ChemPubSoc Europe

DOI: 10.1002/chem.201405736

CHEMISTRY
A European Journal
Communication

Relay Catalysis |*Hot Paper*|

Catalyst-Dependent Selectivity in the Relay Catalytic Branching Cascade

Avinash H. Bansode,[a] Aslam C. Shaikh,[a] Rahul D. Kavthe,[a] Shridhar Thorat,[b] Rajesh G. Gonnade,[b] and Nitin T. Patil*[a]

Abstract: The synthesis of small organic molecules as probes for discovering new therapeutic agents has been an important aspect of chemical biology. One of the best ways to access collections of small molecules is to use various techniques in diversity-oriented synthesis (DOS). Recently, a new form of DOS, namely "relay catalytic branching cascades" (RCBCs), has been introduced, wherein a common type of starting material reacts with several scaffold-building agents (SBAs) to obtain structurally diverse molecular scaffolds under the influence of catalysts. Herein, the RCBC reaction of a common type of substrate with SBAs is reported to give two different types of molecular scaffolds and their formation is essentially dependent on the type of catalyst used.

The ability of small molecules to interact with macromolecules and perturb their function has emerged as a powerful tool for interrogating biological events, and forms the basis of much modern drug discovery.[1] Traditionally, nature has been the source of a rich library of small molecules. Natural products, which are indeed complex and diverse in structure, have been used for centuries as medicines and have had a profound impact on human lives. However, some difficulties are associated with using natural products in screening experiments, such as: a) their low abundance; b) difficulties associated with purification and characterization; c) inability to provide several analogues, which are necessary for structure–activity relationship (SAR) studies; and d) the structural complexity of natural products, which makes chemical derivatization, a process especially relevant to drug discovery, extremely challenging. These are among the main reasons for the urgent demand for the high-throughput screening of natural-product-like/drug-like small molecules and the subsequent evaluation of their biological activities to examine if they are potential therapeutic agents. Therefore, new strategies must be developed for creating new collections of drug-like small molecules.

Diversity-oriented synthesis (DOS)[2] aims to prepare collections of skeletally diverse small molecules.[3] As a result of their non-focused nature, DOS libraries are expected to cover a significant chemical space,[4] impacting our understanding of biological processes. Therefore, it is not surprising that much attention has to be paid to develop a more general and efficient strategy in DOS, to access scaffold diversity.[5] Several strategies, such as the build/couple/pair strategy,[6] the "click, click, cyclize" strategy,[7] and the fragment-based approach,[8] among others[9] have been reported in the literature. Recently, the branching cascade technique has gained the attention of the scientific community, as this technique has the potential to transform a common type of starting material into diverse and distinct molecular frameworks under the influence of either reagents or conditions.[10] Kumar and co-workers reported an eightfold branching cascade targeting diverse and complex molecular frameworks from a chromone-based starting material.[11] Subsequently, O'Connell and Stockman reported a twelvefold branching cascade to access a range of carbo-, aza-, and oxocycles, with fused, spiro, and bridged polycyclic structures from a ketodiester.[12] Recently, we developed an electrophile-induced branching cascade as an interesting and a very direct approach for the efficient generation of a library of drug-like polyheterocycles.[13] Although there are several reports on branching cascades;[8–11] until recently, there had been no report on catalytic branching cascades. Very recently, we introduced the relay catalytic branching cascade (RCBC)[14] as a new technique to access a series of multifunctional polyheterocyclic scaffolds in an efficient manner (Scheme 1).[15]

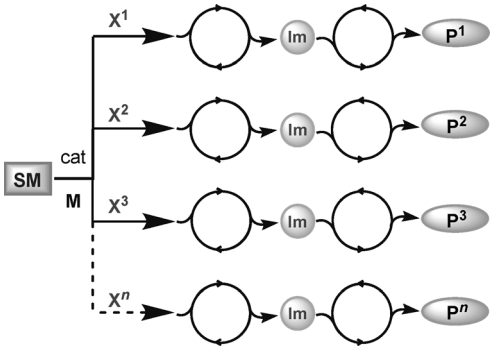
Herein, we report that the product formation in RCBC essentially depends on the type of catalysts used (Scheme 2). This kind of catalyst-dependent selectivity should be of considerable interest as two sets of libraries can be readily accessed from the same type of starting materials. To our knowledge, this study represents the first example of catalyst/reagent-dependent selectivity in branching cascades.

As a part of our ongoing interest in the exploration of π-acid catalysts and their application in branching cascades, we envisaged that an alkyne would undergo hydroxy group-assisted hydroamination reactions with various scaffold-building agents (SBAs) to generate imines (Scheme 3).[16] The incipient imine would then undergo the Mannich reaction or a Mannich reaction/dehydrative cyclization sequence, depending on the type of catalyst used, to generate two different sets of hetero-

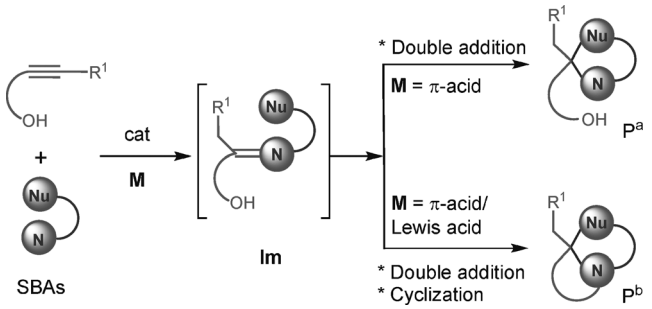
[a] *A. H. Bansode, A. C. Shaikh, Dr. R. D. Kavthe, Dr. N. T. Patil*
Organic Chemistry Division, CSIR-National Chemical Laboratory
Dr. Homi Bhabha Road, Pune - 411 008 (India)
E-mail: n.patil@ncl.res.in

[b] *S. Thorat, Dr. R. G. Gonnade*
Center for Materials Characterization, CSIR-National Chemical Laboratory
Dr. Homi Bhabha Road, Pune - 411 008 (India)

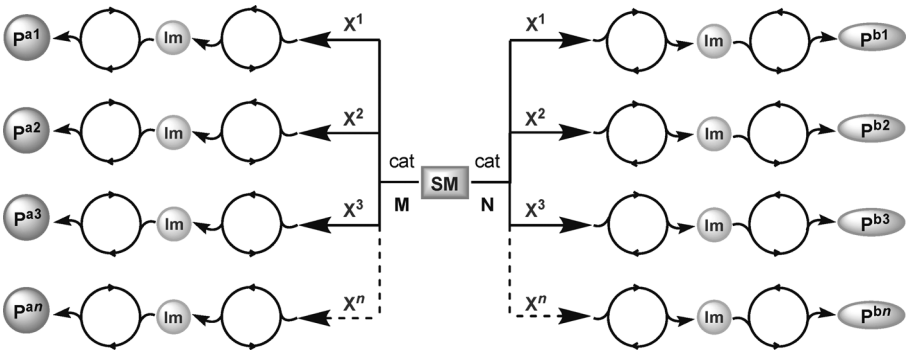
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201405736.



Scheme 1. Relay catalytic branching cascade (RCBC): Previous work.[14,15] **SM** = starting material; cat **M** = catalyst; **X** = cascade-triggering molecules; **Im** = intermediates; **P** = products



Scheme 3. Catalyst-dependent selectivity in RCBC: Reaction of alkynols (a common type of substrates) with variables scaffold-building agents (SBAs).



Scheme 2. Catalyst-dependent selectivity in RCBC: This work. **SM** = starting material; cat **M** and cat **N** = catalysts; **X** = cascade-triggering molecules; **Im** = intermediates; **P** = products.

cyclic scaffolds $\mathbf{P^a}$ or $\mathbf{P^b}$. It was clear that the judicial choice of catalysts (π-acid Vs π-acid with Lewis acidity) would be beneficial to control the reaction at $\mathbf{P^a}$ or to speed up the reaction to $\mathbf{P^b}$ from $\mathbf{P^a}$.

The alkynols **a 1**–**a 10** (Figure 1) and SBAs **1**–**11** (Figure 2) required for this study are either commercially available or can be readily prepared in high yields.[17] At the outset of this study, our efforts were directed to search for appropriate catalysts that would work well for a broad range of alkynols and SBAs. Careful optimization studies led us to establish two sets of reaction conditions; (1) [$Ph_3PAuOTf$], MeOH, 40–80 °C, and (2) $PtCl_4$, MeOH, 80–100 °C. Under the catalysis of [$Ph_3PAuOTf$], products $\mathbf{P^a}$, which resulted from the double addition of nucleophile to alkynes, were obtained; whereas, the reactions catalyzed by $PtCl_4$ gave the products $\mathbf{P^b}$. The detailed results are summarized in Scheme 4.

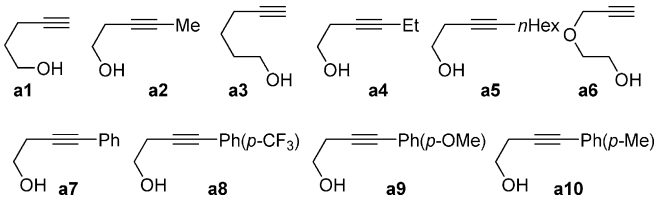


Figure 1. Structures of alkynols **a 1**–**a 10**.

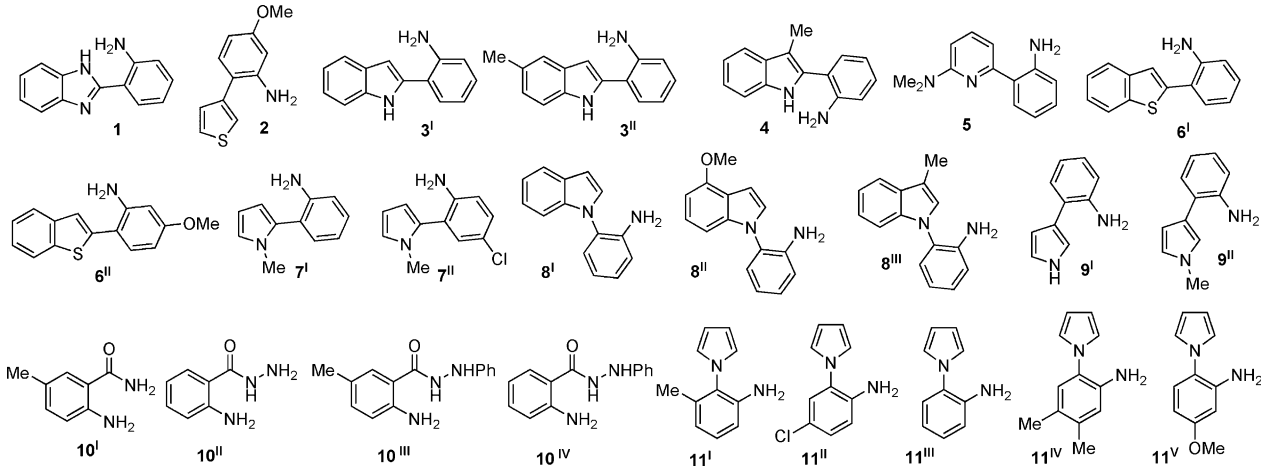
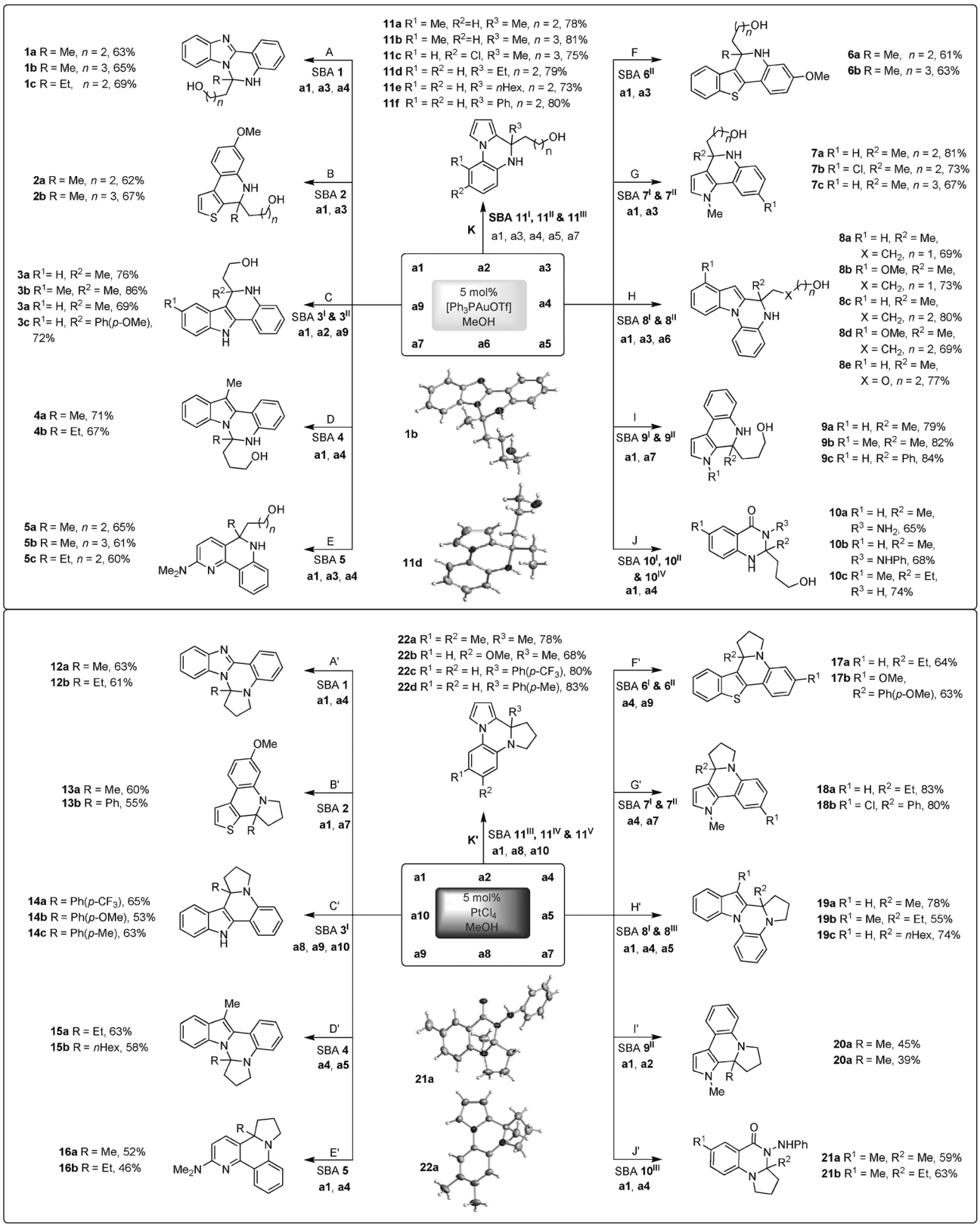


Figure 2. Structures of scaffold-building agents **1**–**11**.



Scheme 4. Molecular diversity through catalyst control in RCBC. Reactions conditions: a) Gold catalysis: Alkynol (0.50 mmol), SBAs (0.50 mmol), [$Ph_3PAuOTf$] (5 mol%) in MeOH (0.5 mL) at 40–80 °C for 12–36 h, as specified in the Supporting Information; b) Platinum catalysis: Alkynol (0.50 mmol), SBAs (0.50 mmol), $PtCl_4$ (5 mol%) in MeOH (0.5 mL) at 80–100 °C for 12–48 h, as specified in the Supporting Information. Note: Alkynols **a 1** and **a 2** produced the same cascade products for branches C and I'. A, B, C…K and A', B', C'…K' represent branches.

In the presence of gold catalyst, 2-(1*H*-benzo[d]imidazol-2-yl)aniline (SBA **1**) reacted with 4-pentyn-1-ol (**a1**), hex-5-yn-1-ol (**a3**), and hex-3-yn-1-ol (**a4**) to afford products dihydrobenzimidazoquinazolines **1a**, **1b**, and **1c** in 63, 65, and 69% yields, respectively (Scheme 4, branch A). In contrast, on reaction with alkynols **a1** and **a4** under platinum catalysis, SBA **1** afforded tetrahydrobenzimidazopyrroloquinazoline products **12a** and **12b** in 63 and 61% yields, respectively (Scheme 4, branch A′). Under Au catalysis, 5-methoxy-2-(thiophen-3-yl)aniline (SBA **2**) reacted with alkynols **a1** and **a3** to give products dihydrothienoquinolines **2a** and **2b** (Scheme 4, branch B), whereas the use of $PtCl_4$ gave tetrahydropyrrolothienoquinoline products **13a** and **13b** from alkynols **a1** and **a7** in moderate yields (Scheme 4, branch B′).

Next, we focused our attention to indole-based SBAs $\mathbf{3^{I}}$, $\mathbf{3^{II}}$, and **4**. Under gold catalysis, the dihydroindoloquinolines **3a–c** and dihydroindoloquinazolines **4a** and **b** were obtained in moderate to good yields (Scheme 4, branches C and D). Similarly, when alkynols were treated with SBAs $\mathbf{3^{I}}$ and **4** under $PtCl_4$ catalysis, the tetrahydroindolopyrroloquinolines **14a–c** and tetrahydroindolopyrroloquinazolines **15a** and **b** were obtained in good yields (Scheme 4, branches C′ and D′). Next, the substrate scope with 6-(2-aminophenyl)-*N*,*N*-dimethylpyridin-2-amine (SBA **5**) was studied under gold catalysis, which gave products dihydrobenzonaphthyridinamines **5a**, **5b**, and **5c** from alkynols **a1**, **a3**, and **a4** in 65, 61, and 60% yields, respectively (Scheme 4, branch E). In the presence of $PtCl_4$, the alkynols **a1** and **a4**, on reaction with SBA **5**, afforded tetrahydrobenzopyrrolonaphthyridinamines **16a** and **16b** in moderate yields (Scheme 4, branch E′). The alkynols **a1** and **a3**, on reaction with 2-(benzo[b]thiophen-2-yl)-5-methoxyaniline (SBA $\mathbf{6^{II}}$) under [$Ph_3PAuOTf$] catalysis gave the expected dihydrobenzothienoquinoline products **6a** and **6b** in 61 and 63% yields, respectively (Scheme 4, branch F). In contrast, the reaction of alkynols **a4** and **a9** with SBAs $\mathbf{6^{I}}$ and $\mathbf{6^{II}}$ in the presence of $PtCl_4$ gave the corresponding tetrahydrobenzothienopyrroloquinoline products **17a** and **17b** in 64 and 63% yields, respectively (Scheme 4, branch F′). The 2-aminophenyl indoles (SBAs $\mathbf{8^{I}}$ and $\mathbf{8^{II}}$) also reacted well under the [PPh_3AuOTf] catalysis to afford dihydroindoloquinoxalines **8a–e** in good yields (Scheme 4, branch H). However, in the presence of $PtCl_4$ catalyst, SBAs $\mathbf{8^{I}}$ and $\mathbf{8^{III}}$ gave tetrahydroindolopyrroloquinoxaline products **19a–c** in moderate yields (Scheme 4, branch H′).

To further probe the scope of this catalyst-dependent selectivity, pyrrole-based SBAs were examined. As expected, SBAs $\mathbf{7^{I}}$, $\mathbf{7^{II}}$, $\mathbf{9^{I}}$, $\mathbf{9^{II}}$, $\mathbf{11^{I}}$, $\mathbf{11^{II}}$, and $\mathbf{11^{III}}$, with substitution at C2, C3 and N positions, reacted with various alkynols to afford dihydropyrroloquinolines **7a–c**, **9a–c** and dihydropyrroloquinazolines **11a–f** in satisfactory to good yields (Scheme 4, branches G, I, and K). This reaction also tolerated halo-substituted pyrrole-based SBAs to give product **7b** in 73% yield, after reaction with alkynol **a1** under gold catalysis (Scheme 4, branch G). The same SBAs reacted smoothly with various alkynols under $PtCl_4$ catalysis to afford the desired tetrahydrodipyrroloquinoline products **18a**, **b**, and **20a**, and tetrahydrodipyrroloquinazolines **22a–d** in moderate to good yields (Scheme 4, branches G′, I′, and K′). The products dihydroquinazolinones **10a**, **10b** and **10c** were obtained from 2-aminobenzamide (SBA $\mathbf{10^{I}}$, $\mathbf{10^{II}}$ and $\mathbf{10^{IV}}$) and alkynols **a1** and **a4** in yields ranging from 65% to 74% under [PPh_3AuOTf] catalysis (Scheme 4, branch J). Similarly, when SBA $\mathbf{10^{III}}$ was treated with **a1** and **a4** under $PtCl_4$ catalysis, the tetrahydropyrroloquinazolinones **21a** and **21b** were obtained in 59 and 63% yields, respectively (Scheme 4, branch J′).

The structures of four skeletally different products, **1b**, **11d**, **21a**, and **22a**, were unambiguously confirmed by single-crystal X-ray crystallographic analysis (Scheme 4).[18]

The broad scope and generality of the developed technique and the ease with which it produces skeletal diversity with fused five, six, and even seven membered ring products is promising. Each and every compound accessed through this technique follows the Lipinski "rule of five".[19] Moreover, the products are a hybrid of privileged scaffolds[17] and have at least one sp^3 carbon to attribute three-dimensional character. Since the scaffolds of known bioactive small molecules play a key role in guiding chemists' navigation of biologically relevant chemical space, the present library would be useful for systematic exploration of molecular diversity and thus for the discovery of novel chemical entities in chemical biology and drug discovery.[20] Very importantly, all of the products exhibits chirality and hence there exists a possibility to access these scaffolds in optically pure forms with the use of chiral catalysts.[21]

In summary, we have achieved catalyst-dependent selectivity in the catalytic branching cascade. The reaction of alkynols (a common type of starting materials) with various SBAs under metal catalysis afforded two different types of molecular scaffold and their formation was dependent on the type of catalyst used. Knowledge in the field of catalysis and DOS should combine the benefits offered from each technique and in doing so provide enhanced opportunities to deliver small molecules; especially in optically active form.[20]

Experimental Section

Representative procedure

To an oven-dried screw-capped vial equipped with a magnetic stir bar was added scaffold-building agent (SBAs **1**–**11**; 0.50 mmol), alkynol (**a1**–**a10**; 0.50 mmol), and metal catalyst ([$Ph_3PAuOTf$] or $PtCl_4$; 5 mol%) in MeOH (0.5 mL). The reaction vial was fitted with a cap, evacuated, and charged with nitrogen. The reaction mixture was heated as specified in the Supporting Information. The reaction mixture was then allowed to cool to ambient temperature, diluted with ethyl acetate (5 mL), and filtered through a plug of silica gel. The filtrate was concentrated and the residue thus obtained was purified by column chromatography on silica gel using EtOAc/petroleum ether or MeOH/DCM as eluent to afford analytically pure compounds.

Acknowledgements

Generous financial support by the DST-New Delhi (No. SB/S1/OC-17/2013) and CSIR-New Delhi (CSC0108 and CSC0130) is gratefully acknowledged. We thank the Director of CSIR-NCL

for providing a generous start-up grant (MLP029626). A.H.B., A.C.S., and R.D.K. thank CSIR-New Delhi for the award of research fellowship. N.T.P. is thankful to Dr. P. R. Rajamohanan for recording NMR spectra.

Keywords: alkynols · cascade synthesis · chemoselectivity · diversity-oriented synthesis · homogeneous catalysis

[1] a) K. C. Nicolaou, *Angew. Chem. Int. Ed.* **2014**, *53*, 9128 – 9140; b) C. J. O'Connor, H. S. G. Beckmann, D. R. Spring, *Chem. Soc. Rev.* **2012**, *41*, 4444 – 4456; c) S. L. Schreiber, *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6699 – 6702; d) D. S. Tan, *Nat. Chem. Biol.* **2005**, *1*, 74 – 84.

[2] S. L. Schreiber, *Science* **2000**, *287*, 1964 – 1969.

[3] a) J. T. Shaw, *Nat. Prod. Rep.* **2009**, *26*, 11 – 26; b) R. J. Spandl, A. Bender, D. R. Spring, *Org. Biomol. Chem.* **2008**, *6*, 1149 – 1158; c) C. Cordier, D. Morton, S. Murrison, A. Nelson, C. O'Leary-Steele, *Nat. Prod. Rep.* **2008**, *25*, 719 – 737; d) R. J. Spandl, M. Díaz-Gavilán, K. M. G. O'Connell, G. L. Thomas, D. R. Spring, *Chem. Rec.* **2008**, *8*, 129 – 142; e) S. Shang, D. S. Tan, *Current Opinion in Chemical Biology* **2005**, *9*, 248 – 258.

[4] Reviews: a) A. Tavassoli, A. D. Hamilton, D. R. Spring, *Chem. Soc. Rev.* **2011**, *40*, 4269 – 4270; b) C. M. Dobson, *Nature* **2004**, *432*, 824 – 828; c) B. R. Stockwell, *Nature* **2004**, *432*, 846 – 854; d) C. Lipinski, A. Hopkins, *Nature* **2004**, *432*, 855 – 861.

[5] a) S. Oh, S. B. Park, *Chem. Commun.* **2011**, *47*, 12754 – 12761; b) T. W. J. Cooper, I. B. Campbell, S. J. F. Macdonald, *Angew. Chem. Int. Ed.* **2010**, *49*, 8082 – 8091; *Angew. Chem.* **2010**, *122*, 8258 – 8267; c) W. R. J. D. Galloway, A. Isidro-Llobet, D. R. Spring, *Nat. Commun.* **2010**, *1*, 80; d) K. Grabowski, K.-H. Baringhaus, G. Schneider, *Nat. Prod. Rep.* **2008**, *25*, 892 – 904; e) M. Kaiser, S. Wetzel, K. Kumar, H. Waldmann, *Cell. Mol. Life Sci.* **2008**, *65*, 1186 – 1201; f) D. R. Spring, *Chem. Soc. Rev.* **2005**, *34*, 472 – 482.

[6] a) E. Ascic, S. T. Le Quement, M. Ishoey, M. Daugaard, T. E. Nielsen, *ACS Comb. Sci.* **2012**, *14*, 253 – 257; b) T. Luo, S. L. Schreiber, *J. Am. Chem. Soc.* **2009**, *131*, 5667 – 5674; c) T. E. Nielsen, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2008**, *47*, 48 – 56; *Angew. Chem.* **2008**, *120*, 52 – 61.

[7] a) Q. Zang, S. Javed, F. Ullah, A. Zhou, C. A. Knudtson, D. Bi, F. Z. Basha, M. G. Organ, P. R. Hanson, *Synthesis* **2011**, 2743 – 2750; b) A. Rolfe, G. H. Lushington, P. R. Hanson, *Org. Biomol. Chem.* **2010**, *8*, 2198 – 2203.

[8] a) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons, D. W. Young, *Procs. Nat. Acad. Sci.* **2011**, *108*, 6799 – 6804; b) C. W. Murray, D. C. Rees, *Nat. Chem.* **2009**, *1*, 187 – 192; c) P. J. Hajduk, J. A. Greer, *Nat. Rev. Drug Discovery* **2007**, *6*, 211 – 219.

[9] a) Z. Wang, S. Castellano, S. S. Kinderman, C. E. Argueta, A. B. Beshir, G. Fenteany, O. Kwon, *Chem. Eur. J.* **2011**, *17*, 649 – 654; b) S. Dandapani, L. A. Marcaurelle, *Curr. Opin. Chem. Biol.* **2010**, *14*, 362 – 370.

[10] a) E. E. Wyatt, S. Fergus, W. R. J. D. Galloway, A. Bender, D. J. Fox, A. T. Plowright, A. S. Jessiman, D. R. Spring, *Chem. Commun.* **2006**, 3296 – 3298; b) O. Kwon, S. B. Park, S. L. Schreiber, *J. Am. Chem. Soc.* **2002**, *124*, 13402 – 13404.

[11] W. Liu, V. Khedkar, B. Baskar, M. Schümann, K. Kumar, *Angew. Chem. Int. Ed.* **2011**, *50*, 6900 – 6905; *Angew. Chem.* **2011**, *123*, 7032 – 7037.

[12] D. Robbins, A. F. Newton, C. Gignoux, J. C. Legeay, A. Sinclair, M. Rejzek, C. A. Laxon, S. K. Yalamanchili, W. Lewis, M. A. O'Connell, R. A. Stockman, *Chem. Sci.* **2011**, *2*, 2232 – 2235.

[13] N. T. Patil, A. Konala, S. Sravanti, A. Singh, R. Ummanni, B. Sridhar, *Chem. Commun.* **2013**, *49*, 10109 – 10111.

[14] N. T. Patil, V. S. Shinde, B. Gajula, *Org. Biomol. Chem.* **2012**, *10*, 211 – 224.

[15] N. T. Patil, V. S. Shinde, B. Sridhar, *Angew. Chem. Int. Ed.* **2013**, *52*, 2251 – 2255; *Angew. Chem.* **2013**, *125*, 2307 – 2311.

[16] a) N. T. Patil, R. D. Kavthe, V. S. Raut, V. S. Shinde, B. Sridhar, *J. Org. Chem.* **2010**, *75*, 1277 – 1280; b) N. T. Patil, R. D. Kavthe, V. S. Shinde, B. Sridhar, *J. Org. Chem.* **2010**, *75*, 3371 – 3380; c) N. T. Patil, R. D. Kavthe, V. S. Raut, V. V. N. Reddy, *J. Org. Chem.* **2009**, *74*, 6315 – 6318. For the selected examples on metal-catalyzed reactions of alkynes tethered with OH/COOH/NHR groups, see: d) X. Wang, S. Dong, Z. Yao, L. Feng, P. Daka, H. Wang, Z. Xu, *Org. Lett.* **2014**, *16*, 22 – 25; e) X. Wang, Z. Yao, S. Dong, F. Wei, H. Wang, Z. Xu, *Org. Lett.* **2013**, *15*, 2234 – 2237; f) Z.-Y. Han, R. Guo, P.-S. Wang, D.-F. Chen, H. Xiao, L.-Z. Gong, *Tetrahedron Lett.* **2011**, *52*, 5963 – 5967; g) C. Wang, Z.-Y. Han, H.-W. Luo, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 2266 – 2269; h) T. Yang, L. Campbell, D. J. Dixon, *J. Am. Chem. Soc.* **2007**, *129*, 12070 – 12071.

[17] See the Supporting Information for details.

[18] CCDC 1029742 (**1 b**), 1029741 (**11 d**), 1029743 (**21 a**), 1029740 (**22 a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[19] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Advanced Drug Delivery Reviews*, **2001**, *46*, 3 – 26.

[20] J. Kim, H. Kim, S. B. Park, *J. Am. Chem. Soc.* **2014**, *136*, 14629 – 14638.

[21] V. S. Shinde, M. V. Mane, K. Vanka, A. Mallick, N. T. Patil, *Chem. Eur. J.* **2014**, DOI: 10.1002/chem.201405061.

Received: October 20, 2014
Published online on ■■ ▮▮, 0000

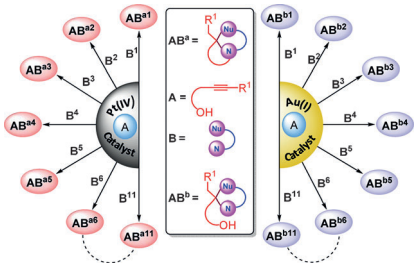
COMMUNICATION

Relay Catalysis

*A. H. Bansode, A. C. Shaikh, R. D. Kavthe, S. Thorat, R. G. Gonnade, N. T. Patil**

■■ – ■■

Catalyst-Dependent Selectivity in the Relay Catalytic Branching Cascade



DOS prompt: Catalyst-dependent selectivity in the relay catalytic branching cascade has been reported. The reaction of a common type of substrate (alkynols, **A**) with variable scaffold-building agents (bis-nucleophiles, **B**) gave two different types of molecular scaffolds (**AB**^{a} and **AB**^{b}) and their formation is essentially dependent on the type of catalyst used.

Catalyst (Au versus Pt)-dependent selectivity……in diversity-oriented synthesis is illustrated by the divergent road in the picture. When the lorry bearing the substrates passes through the golden gate or the platinum gate, two different types of molecular scaffolds are formed. Two buildings for storing these molecules represent the library of molecular scaffolds generated by this approach. For more details, see the Communication by N. T. Patil et al. on page ■■ ff.