VIP Cascade-Reaction Design

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Branching Cascades: A Concise Synthetic Strategy Targeting Diverse and Complex Molecular Frameworks**

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Dedicated to Professor Lutz F. Tietze

Scaffold diversity and molecular complexity are prerequisites for a small-molecule collection[1] to deliver either drug candidates or chemical probes for drug discovery and chemical-biology investigations, respectively.[2] Therefore, synthetic strategies that enable the construction of diverse and complex molecular architectures, in particular those based on natural product frameworks,[3] present interesting and demanding challenges to the art of organic synthesis.[4] Cascade or domino reaction sequences,[5] in which more than one reaction occurs consecutively in a one-pot process and molecular complexity is rapidly built up, can immensely improve the efficiency of such synthetic endeavors.[5a,6]

To address the formidable challenge of incorporating skeletal diversity in a compound collection, the "branching pathway" strategy has been proposed as a form of diversity-oriented synthesis (DOS).[7] In this strategy, a common substrate is transformed into diverse and distinct molecular scaffolds under the influence of different reagents (Figure 1a).[8] However, this approach exploits only intermolecular transformations and as a consequence yields only limited skeletal diversity, often following a multistep synthesis.[8a,b] For the enrichment of a compound library with molecular complexity and scaffold diversity,[9] the common precursor should facilitate a wide range of complexity-generating transformations in a rapid and concise manner.[10] Herein we introduce "branching cascades" as an efficient and concise synthetic strategy that employs cascade reaction sequences in a branching pathway to generate complex and diverse molecular frameworks for the desired focused compound collections. In our approach, different cascade-triggering molecules X, Y, or Z trigger different cascade reaction sequences by exploiting the diverse functional sites (F^1, F^2, F^3) on the common multifunctionalized precursor to yield structurally diverse, complex, and functionalized molecular frameworks (Figure 1b).

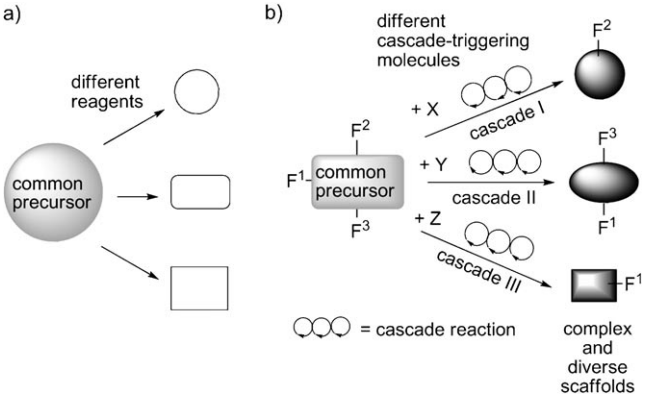

Figure 1. a) Branching pathway in DOS. b) Branching cascades.

Substrate **1**,[11] which can be prepared readily in high or even quantitative yield,[12] was chosen as a common precursor for the branching-cascade strategy. It contains multiple electrophilic sites, a couple of pronucleophilic moieties, and a vinylogous ester (a leaving group) to facilitate the interplay of diverse cascade reaction sequences (Scheme 1).

To exploit the dispersed electrophilicity in **1** for various cascade reaction sequences to yield different molecular frameworks, we screened a batch of 21 nucleophiles that included ten bisnucleophiles (N,N, N,O, N,C, and O,C bisnucleophiles), six mononucleophiles, four zwitterionic species, and *tert*-butylmalonate (Scheme 1) for substrate conversion, product profiles, and optimal reaction conditions. We screened the reactions by using a Radleys Carousel Reaction Station with 12 reaction tubes under an argon atmosphere at room temperature. Mononucleophiles were screened as such at different concentrations (for HCl salts of hydroxylamines, an equimolar amount of triethylamine was used), and the bisnucleophiles were screened in the presence and absence of an external base. After a quick aqueous workup, LC–MS analysis of the crude reaction mixture was performed. Reactions with high conversion and cleaner product profiles were then optimized separately (when required) for better results. It was a pleasant surprise to find that 10 of the 21 nucleophiles used provided sufficiently clean reaction profiles and yielded 12 diverse and complex ring systems (**23**–**30**, **40**, **43**, **44**, and **47**), including natural product

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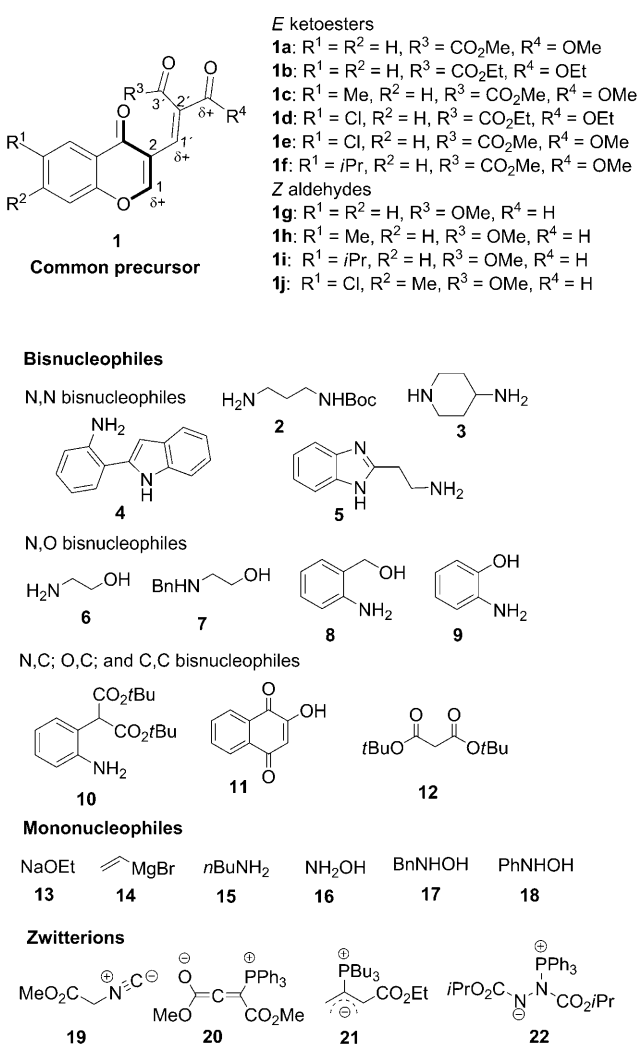
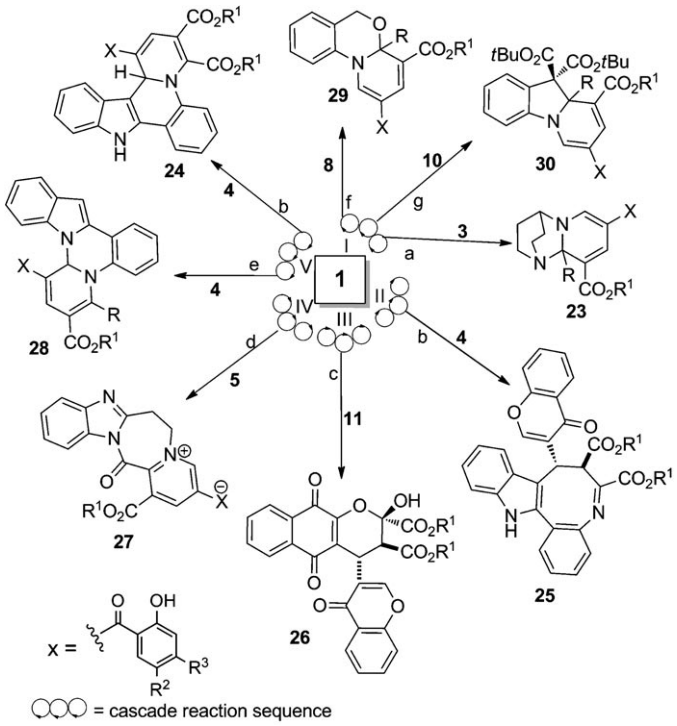


Scheme 1. Branching-cascade substrates and nucleophiles. Bn = benzyl, Boc = *tert*-butoxycarbonyl.

related and unprecedented molecular frameworks (Schemes 2, 3, and 5).

A clear reactivity pattern of the nucleophiles with the common substrate was observed. Whereas many bisnucleophiles reacted nicely with ketoesters **1**, the corresponding reactions with aldehydes **1** often yielded mixtures of products with varying conversion. Of the tested mononucleophiles and zwitterions, only a few performed well in the branching cascades, although they displayed unbiased reactivity towards ketoester and aldehyde substrates **1**. The unsuccessful nucleophiles included diaminoalkane **2** and di-*tert*-butylmalonate (**12**), which yielded a complex mixture of products; amino alcohols **6** and **7**, which reacted sluggishly and gave products that showed decomposition during column-chromatographic purification; and *o*-aminophenol (**9**), which did not yield any specific product consistently.

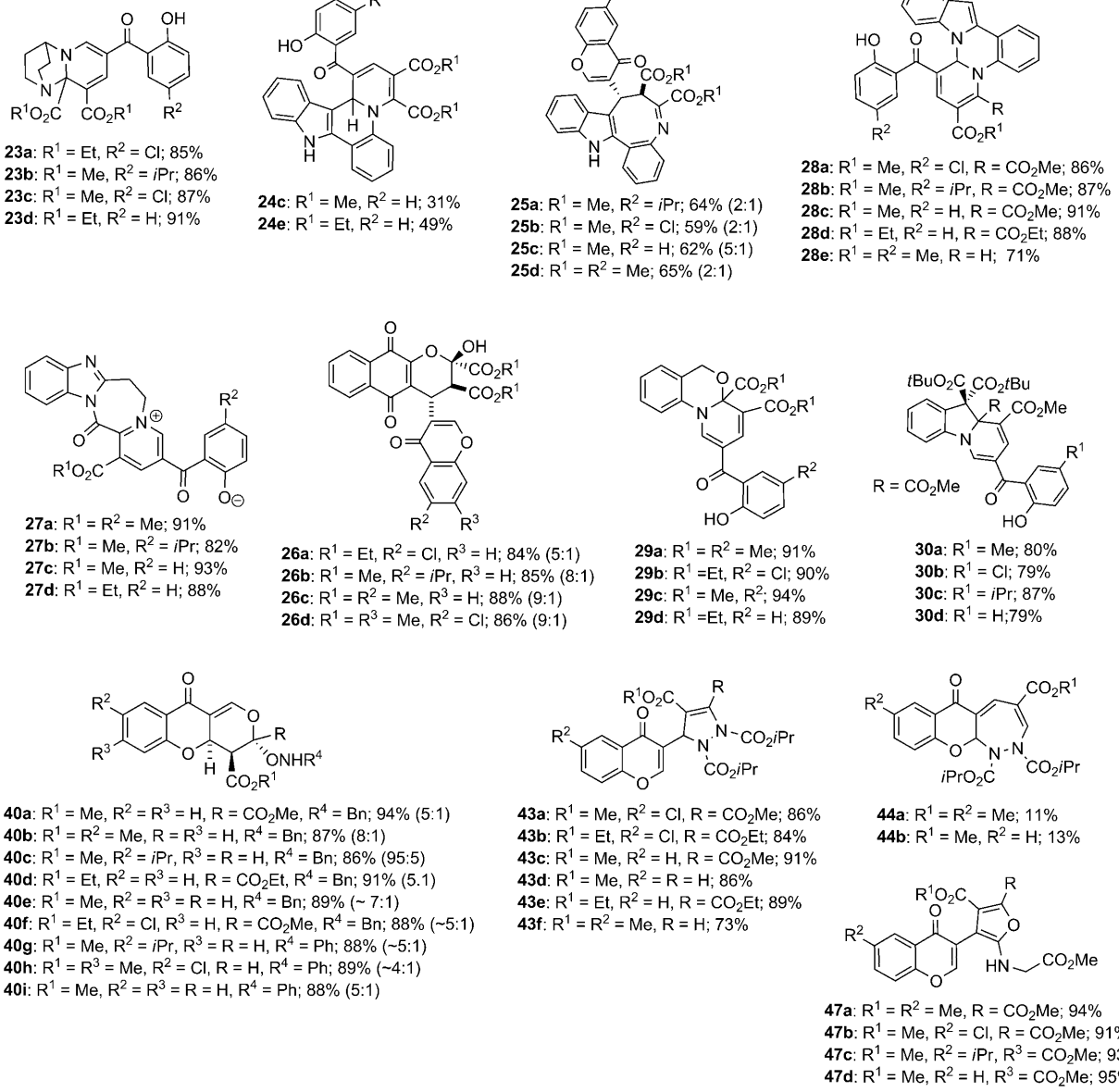
Among the successful N,N bisnucleophiles in the branching-cascade strategy, 4-aminopiperidine (**3**) led to the formation of the complex tetrahydro-1,4-ethanopyrido[1,2-*a*]pyrimidine ring system **23** in high yields (Scheme 2). Interestingly, the use of another N,N bisnucleophile, the 2-



Scheme 2. Branching cascades leading to diverse scaffolds: a) ketoester **1** (1 mmol), **3** (1.2 mmol), CH_2Cl_2, room temperature, 4 h; b) ketoester **1** (1 mmol), **4** (1.1 mmol), CH_2Cl_2, room temperature, 3–6 h; c) ketoester **1** (1 mmol), **11** (1.2 mmol), Ac_2O/AcOH (1:3; 4 mL), 150 °C, 5 min; d) ketoester **1** (1 mmol), **5** (1 mmol), CH_2Cl_2, room temperature, Et_3N (3.0 mmol), 4 h; e) ketoester/aldehyde **1** (1 mmol), **4** (1.2 mmol), CH_2Cl_2, room temperature, Et_3N (3.0 mmol), 6 h; f) ketoester **1** (1 mmol), **8** (1.2 mmol), CH_2Cl_2, room temperature, 3 h; g) ketoester **1** (1 mmol), **10** (1.2 mmol), EtOH (10 mL), 60 °C, 2,6-lutidine (1.5 mmol), AgOTf (0.1 mmol), 8 h. Tf = trifluoromethanesulfonyl.

(2-aminophenyl)indole **4**, led to the formation of two different ring systems under different reaction conditions. When ketoester substrates **1** were stirred with **4** in dichloromethane at room temperature, novel chromone-substituted benzo[2,3]azocino[4,5-*b*]indoles **25** were formed. The structural assignment of compounds **25** was corroborated by complete spectroscopic analysis and further supported by a palladium-catalyzed hydrogenation of the iminoester moiety in **25a** to yield the corresponding amine (see the Supporting Information for details). This cascade reaction sequence, however, yielded a minor product with a different molecular architecture, that is, dihydroindolo[3,2-*c*]pyrido[1,2-*a*]quinoline **24**, in varying yields (Scheme 3).[13] In the presence of equimolar triethylamine, the bisnucleophile **4** cleanly transformed **1** into another ring system, indolo[1,2-*c*]pyrido[1,2-*a*]quinazoline **28**, in excellent yields (Schemes 2 and 3). Apparently, different branching cascades prevailed under basic and nonbasic reaction conditions and thus led to different molecular architectures.

Another N,N bisnucleophile, 2-(1*H*-benzo[*d*]imidazol-2-yl)ethanamine (**5**), transformed ketoester substrates **1** into novel internal pyridinium salts **27** through yet another cascade reaction sequence. Complete spectroscopic analysis supported by palladium-catalyzed hydrogenation of the



Scheme 3. Diverse and complex ring systems from branching cascades.

pyridinium ring in **27a** to a 1,2-dihydropyridine (see the Supporting Information) corroborated the structural assignment of compounds **27**.

Surprisingly, of the four N,O bisnucleophiles tested in the branching-cascade strategy, only 2-aminobenzyl alcohol (**8**) added to the scaffold diversity by transforming ketoester substrates **1** into dihydrobenzo[*d*]pyrido[2,1-*b*][1,3]oxazine systems **29** in excellent yields (Schemes 2 and 3).

Two more bisnucleophiles that proved interesting cascade-triggering molecules in the branching-cascade strategy were the N,C- and O,C-bisnucleophiles **10** and **11**, respectively. Both of these nucleophiles displayed very sluggish reactivities in the initial screening and required further optimization of the reaction conditions. Interestingly, the use of di-*tert*-butyl-2-(2-aminophenyl)malonate (**10**) led to the formation of benzoindolizine **30** (Scheme 2): a scaffold that is part of many biologically active natural products.[14] The use of silver triflate as a catalyst in ethanol at 60 °C led to very good yields for this cascade reaction sequence (Schemes 2 and 3).[15]

Although **11**, an O,C-bisnucleophile, did not show any promising reactivity in the initial screening, we did not give up on tapping its potential to provide natural product based polycyclic quinones, in particular medicinally important pyranonaphthoquinones.[16] Gratifyingly, the treatment of ketoester substrates **1** with **11** in the presence of acetic anhydride/acetic acid (1:3) at 150 °C for a few minutes yielded chromone-substituted pyranonaphthoquinones **26** in good yields with good diastereoselectivity (see the Supporting Information).[17] Although aldehyde substrates **1** reacted well with **11** under these conditions, the corresponding products were not stable enough and could not be purified.

The branching cascades were used to efficiently transform the common substrate into diverse molecular frameworks decorated with functionalities that could be further explored for the generation of focused compound collections.[10a] A careful analysis of the ring structures formed and their substitution pattern, for example, the presence of the *o*-hydroxyphenone moiety (generated by chromone-ring opening) in some of the products, suggested the involvement of common intermediates in the different cascade reactions operating (Scheme 2). Overall, bisnucleophiles appear to follow five different cascade reaction sequences that generate eight diverse and complex ring systems (Scheme 4).

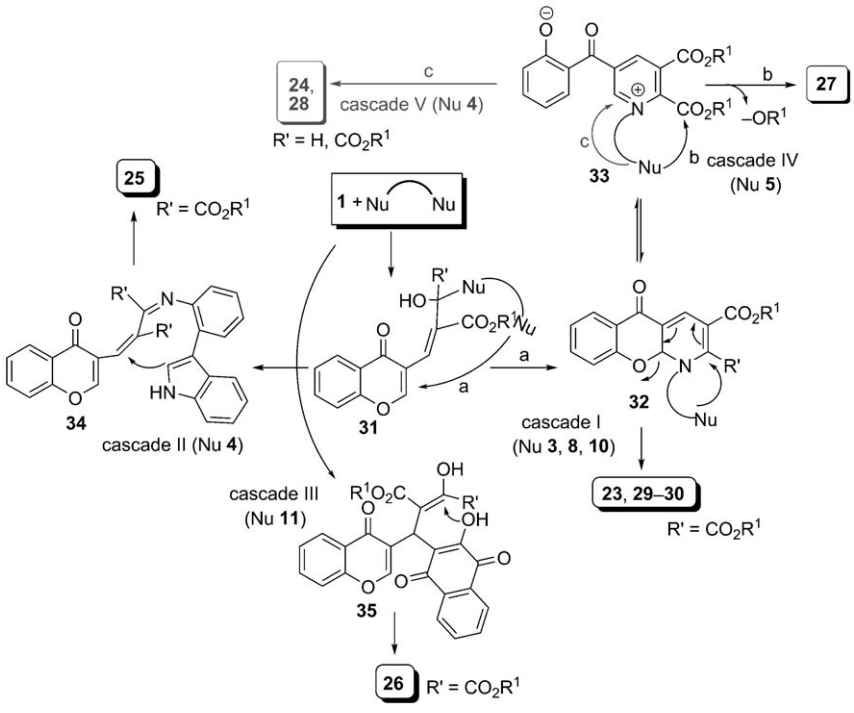
In the first cascade reaction sequence (cascade I, Scheme 4), bisnucleophiles that have at least one amino group along with another nucleophilic site add to the ketoester (or aldehyde) to form an intermediate **31**, which undergoes dehydrative cyclization to yield a cyclic aminal **32**. A second nucleophilic addition by bisnucleophiles **3**, **8**, and **10** to the enamine moiety of **32** with concurrent chromone-ring opening yields scaffolds **23, 29**, and **30**, respectively (Schemes 2 and 4). The formation of azocines **25** follows the cascade reaction sequence II (Scheme 4). In this reaction sequence, the generation of a highly conjugated iminoester **34** from **31** is followed by an intramolecular 1,4-addition of the indole. In the case of the nucleophile *o*-hydroxynaphthoquinone (**11**), a conjugate addition to ketoester substrates **1** leads to intermediate **35**, which undergoes cyclization to form anomerically stabilized tricyclic acetals **26** through branching cascade III (Scheme 4).

Intermediate **32** can exist in a zwitterionic form **33**, in which more than two electrophilic sites are available for a second nucleophilic addition. Whereas the bisnucleophile **5** attacks the ester carbonyl functionality to yield compounds **27** as internal salts (cascade IV), N-addition of the indole amide derived from **4** (with a base) to the iminium cation in **33** provides **28**, and the addition of indole **4** (without a base) through C3 to the same site in **33** yields **24** through cascade sequence V (Scheme 4).

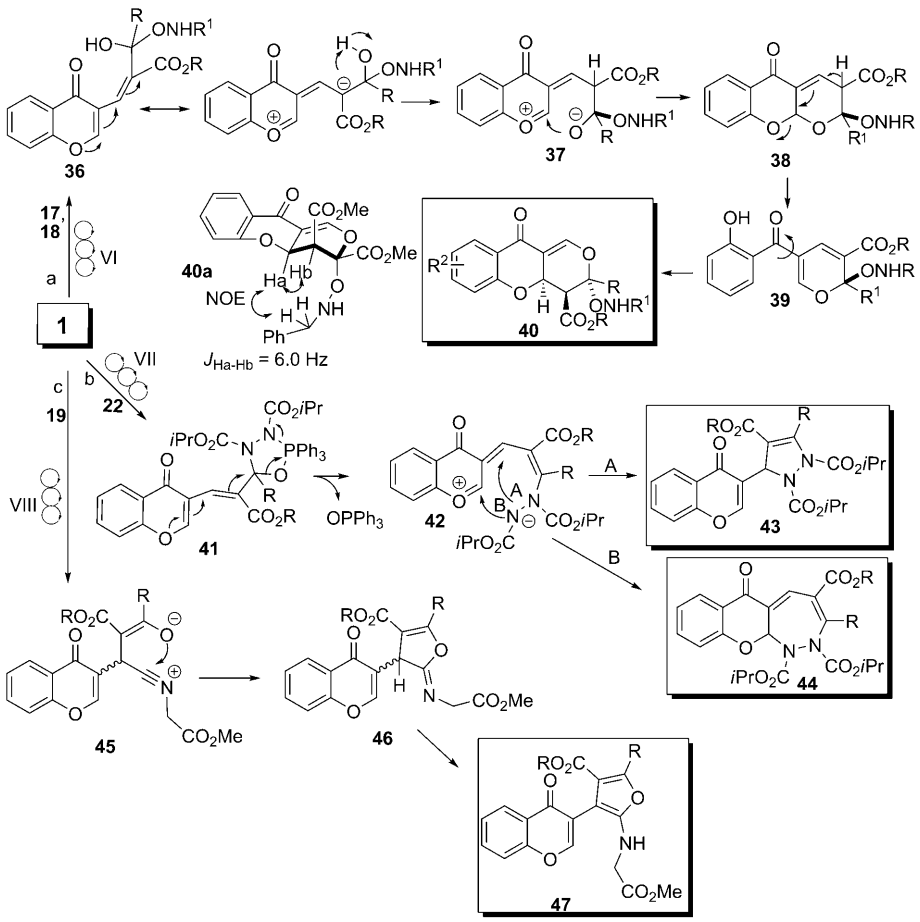
Disappointingly, mononucleophiles **13–16** yielded mixtures of inseparable products in the initial reaction screening. However, *N*-benzyl- and *N*-phenylhydroxylamines **17** and **18**, respectively, were found to be useful cascade-triggering substrates. These nucleophiles provided natural product related highly substituted tricyclic benzopyrones **40** in excellent yields and with appreciable diastereoselectivity (Scheme 3).[18] In this branching cascade (cascade VI, Scheme 5), the hydroxylamines act as O nucleophiles[19] rather than N nucleophiles and add to the keto or aldehyde group of the common substrate **1** to give an intermediate **36**, which cyclizes to yield an acetal **38**. Chromone-ring opening leads to a dihydropyran **39**, which undergoes intramolecular conjugated addition of the phenol to provide benzopyrones **40**. The conjugate addition of the phenol in **39** might occur preferentially *anti* to the initially added hydroxylamine for steric reasons and thus lead to the observed stereoselectivity in the formation of anomerically stabilized benzopyrone acetals **40** (Scheme 5). The structure and relative configuration of **40** are corroborated by the results of comprehensive NMR spectroscopic studies (see the Supporting Information for details).

Among the zwitterions[20] examined in the initial reaction screening, **20** did not react at all, and the allene-derived zwitterion **21** yielded only a trace amount of an unidentified product. The Huisgen zwitterion **22** (Scheme 1) had been investigated thoroughly for its reactivity with various aldehydes and ketones, including chalcones.[21] On the basis of its reported chemoselectivity, we were curious to find out whether the expected intermediate **42**, which is formed by the addition of **22** to **1**, would undergo a conjugate 1,4-addition to yield **43** or a 1,2-addition which could provide a novel chromenodiazepine ring system **44** (cascade VII, Scheme 5).[22] The major product in all the cases, however, in particular in reactions of ketoesters **1**, was the chromone-substituted pyrrole ring system **43**. Only in some cases, in reactions of aldehydes **1**, could we isolate **44** as a minor product. Nevertheless, compounds containing a pyrazole substituent on the privileged chromone moiety have structural features of the flavonoid natural products and might enrich the collection with useful related biological activities.

The zwitterion **19**, that is, methyl isocyanoacetate, displayed unbiased reactivity towards ketoester and aldehyde substrates **1** and yielded benzopyrones



Scheme 4. Proposed mechanisms of branching cascades with bisnucleophiles.



Scheme 5. Branching cascades with mononucleophiles and zwitterions: a) **1** (1 mmol), **17**/**18** (1.2 mmol), CH_2Cl_2, room temperature, overnight; b) **1** (1 mmol), DIAD (1.2 mmol), PPh_3 (1.3 mmol), THF, room temperature, 2–5 h; c) **1** (1 mmol), **19** (1.1 mmol), room temperature, 3–6 h. DIAD = diisopropyl azodicarboxylate.

47 containing a substituted furan ring in high yields (Schemes 3 and 5). We assume that an initial conjugate addition of **19** to C1′ of **1** leads to the formation of oxanion **45**, which adds to the proximate iminium cation to provide **46**. The isomerization/aromatization of **46** provides the final product **47** in this branching cascade (Scheme 5, cascade VIII).

In summary, we have devised a synthetic strategy that incorporates molecular complexity and scaffold diversity in a compound collection rapidly and efficiently by making use of tunable and diverse cascade reaction sequences. This approach based on branching cascades readily covers a large scaffold space by generating novel, natural product related and therapeutically important ring systems. The strategy is also powerful enough to deliver new chemical entities and chemical transformations of rather broad scientific interest.

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[11] CCDC 820700 (**1a**) and 820699 (**43c**) 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.

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