **13** were used as substrates, and the expected cascade products were obtained in very high yields. SBAs **12** and **13** reacted with terminal (**aa1**) and internal (**aa2**) alkynoic acids, leading to the formation of various scaffolds, such as imidazolo quinazolinones (branch L) and tetrazolo quinazolinones (branch M).



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The reactions of amino benzothiophenes **14** and **15** afforded C2- and C3-cyclized products, respectively, with good yields (branch N and branch O). SBA **22** (2-(2-aminophenyl)thiophene) also reacted well under the established conditions, affording dihydropyrrolo[1,2-*f*]thieno[3,2-*c*]quinolinone **22a** and **22b** with 71 and 79% yield, respectively (branch V).

Interestingly, biaryl 1,4-diamines **16** and **16'** reacted with alkynoic acid **aa1** to give strained seven-membered pyrrolo diazepinones in good yields (branch P). Moreover, pyrido phenanthridinone scaffolds were also obtained from 3'-methoxybiphenyl-2-amine (SBA **17**; branch Q). Gratifyingly, the pyridine-based SBA **18** also worked well in this transformation and produced fused-ring products with moderate yields (branch R). It should be noted that the electron-donating effect of the *N,N*-dimethylamine group at position 6 of the pyridine moiety plays a key role in this reaction, as the product is not formed in the absence of this group. With regard to the prevalence and importance of seven-membered benzodiazepine scaffolds, we explored the reactivity of SBA **19** and, fortunately, the reaction worked very well (branch S). SBA **23**, which features a naphthalene core and an aliphatic side chain with an NH<sub>2</sub> group, also produced a product with a seven-membered ring through cyclization at the  $\beta$ -position of the naphthalene (branch W). The protocol was equally successful for 2-(furan-3-yl)aniline **20** and 2-furanyl ethanamine **21** as substrates, leading to the formation of dihydrofuro[2,3-*c*]pyrrolo[1,2-*a*]quinolinone and tetrahydrofuro[2,3-*g*]indolizinones, respectively (branch T and branch U). SBAs **24** and **24'** (2-aminophenylbenzofurans) also reacted well under the optimized conditions and afforded dihydrobenzofuro[3,2-*c*]pyrrolo[1,2-*a*]quinolinones in good yields (branch X).

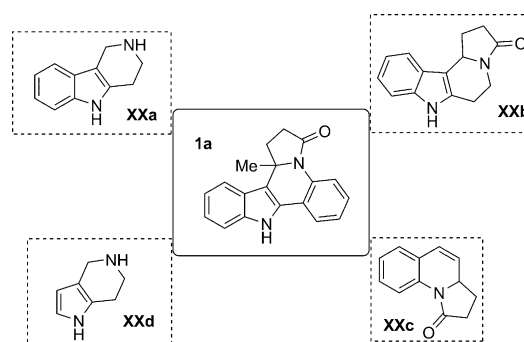
Next, we turned our attention to reactions of pyrrole-based SBAs. As anticipated, all reactions with pyrrole-based SBAs, such as **25**, **26**, **27**, **28**, and **29**, worked well and afforded fused heterocyclic products with five-, six-, and seven-membered rings. SBAs **25**, **26**, and **27** produced benzo dipyrrolo diazepinone scaffolds with seven-membered rings (branches Y, Z, and AA, respectively). The reactions of SBAs **28** and **28'** resulted in C3-cyclized isoindolo[2,1-*a*]pyrrolo[3,2-*c*]quinolinones with six-membered rings (branch AB), whereas SBAs **29** and **29'** produced C2-cyclized dipyrrolo quinolinones (branch AC) with high to moderate yields. SBA **30** (dimethoxyphenyl ethanamine) reacted well with alkynoic acids **aa1** and **aa3** under the optimized reaction conditions to produce tetrahydropyrrolo[2,1-*a*]isoquinolinones **30a** and **30b** in 90 and 61% yield, respectively (branch AD).

The broad scope and generality of the RCBC technique and the ease with which skeletally diverse products with fused five-, six-, and even seven-membered rings can be produced is obvious. Of note, over one gram of each **11a** and **30a** (obtained in 90 and 92% yield, respectively) was prepared by this method, thus demonstrating the scalability of our approach. The structures of seven skeletally different final compounds, that is **6b**, **12a**, **14b**, **16a**, **18a**, **20a**, and **28c**, were unambiguously confirmed by single-crystal X-ray crystallographic analysis.<sup>[17]</sup>

Nitrogen-containing heterocycles are widespread motifs in natural products and biologically active molecules. They

have been assigned as privileged structures in drug development because of their rigid conformation, which in turn results in their ability to bind to a multitude of receptors through a variety of favorable interactions. Therefore the synthesis of nitrogen-containing polycyclic heteroaromatic compounds is an important goal in organic synthesis. In this regards, the approach reported herein is appealing because it offers the possibility to generate a library of thousands of nitrogen-containing compounds in an efficient manner. Because all products that are obtained through the RCBC technique are chiral, the scaffolds can be accessed in an optically pure form.

Each scaffold is unique and has several privileged structures embedded within it.<sup>[18]</sup> For instance, branch A of the RCBC (Scheme 3) produced dihydroindolo[3,2-*c*]pyrrolo[1,2-*a*]quinolinone **1a**, and embedded into this single structure are important pharmacophores (Scheme 4),



Scheme 4. RCBC product **1a** as a hybrid scaffold.

such as tetrahydro pyridoindole **XXa**,<sup>[19]</sup> tetrahydro indolizinoindolone **XXb**,<sup>[20]</sup> dihydro pyrroloquinolinone **XXc**,<sup>[21]</sup> and tetrahydro pyrrolopyridine **XXd**.<sup>[22]</sup> Because various privileged structures are present in a single scaffold, it can be easily envisioned that such hybrid structures could find potential applications in modern drug discovery programs. Because these scaffolds are expected to cover a significant chemical space,<sup>[3]</sup> their great potential to the understanding of biological interactions can be anticipated.

In summary, we introduced the relay catalytic branching cascade (RCBC) as a new technique to access a series of multifunctional polyheterocyclic scaffolds in an efficient manner. The key feature of our approach is its extraordinary scope, because it allows the preparation of a library of compounds with a high skeletal diversity and a broad scope for further diversification. Considering the multitude of reactions that can be catalyzed by metal-based and organo-catalysts at the same time, and given the vast number of common types of substrates and variables, we envision tremendous potential in diversity-oriented synthesis. This approach should have especially broad applicability, given that metal catalysis can be combined with organocatalysis, thus leading to cooperative-catalytic branching cascades (CCBC).<sup>[13b,15]</sup> Additional challenges for this chemistry could include the development of an enantioselective protocol that works well for a broad range of SBAs, thus leading to

enantioselective RCBC. Further studies to exploit this approach are currently underway in our laboratory.

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