Radical aryl migration enables diversity-oriented synthesis of structurally diverse medium/macro- or bridged-rings

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Medium-sized and medium-bridged rings are attractive structural motifs in natural products and therapeutic agents. Due to the unfavourable entropic and/or enthalpic factors with these ring systems, their efficient construction remains a formidable challenge. To address this problem, we herein disclose a radical-based approach for diversity-oriented synthesis of various benzannulated carbon- and heteroatom-containing 8-11(14)-membered ketone libraries. This strategy involves 1,4- or 1,5-aryl migration triggered by radical azidation, trifluoromethylation, phosphorylation, sulfonylation, or perfluoroalkylation of unactivated alkenes followed by intramolecular ring expansion. Demonstration of this method as a highly flexible tool for the construction of 37 synthetically challenging medium-sized and macrocyclic ring scaffolds including bridged rings with diverse functionalities and skeletons is highlighted. Some of these products showed potent inhibitory activity against the cancer cell or derivative of human embryonic kidney line in preliminary biological studies. The mechanism of this novel strategy is investigated by control experiments and DFT calculations.
collections and high-throughput screening of small-molecule libraries have become of paramount importance for discovering promising drug leads and biological probes. To meet this urgent need, the development of diversity-oriented synthesis approach for the rapid creation of complex molecules in the library has received increasing attention in both medicinal chemistry and chemical synthesis. Although benzannulated medium- or medium-bridged rings constitute the basic skeletons of many important naturally occurring and biologically active molecules, they are really rare among the top 200 drugs. The main reason is probably the difficulty in developing general strategies for the diversity-oriented synthesis of such library of structures. The achievement of high efficiency remains a formidable challenge with conventional cyclization-based methods, mainly due to unfavourable enthalpic and entropic reasons. To address this, an alternative, more flexible strategy is the use of ring expansion reactions of bicyclic or polycyclic substrates to the desired medium-sized rings. For example, Harrowven has reported a ring expansion approach involving radical sp2-substitution triggered by sp2-radical intermediates generated from the dehalogenation of aryl or vinyl halides in the presence of toxic tin hydride reagents. Recently, Tan and co-workers have developed an elegant biomimetic diversity-oriented synthesis of benzannulated medium-sized rings with rationally designed substrates via oxidative deaminatization followed by ring-expanding rearomatization. However, most reported methods rely heavily on the inherent nature of special substrates with preformed polycycles and/or highly strained small rings, which usually require tedious multistep preparation under harsh reaction conditions. In addition, enantioselective ways to such chiral scaffolds have been rare because of the lack of efficient asymmetric approaches. Therefore, a general protocol for stereoselective and diversity-oriented synthesis of benzannulated medium- and related bridged-ring libraries, employing readily available starting materials and reagents under step/atom-economic and user-friendly synthetic conditions, is still highly desirable.

Unactivated alkenes are one of the most abundant feedstocks and thus represent excellent building blocks for chemical synthesis. The selective addition of diverse radicals to unactivated alkenes represents an efficient way for the functionalization of such alkenes. In addition, great advances have been achieved in the field of aryl migration following radical ipso substitution at an aromatic ring for constructing new organic compounds. Despite these advances, no radical-based protocol has been available for the conversion of unactivated alkenes into medium- to large-sized and related bridged ring libraries via aryl migration, especially for access to such chiral skeletons. To address these challenges, we rationally designed alkanyl alcohols bearing cyclic benzyl alcohol groups, which are more readily accessible than those polycyclic substrates required in conventional methods. (Fig. 1b). It is expected that an inherently high-energy sp2-carbon-centred alkyl radical could be in situ generated from the addition of appropriate radicals to the unactivated alkanyl moiety of 1. Driven by the formation of a lower energy neutral ketyl radical C (refs 32–34), intermediate A would undergo an intramolecular radical remote 1,4- or 1,5-aryl migration/ring expansion sequence to provide desired medium-ring products. Furthermore, we envisioned that the use of easily available optically pure alcohols would lead to enantioenriched medium-sized rings through a remote chirality transfer strategy. Hence, this strategy can overcome the unfavourable entropic and/or enthalpic factors typically encountered by conventional cyclization-based approaches. Nonetheless, the realization of such cascade sequence reactions remains an underdeveloped process. Several challenges are associated with the development of this reaction, such as (1) the unfavourable kinetic and/or thermodynamic factors to realize regioselective medium ring formation over other competitive 1,2-difunctionalizations of alkenes with oxygen-based nucleophiles, (2) the compatibility between unactivated alkanyl substrates and various radical precursors with different reactivity properties, (3) the identification of mild reaction conditions to achieve high degree of enantiocntrol through remote chirality transfer strategy.

With this strategy, we report herein a practical strategy for diversity-oriented synthesis of benzannulated 8-11(14)-membered cyclic ketones along with concurrent installation of various functional groups from readily available starting materials. This strategy was realized through a concerted remote 1,4- or 1,5-aryl migration/ring expansion sequence triggered by radical azidation, trifluoromethylthiation, phosphorylation, sulfonylation or perfluoroalkylation of unactivated alkenes. Given the prevalence of medium-bridged amines and relative chiral compounds in medicinal chemistry, we further demonstrate a distinct pathway for the convenient collection of useful medium-bridged amines with a high degree of skeletal complexity and functional diversity. In the context of a diversity-oriented synthesis of medium- and bridged-ring library, our strategy has displayed some exceptional advantages: (1) 1,4- and 1,5-aryl migration could be realized with the easily accessible substrates. (2) This method tolerates different opening-ring sizes of carbo- and heterocyclic alcohols from 5 to 11-membered ring, thus leading to a skeletal diversity medium- and large-ring collection. (3) A variety of radical sources, including azide, trifluoromethyl, phosphonyl, sulfonyl, perfluoralkyl radical, are used as suitable radical precursors. (4) The functional groups in formed products serve as versatile handles for further diversification to afford diverse natural analogues in parallel. Therefore, this discovery will be a highly flexible tool for diverse collection of a variety of medium-sized rings and related bridged ring libraries with over 37 distinct scaffolds as well as the identification of some compounds with potent inhibitory activity against the cancer cell or derivative of human embryonic kidney lines. Noteworthy is that many formed benzannulated medium-sized or medium-bridged rings constitute the key synthetic intermediates and unnatural analogues of many important naturally occurring and biologically active molecules such as benzannulated cyclooctanes, nonadride family (neurological disorders inhibition) and colchicine derivatives (anticancer activity) (Fig. 2).

Results

Azidation-initiated medium/macro-sized ketones’ synthesis. Modular synthetic access to these model substrates would be readily achieved in good yields by straightforward and efficient one-step transformation from inexpensive starting materials (see details in Supplementary Information). Since the development of methods for the incorporation of an azide moiety into organic compounds has enormous significance in chemistry, biology and materials sciences, we started our investigation to target the challenging nine-membered ketone formation along with the concurrent installation of an azide group based on the proposed pathway. As such, the reaction of substrate 1A with iodine (III) reagent azidodianine (2A), first reported by Zhankin and co-workers, was selected for the optimization of reaction conditions (Supplementary Table 1). We were delighted to find that the desired nine-membered product 3A was indeed observed.
in the presence of CuI (10 mol%), albeit with 47% yield, suggesting that the remote radical 1,4-aryl migration is much more favourable than other reaction pathways in the current catalytic system. Upon optimizing the reaction conditions through variation of the copper catalysts, catalyst loadings, solvents and the molar ratio of the reactants, we identified the following protocol as optimal: reaction of 1A and 2a with the molar ratio of 1.0:1.2 in the presence of CuCN (10 mol%) in EtOAc at 60 °C for 12 h, 3A was obtained in 72% isolated yield (Table 1). With the optimized reaction conditions established, we first examined the substrate scope of alkenyl alcohols featuring a six-membered ring and the results are summarized in Table 1. A range of substrates with 1,2,3,4-tetrahydronaphthalene moieties bearing mono-substituents, such as electron-withdrawing (-Br (1A), -F (1B)), electron-neutral (-H (1C)), and electron-donating (-OMe (1D)) groups, were found to be suitable to give the corresponding products 3A-3D in 41–72% yields. Moreover, the reaction of 1E with 2,5-dimethyl groups on the aryl ring proceeded smoothly to generate 3E (49% yield). Remarkably, the products 3A-3E are quite similar to the core structure of key intermediates towards the synthesis of glaucanic acid 6. It is noteworthy that the alkenyl alcohols with heteroatom-tethering groups, such as sulfonamide- and sulfur-tethered substrates 1F and 1G, were also well tolerated to produce heterocyclic ketones 3F and 3G in 76% and 68% yields, respectively. To increase the diversity of such a library, the more challenging benzannulated 10- and 11-membered ketone products 3H-3J were also obtained in 74–82% yields from the corresponding substrates under the current reaction system. The high efficiency of the present protocol in preparing macrocyclic ring system was demonstrated in the isolation of 14-membered ketone 3K in 65% yield from 11-membered alkenyl alcohol 1K, which further extended the compound library. Notably, substrate 1L containing another reactive olefin also afforded the desired 14-membered alkenyl ketone 3L in 56% yield with the additional olefin being intact. Meanwhile, the alkenol 1M containing an internal alkene in the presence of 1.5 equiv of 1,10-phenanthroline afforded the desired product 3M as a 1.5:1 mixture of diastereomers in 55% yield.

**Construction of trifluoromethylated medium-sized ketones.**

The increasing importance of trifluoromethyl organic molecules in agrochemicals, pharmaceuticals and molecular materials has spurred vigorous research efforts towards new versatile methodologies for the generation of the C-CF₃ bond. Impressive...
Advances have been achieved in developing methods for direct introduction of the CF₃ group into organic compounds by using radical trifluoromethylating reagents [35,36]. In this context, we focused our attention on realizing the incorporation of a CF₃ group with concurrent construction of benzannulated medium-sized rings (Table 2). To our delight, after some optimization efforts (Supplementary Table 2), we found that the reaction of 1A with Togni’s reagent [46,2b (2.0 equiv) proceeded smoothly in the presence of CuCN (10 mol%), giving the desired product 4A in 64% yield with high chemoselectivity (Table 2a). A variety of alkenyl alcohols 1, bearing either electron-withdrawing or electron-donating groups on the phenyl ring, reacted smoothly with 2b to give the expected products 4B-4D in 49–61% yields. Notably, the alkenyl alcohols with heteroatom-tethering groups (1F and 1G) or seven-membered cycles (1H and 1I) were also suitable substrates to deliver nine- and ten-membered hetero- or carbocyclic ketones 4F-4I (35–75% yields). To verify the application of the current method in the synthesis of the core structures or their derivatives of natural products are synthesized in next section.

**Table 1 | Substrate scope with azidation reaction to medium and macrocyclic ketones**

| Product | R² | Yield (%) |
|---------|----|-----------|
| 3A      | Br | 72%       |
| 3B      | F  | 70%       |
| 3C      | H  | 62%       |
| 3D      |     | 41%       |
| 3E      |     | 49%       |
| 3F      |     | 76%       |
| 3G      |     | 68%       |
| 3H      |     | 74%       |
| 3I      |     | 82%       |

*Reaction conditions: 1 (0.3 mmol), 2a (0.36 mmol), CuCN (0.03 mmol), EtOAc, 60 °C, 12 h. 
1.2a (2.0 equiv), 1,10-phenanthroline (1.5 equiv), EtOAc, 60 °C, 24 h.
2. Yields of isolated product based on 1.

**Figure 2 | Representative natural products and biologically active molecules with benzannulated medium-sized rings and bridged amines.** Several core structures or their derivatives of natural products are synthesized in next section.
Table 2 | Substrate scope with trifluoromethylation reaction to medium-sized ketones**.

| Substrate | Reaction Conditions | Solvent | Yield (%) | Diastereoselectivity |
|-----------|--------------------|---------|-----------|--------------------|
| 1         | m = 0; n = 0-2     | C, 60-80 °C | m = 0; n = 0-2 | X = CH₂, O, NTs, S |
| 2b        | CuCN (10 mol%)     | DCE-DMSO (10:1) | 100 °C | 54% |
| 4        |                   |         |           |                   |

(a) m = 0:

| Substrate | Reaction Conditions | Solvent | Yield (%) | Diastereoselectivity |
|-----------|--------------------|---------|-----------|--------------------|
| 4A        | R² = Br, 4A, 64%   | C, 12 h |           |                   |
| 4B        | R² = F, 4B, 61%    | C, 12 h |           |                   |
| 4C        | R² = H, 4C, 54%    | C, 12 h |           |                   |

(b) m = 1:

| Substrate | Reaction Conditions | Solvent | Yield (%) | Diastereoselectivity |
|-----------|--------------------|---------|-----------|--------------------|
| 4D        | R² = H, 4D, 60%    | C, 12 h |           |                   |
| 4E        | R² = F, 4E, 61%    | C, 12 h |           |                   |
| 4F        | R² = Br, 4F, 54%   | C, 12 h |           |                   |
| 4G        | R² = H, 4G, 67%    | C, 12 h |           |                   |
| 4H        | R² = F, 4H, 75%    | C, 12 h |           |                   |
| 4I        | R² = Br, 4I, 64%   | C, 12 h |           |                   |

(c)

| Substrate | Reaction Conditions | Solvent | Yield (%) | Diastereoselectivity |
|-----------|--------------------|---------|-----------|--------------------|
| 1X        | TBD (20 mol%)      | ETOAc, 100 °C |           |                   |
| 4X        | TBD (20 mol%)      | ETOAc, 100 °C | C, 24 h | 65% |

**Yield of isolated product based on 1.

*Reaction conditions: 1 (0.2 mmol), 2b (0.4 mmol), CuCN (10 mol%), ETOAc, 80 °C, 12 h.
**Reaction conditions: 1 (0.2 mmol), 2b (0.4 mmol), TBP (20 mol%), DCE-DMSO (10:1), 100 °C, 10 h.
***Yield of isolated product based on 1.

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To expand the synthetic utility of this methodology for access to novel benzannulated medium-sized skeletons, we explored the use of allylbenzene derivatives as the substrates in place of styrene derivatives (Table 2b). After some experimentation (Supplementary Table 4), such a process for the formation of benzannulated ten-membered ketones could be successfully realized directly from readily available alkenyl alcohols. For example, substrates 1 bearing various functional groups (1O-1Q) on the aryl ring, heteroatom-tethering groups (such as oxygen- and sulfonamide-tethered substrates 1R and 1S), and methyl-substituted 1,2,3,4-tetrahydronaphthalene group (1T), reacted efficiently to afford the corresponding products 4O-4T in 51–70% yields. The structure of the product 4O was also established by X-ray crystallographic analysis (Supplementary Fig. 1). Particularly noteworthy is that the 11-membered ketone 4U could also be constructed with the current process, albeit in moderate yield with substrate 1U bearing a seven-membered ring. It is noteworthy that the current method could be extended to the aliphatic substrate 1V. Under the standard reaction conditions, product 4V was obtained in 65% yield, indicating that the reaction was not significantly affected by switching the benzylic alcohol (1O) to an aliphatic substrate (1V). The resemblance of 4W to the core structure of a key intermediate towards the synthesis of byssolacholic acid analogues3 prompted us to test substrate 1W. It was found that 4W was generated smoothly as well, further elaborating the powerful utility of the current method in natural product synthesis. An interesting result was that the reaction of gem-disubstituted alkenyl alcohol 1X generated the unexpected product 4X in 41% yield as a 2:1 mixture of diastereomers, probably via a 1,2-hydrogen atom
transfer of intermediate A followed by a 1,4-aryl migration process (Table 2c).

Synthetic application towards diverse radicals. The high efficiency of the above diversity-oriented synthesis approach encouraged us to expand the scope to other radical precursors. As expected, the reaction of substrate 1Q with Ph2P(O)H (5a, 2.0 equiv) in the presence of AgNO3 (0.5 equiv) delivered phosphonyl-containing ten-membered ketone 6 (Fig. 3a and Supplementary Table 5). Furthermore, the phosphonyl-containing ten-membered ketone 7 with a sulfonamide-tethering group was obtained in 65% yield. Moreover, dibenzylphosphine oxide 5b also participated in this reaction to give product 8 in 66% yield, suggesting the feasibility of other types of phosphonyl radicals in this reaction. In addition to phosphonyl radical, in situ generated sulfonyl radical was also a suitable reaction partner: the reaction of substrate 11 with 1.5 equiv of 3,5-bis(trifluoromethyl)benzenesulfonyl chloride 9 in the presence of Cul (10 mol%) and AgNO3 (0.75 equiv) afforded the corresponding ketone 10 in 69% yield (Fig. 3b). The final success of C5F5 radical installation to generate 12 with perfluorobutanesulfonyl chloride (11, 1.5 equiv) via extrusion of sulfur dioxide under the otherwise identical reaction conditions was in great support of the wide application of the present methodology with different radicals in enriching the library of medium- and large-sized compounds (Fig. 3c).

Chirality transfer strategy and mechanistic investigations. On the basis of the concerted nature of the intramolecular radical aryl migration/ring expansion process as proposed in Fig. 1c, we expected that the stereochemical information of the tertiary alcohol would be completely transferred to the remote newly formed carbon chiral centre in a highly stereoselective way to construct optically pure medium-sized ketone. However, this chirality transfer strategy might be difficult due to the presence of several highly reactive radical intermediates, as well as the requirement of discrimination between the two enantiomeric faces in the intermediate B. To our delight, we found that the desired product (S)-3A was obtained in 70% yield with 99% ee via an almost complete chirality transfer strategy upon treatment of (R)-1A (99% ee) with 2a under the otherwise identical conditions (Fig. 4a). Remarkably, almost complete chirality transfer could also be achieved for substrates (R)-1A and (S)-1A upon treatment with Togni’s reagent 2b under the standard conditions to give (S)-4A and (R)-4A with 99% ee (58% yield) and 98% ee (60% yield), respectively, thus indicating the present transformation is highly stereoselective (Fig. 4a). The absolute configurations of the substrate (R)-1A and the product (R)-4A were established by X-ray crystallographic analysis (Supplementary Fig. 1), and those of other materials and products were assigned by analogy (Fig. 4a). To further evaluate the practicality of this methodology, we expanded the substrate scope with the enantiomerically pure allylbenzene derivative 1Q*. Treatment of substrate 1Q* with 2b or 5b under the otherwise identical conditions also underwent almost complete chirality transfer to give the corresponding enantioenriched benzannulated ten-membered trifluoromethyl- and phosphorus-containing ketones 4Q* and 8* in 64% and 70% yields with 96% and 95% ee, respectively (Fig. 4b,c).

To gain some more insights into the reaction mechanism, we tested some model reactions in the presence of radical scavengers such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) (for azidation, trifluoromethylation or phosphorylation reaction), 2,6-di-tert-butyl-4-methylphenol (BHT) (for azidation reaction) or 1,4-dinitrobenzene (for trifluoromethylation or phosphorylation reaction) under the standard conditions, and found that the reactions were significantly inhibited by these reagents (Supplementary Fig. 2), suggesting that a radical process is involved in these reactions. To probe the origin of the observed stereoselectivity, we further investigated the reaction mechanism computationally using M11 method. The generally assumed alkyl sp3-carbon-centred radical species 1Q was chosen as the starting point to locate two reaction pathways responsible for the stereoselective reactions. The calculated results revealed that this reaction occurs stepwise, involving the formation of the bicyclic...
The sequential cascade reaction is exothermic by 2.0 kcal/mol. These calculations are as follows: (i) The addition of the used basis sets. For C, H, O, F atoms, the 6-31G** basis set was used and for Br atoms, the Aug-cc-PVTZ basis set was used). (ii) The energy of transition state TS1Q1, leading to the major (S)-product 3Q1, is lower than that of transition state TS1Q1’, leading to the minor (R)-product 3Q1’. As such, reaction barriers of the aryl migration step could be used to mirror the observed stereoselectivity. (iii) As going from 1Q1 to 3Q1, the spin density of the above two species (Fig. 4d). The spin density of 1Q1 is exclusively localized on the carbon atom of the substrate, while that of 3Q1 is partially distributed on the carbon atom with significant radical character on the O atom and the phenyl group. This reveals that the presence of a OH group as a π-donating moiety can significantly stabilize the resultant radical species 3Q1, providing an important driving force that makes the formation of ketyl radical species 3Q1 thermodynamically favourable and increases the power of the overall process substantially to generate medium-sized ring systems. DFT calculations on an alternative mechanism involving a Cu species have also been performed49,50, showing that the reaction of the alkyl radical 1Q with CuII species is highly energetically unfavourable, as revealed by a 6.1 kcal higher reaction barrier of the forming Cu intermediate than the radical aryl migration process of alkyl radicals 2Q1/2Q1'. The reaction of the alkyl radical 1Q with CuII species is highly energetically unfavourable, as revealed by a 6.1 kcal higher reaction barrier of the forming Cu intermediate than the radical aryl migration process of alkyl radicals 2Q1/2Q1'.
radical intermediate 1Q$_5$ (Supplementary Fig. 3). Therefore, all these experimental and calculated results, together with the observed highly efficient radical chirality transfer during the ring expansion, are in support of our initial proposal as shown in Fig. 1c, in which the selective addition of a variety of in situ generated radicals to unactivated alkenes could trigger ring expansion via remote 1,4- or 1,5-aryl migration processes.

**Diverse synthetic applications.** An important aspect of this current methodology is that both medium-sized carbó- and heterocyclic ketones and C-X (X=N$_3$, CF$_3$, P(O)R$_2$, SO$_2$Ar, C$_4$F$_9$) are efficiently constructed. Consequently, the resultant functionalized compounds can serve as a convenient handle to access other valuable medium-sized and related compounds. Medium-bridged lactams, exhibiting unique reactivity dissimilar to that of traditional amides due to the limited n$_3$→π*C–O conjugation, have been used as important building blocks in accessing pharmaceutical and natural relevant molecules. Therefore, a number of methodologies have been developed for the synthesis of these useful scaffolds. However, convergent one-step or one-pot methods to prepare such complex skeletons are extremely rare especially with high levels of enantiocontrol, and often require the use of inconvenient polycyclic substrates via tedious multistep synthesis with poor selectivity. To demonstrate one important synthetic utility of this methodology, we reasoned that intramolecular Schmidt-Aubé reaction$^{31,52}$ of the resultant azido-substituted medium-sized ketones 3 in the presence of an appropriate Brønsted acid might afford medium-bridged lactam derivatives. Our original screening of reaction conditions proved that the treatment of 3A with TfOH easily afforded the desired bridged lactam 13 in 85% yield, with complete regioselectivity (Supplementary Table 6). To further simplify the reaction protocol, we investigated the possibility of performing the two distinct reaction sequence in a one-pot fashion. To our delight, after optimization of different reaction parameters (Supplementary Table 7), a simple one-pot procedure was realized: alkenyl alcohols 1 were firstly converted into azido-substituted medium-sized ketones 3 in the presence of CuCN (10 mol%) with EtOAc as solvent. Then, after replacement of the solvent EtOAc with DCM, 3 were subjected to the intramolecular Schmidt-Aubé reaction with TfOH to afford the medium-bridged lactams 13–16 with distinct backbones in 40–62% yields (Fig. 5a). Moreover, the enantioenriched (S)-13 was easily obtained in 60% yield with >99% ee from (R)-1A (>99% ee) following the one-pot procedure (Fig. 5b). It is encouraging to note that the present process is a rather general protocol for the one-pot synthesis of useful complex medium-bridged lactams in high efficiency, which is clearly complementary to previous conventional synthetic methods$^{39}$. Most importantly, our procedure is also applicable to the synthesis of a novel type of chiral bridged tertiary amines at the bridgehead position, which have a great potential for applications as effective asymmetric organocatalysts or ligands$^{53}$ and could be further converted into other alkaloid analogues of potential medicinal importance$^{39}$. For example, the reduction of the resultant (S)-13 with LiAlH$_4$ efficiently delivered the medium-bridgehead tertiary amine (S)-17 in 79% yield without a decrease in the ee value (Fig. 5b).

The easy access to azido-substituted medium-sized ketones prompts us to exploit the synthetic application of the current methodology to the rapid accumulation of analogues of isopavine alkaloids, which possess important pharmacological activities (Fig. 2). As envisioned, the PPh$_3$-promoted intramolecular Staudinger/aza-Wittig reaction of 3, followed by subsequent NaBH$_4$ reduction of in situ generated imines provided amines 18–20 smoothly in 77–92% yields (Fig. 6a). Finally, the amines were directly converted to isopavine analogues 21–23 in 82–93% yields by reductive amination with formaldehyde in the presence of NaBH$_4$ (Fig. 6a). In addition, the resultant ketone group in the obtained medium-ring product inspires us to extend the ring expansion strategy towards lactams via Beckmann rearrangement. An example was the efficient conversion of CF$_3$-containing nine-membered ketone 4A to the ten-membered lactams 24 and 25 in 15% and 34% overall yields via Beckmann rearrangement of the corresponding E- or Z-oximes, respectively (Fig. 6b); such synthetically challenging medium-ring lactams are widespread subunits in biologically active natural products and therapeutic agents.$^{54}$ Meanwhile, 3A successfully underwent the click reaction to give the corresponding triazole 26 in 85% yield (Fig. 6c). Furthermore, manipulation of functional groups at other sites of medium-sized ketones 3 as the bridgehead position, which have a great potential for applications as effective asymmetric organocatalysts or ligands$^{53}$ and could be further converted into other alkaloid analogues of potential medicinal importance$^{39}$. For example, the reduction of the resultant (S)-13 with LiAlH$_4$ efficiently delivered the medium-bridgehead tertiary amine (S)-17 in 79% yield without a decrease in the ee value (Fig. 5b).

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small cell lung carcinoma, with IC50 values of 10.8 and 19.5 exhibited good cytotoxicities against both H1299 (human non-

Biological studies revealed that compounds 3I

evaluate the biological activity of our products. Our preliminary

versatile transformations (II). (a) Rapid accumulation of a small library of isopavine analogues. (b) Preparation of medium-sized lactams via Beckmann rearrangement. (c,d) Click chemistry and preparation of sulfone.

the ring proved also feasible. For example, sulfur-tethered ketone 4G could be selectively oxidized to deliver sulfonyl-substituted nine-membered ketone 27 in 62% yield (Fig. 6d).

Cheminformatic analysis. We have used a cheminformatic approach involving principal component analysis to evaluate the diversity of our compound library compared with natural products, drug-like compounds and drugs18 (see Supplementary Figs 4–10 and Supplementary Tables 8 and 9). The results reveal comparably diverse but distinct chemical spaces occupied by our synthetic molecules and similar benzannulated medium-ring natural products. In addition, compared with the naturally occurring counterpart, our compound library displays less overlaps with the chemical spaces determined by drug-like compounds and drugs. Both of these two features indicate a wide and less-explored chemical space spanned by our compound library, thus demonstrating its great potential for future drug discovery.

Preliminary biological studies. The structure resemblance to a variety of biologically active compounds also encourages us to evaluate the biological activity of our products. Our preliminary biological studies revealed that compounds 3I, 13 and 15 exhibited good cytotoxicities against both H1299 (human non-small cell lung carcinoma, with IC50 values of 10.8 and 19.5 µM for 3I and 15, respectively) and 293T (derivative of human embryonic kidney transformed by adenovirus, with IC50 values of 18.5 and 10.9 µM for 13 and 15, respectively) cell lines (Supplementary Table 10).

Discussion

In summary, we have developed a strategically novel, general and powerful approach for diversity-oriented synthesis of skeletal-and functionally diverse benzannulated medium- and macro-ring scaffolds through 1,4(5)-aryl migration/ring expansion triggered by addition of the diverse radicals to alkenes. Furthermore, the newly developed protocol provides a facile and straightforward access to useful medium-bridged amine derivatives, such as the analogues of the azocine nucleus and the isopavine family. This protocol features a diverse product scope including a variety of carbo-, oxygen-, nitrogen- or sulfur-containing 8 to 14-membered cyclic ketones and medium-bridged amines with over 37 distinct skeletally complex scaffolds as well as the identification of some compounds with potent activity in anticancer and proliferation inhibition, wide functional group compatibility, high enantioselectivity (up to 99% ee) by a chirality transfer strategy, and readily available substrates and reagents. The mechanism of this novel strategy was also investigated by control experiments and DFT calculations. Considering the broad utility for diversity-oriented synthesis of various medium rings and bridged rings of this new protocol, we further anticipate that this efficient strategy will motivate the design of other related processes for the more efficient synthesis of complex natural products and other bioactive molecules.

Methods

General procedure for azidation reactions. Under argon, a 25 ml Schlenk tube equipped with a magnetic stir bar were charged with 1 (0.3 mmol, 1.0 equiv), 2a (104 mg, 0.36 mmol, 1.2 equiv), CuCN (2.7 mg, 0.03 mmol, 0.1 equiv) and EtOAc
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Author contributions

L.L., Z.-L.L. and F.-L.W. performed experiments. Z.G. performed DFT calculations. Y.-F.C. and N.W. helped with characterizing all new compounds. X.-W.D. performed cheminformatic analysis. C.F., J.L. and C.H. performed biological studies. B.T. revised the paper. X.-Y.L. conceived and directed the project and wrote the paper.

Additional information

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