


HIGHLIGHT

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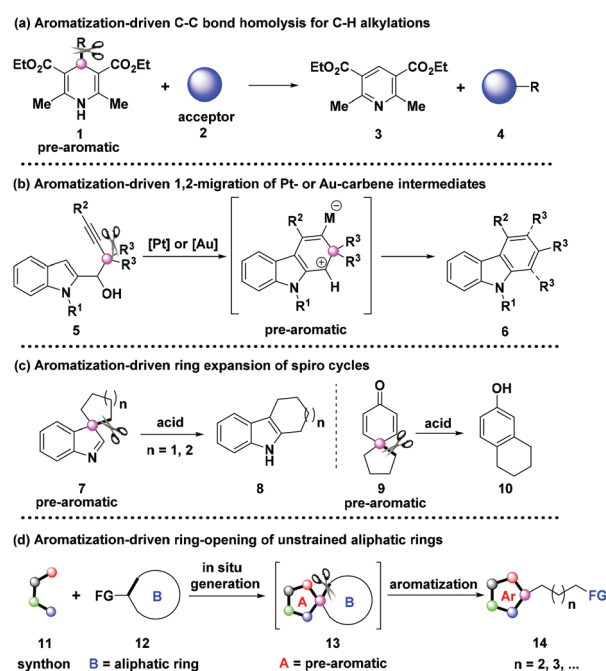
Aromatization-driven deconstruction/
refunctionalization of unstrained ringsFangzhi Hu, ^a Liang Wang, ^{a,b} Lubin Xu^a and Shuai-Shuai Li ^{*a,b}Aromatization-driven ring-opening/functionalization of common unstrained rings has been developed with the *in situ* generation of pre-aromatic fused spiro heterocycles as the key step, featuring (1) simple operation *via* a convenient one-pot reaction and (2) broad scope of various ring systems which do not require pre-activation.

As is well known, aromatization is an important thermodynamic driving force for the formation of stable aromatic rings in organic synthesis.¹ And the C–C bond activation as a significant route for molecular modification is a hot research field.² Remarkably, the exploitation of aromatization-driven C–C bond cleavage can be traced back to 1972 with the assistance of transition metals.³ However, since then, the utilization of aromatization as a driving force for C–C bond cleavage has been unappreciated for a long time, and only a few relevant studies have been reported.^{3,4} Recently, this strategy has been revived gradually for elaborate transformations and has drawn increasing attention from chemists.^{5–8} For example, Melchiorre,^{6a} Molander,^{6b} and Chen^{6c} developed C–H alkylation reactions independently by employing the aromatization-driven C–C bond homolysis strategy of 4-alkyl-1,4-dihydropyridines **1** (Scheme 1a). The Ma group performed the pioneering work on the aromatization-driven 1,2-migration of Pt- or Au-carbene intermediates for the synthesis of carbazoles (Scheme 1b).⁷ Besides, You^{8a–e} and other groups^{8f–g} reported the aromatization-driven ring-expanding rearomatization of spiroindolenines **7** for the construction of polycyclic indoles **8** *via* acid-mediated migration, respectively. In addition, the spirocyclization-dienone-phenol rearrangement cascade reactions have been reported as well with the promotion of aromatization (Scheme 1c).⁹ Yet the major reason that restricts the wide application of aromatization as a driving force for synthetic transformations is the difficulty in the *in situ* generation of pre-aromatic substrates, which usually need to be prefabricated through tedious steps.

Aliphatic rings are ubiquitous in various kinds of organic compounds including pharmaceutical drugs, natural products, and functional materials.¹⁰ Thus, employing the widely-

sourced aliphatic rings as starting materials for deconstruction and re-functionalization would be significantly important for the development of organic synthesis and industrial production. However, for a long time, chemists have been limited in the cleavage of strained rings, which were equipped with an inherent thermodynamic driving force for releasing the ring strain (Fig. 1).¹¹ The C–C bond cleavage/editing of unstrained aliphatic rings is a compelling challenge owing to the high C–C bond dissociation energy.

This highlight article aims to provide a concise overview of the aromatization-driven ring deconstruction strategy of



Scheme 1 Representative types of aromatization-driven C–C bond cleavage.

^aCollege of Chemistry and Pharmaceutical Sciences, Qingdao Agricultural University, Qingdao 266109, China. E-mail: ftyshuashuai@126.com^bCollege of Chemistry and Molecular Engineering, Qingdao University of Science and Technology, Zhengzhou Rd. #53, Qingdao 266042, P. R. China

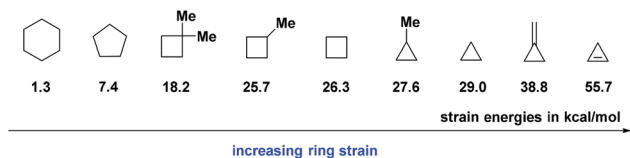


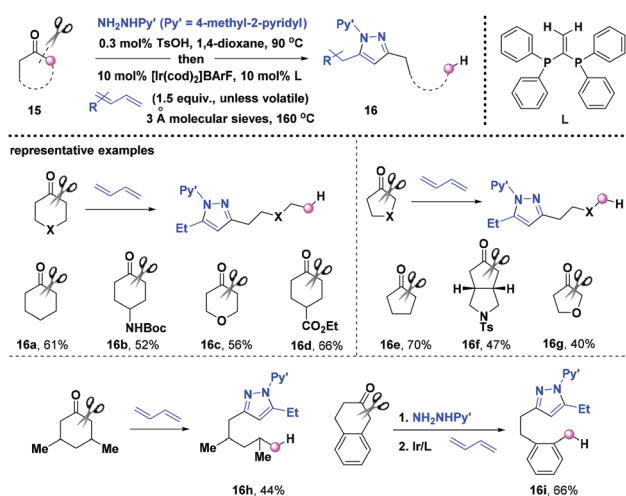
Fig. 1 Strain energies of different sizes of aliphatic rings.

readily available unstrained cycloalkanones and cycloalkanamines *via* radical-mediated C–C bond fragmentation. The protocol features the *in situ* generation of pre-aromatic fused spiro cycles **13**, as shown in Scheme 1d, which might bring a distinct research direction for the development of organic chemistry.

Aromatization-driven C–C bond cleavage of unstrained cycloalkanones

C–C bond activation/functionalization of cycloalkanones emerged as a useful method for synthesizing complex scaffolds. Seminal work by Jun developed the rhodium(i)-catalyzed ring-opening of medium to large cycloalkanone imines to provide various aliphatic chain decorated ketones in 2001.¹² Afterwards, the pursuit for the C–C bond activation/functionalization of cycloalkanones went on uninterrupted, but only sporadic works were reported for unstrained ring activation.¹³ Among them, the Dong group has made outstanding contributions to the transition-metal catalyzed unstrained C–C bond activation with the assistance of *in situ* formed directing groups.^{13b–e}

Very recently, Dong and co-workers reported the efficient ring-opening reactions of unstrained cycloalkanones based on radical fragmentation involved aromatization-driven C–C bond activation (Scheme 2).¹⁴ These deacylative transformations pro-

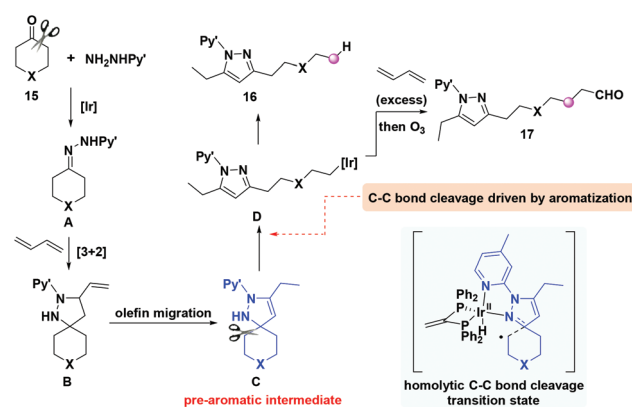


Scheme 2 Deconstructive pyrazole synthesis from unstrained cycloalkanones.

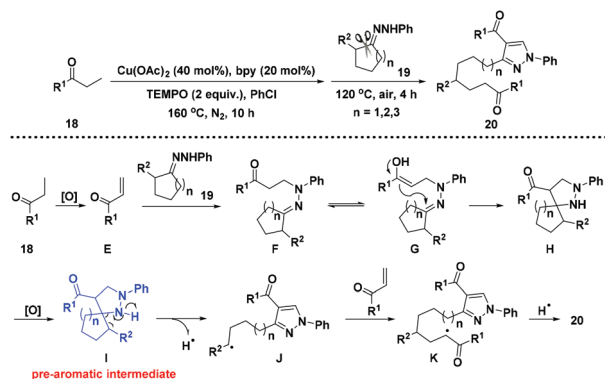
vided various skeleton-functionalized aliphatic chains linking pyrazole *via* a three-component coupling in the presence of an iridium/phosphine combination. Considering the less-accessible carbocyclic pre-aromatics, the authors designed the three component involved 1,3-dipolar addition to prepare the precursor of the pre-aromatized heterocycle which serves as the key intermediate for the subsequent conversion. Various cycloalkanones **15** with different substitutions and ring sizes are available for the aromatization-driven deconstructive transformations. In addition, good regioselectivity has been observed when unsymmetrical ketones and heterocyclic ketones were used, and the bond scission preferentially occurred at more substituted carbons or the α -position of heteroatoms. Besides, various natural products were well tolerated for the C–C bond transformation.

Based on mechanistic studies and DFT calculations, an aromatization-promoted homolytic C–C cleavage/radical recombination mechanism was proposed (Scheme 3). The initial [3 + 2] cycloaddition occurs between 1,3-butadiene and the hydrazone intermediate **A**, generating cyclic adduct **B** which could be isolated. Then olefin migration takes place to afford the dihydropyrazole intermediate **C** which serves as the pre-aromatic substrate to drive the following homolytic C–C bond cleavage with the promotion of an iridium catalyst. The control experiments indicate that no C–C cleavage occurs without the endocyclic double bond or the five-membered ring structure, which demonstrates the significant role of the intermediate **C**. Subsequently, the aromatization-driven deconstruction of the unstrained ring occurs, providing the iridium complex **D** bearing aromatized pyrazole. Then the C–H reductive elimination or coupling with 1,3-butadiene of iridium complex **D** takes place to afford the corresponding products **16** and **17**, respectively. In addition to cycloalkanones, the deacylative transformations are suitable for a variety of linear ketones as well, which offer strategic bond disconnections for editing of the molecular skeleton.

In addition, Fan and co-workers described the ring-opening reactions through [3 + 2] cycloaddition of enone with unstrained cyclic ketone hydrazone followed by an aromatization-driven



Scheme 3 Plausible mechanism for deconstructive pyrazole synthesis from unstrained cycloalkanones.



Scheme 4 Ring-opening reactions for the synthesis of 4-acylpyrazole from unstrained cyclic ketone hydrazine.

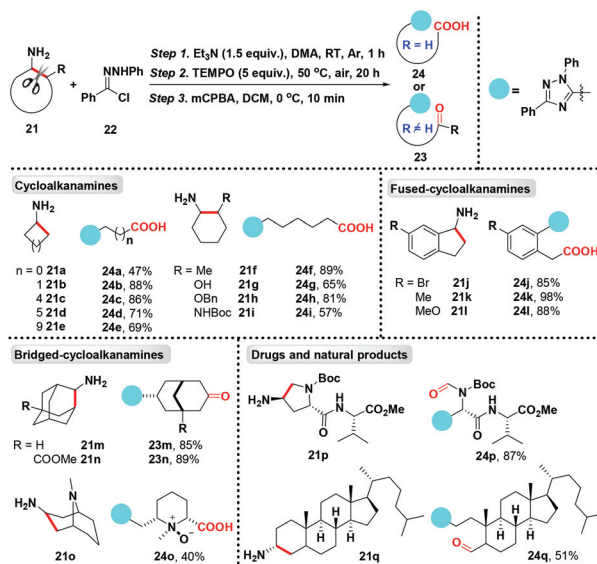
homolytic C–C bond cleavage/radical reorganization (Scheme 4).¹⁵ In this reaction, the *in situ* generated pre-aromatic I is considered as the key intermediate likewise to drive the subsequent C–C bond disconnection for aromatization.

Aromatization-driven C–C bond cleavage of unstrained cycloalkanamines

Cycloalkanamines as essential structural units are widely found in natural products, pharmaceuticals, and agrochemicals. The development of convenient methods to make use of the widespread cycloalkanamines is extremely meaningful for modern chemical production. At present, the utilization of cycloalkanamines *via* ring-opening reconstruction is underdeveloped, and the scarce cases that are reported are almost limited to strained rings.¹⁶

For example, Zheng and co-workers conducted the pioneering work on the photogenerated amine radical cation-involved ring-extension reactions of cyclopropyl- and cyclobutyl-anilines with alkenes and alkynes.^{16a–d} Recently, Waser and co-workers described an oxidative ring-opening strategy to transform aminocyclopropanes into 1,3-dielectrophilic carbon intermediates bearing a halide atom (Br, I) and a *N,O*-acetal which could be converted into a wide range of α,γ -difunctionalized amines in a one-pot or two-step operation.^{16e}

Despite the developments mentioned above on the application of cycloalkanamines as building blocks through ring-reconstruction and functionalization, ring-opening of unstrained cycloalkanamines still remains a compelling challenge. This situation can be attributed to ring-strain release as a thermodynamic driving force for strained cycloalkanamines, and the high reverse *exo*-cyclization rate constant of nitrile and imine for unstrained cycloalkanamines, especially for 5- or 6-membered cycloalkanamines.^{11,17} In this context, Han and co-workers achieved the introduction of aromatization as both dynamic and thermodynamic driving forces for driving ring-opening of unstrained primary cycloalkanamines.¹⁸ In this



Scheme 5 Deconstruction/functionalization of unstrained primary cycloalkanamines.

metal-free reaction, the deconstruction/functionalization of unstrained primary cycloalkanamines has been developed unprecedentedly, producing carbonyl compound tethered aliphatic chains and 1,2,4-triazole directly through the autooxidative aromatization-driven C(sp³)-C(sp³) bond cleavage (Scheme 5). Similarly, the C–C bond cleavage of cycloalkanamines preferentially at more substituted carbons or the α -position of heteroatoms was achieved. The wide substrate scope tolerance of this protocol has been revealed by meticulous evaluations, including monocyclic, bicyclic, bridged, and complex natural product derivatives containing primary cycloalkanamine moieties, which indicated its potential application in the pharmaceutical and chemical industries. In addition, the *in situ* generation of the pre-aromatic heterocycle remains the core of this transformation, which is consistent with Dong and Fan's work.

In the proposed catalytic cycle (Scheme 6), the initial nucleophilic substitution occurs between cycloalkanamine 21 and hydrazonyl chloride 22 to produce hydrazonamide L which is auto-oxidized by air to generate aminyl radical M. M then undergoes 1,5-H shift and oxidative annulation to form pre-aromatic intermediate N. N is further oxidized by air to form pre-aromatic intermediate O. O then undergoes aromatization-driven C–C cleavage to yield product P. P is then converted to Q, which is further converted to R. R is then converted to S, which is further converted to T. T is then converted to U, which is further converted to V. V is then converted to W, which is further converted to X. X is then converted to Y, which is further converted to Z. Z is then converted to AA, which is further converted to AB. AB is then converted to AC, which is further converted to AD. AD is then converted to AE, which is further converted to AF. AF is then converted to AG, which is further converted to AH. AH is then converted to AI, which is further converted to AJ. AJ is then converted to AK, which is further converted to AL. AL is then converted to AM, which is further converted to AN. AN is then converted to AO, which is further converted to AP. AP is then converted to AQ, which is further converted to AR. AR is then converted to AS, which is further converted to AT. AT is then converted to AU, which is further converted to AV. AV is then converted to AW, which is further converted to AX. AX is then converted to AY, which is further converted to AZ. AZ is then converted to BA, which is further converted to BB. BB is then converted to BC, which is further converted to BD. BD is then converted to BE, which is further converted to BF. BF is then converted to BG, which is further converted to BH. BH is then converted to BI, which is further converted to BJ. BJ is then converted to BK, which is further converted to BL. BL is then converted to BM, which is further converted to BN. BN is then converted to BO, which is further converted to BP. BP is then converted to BQ, which is further converted to BR. BR is then converted to BS, which is further converted to BT. BT is then converted to BU, which is further converted to BV. BV is then converted to BW, which is further converted to BX. BX is then converted to BY, which is further converted to BZ. BZ is then converted to CA, which is further converted to CB. CB is then converted to CC, which is further converted to CD. CD is then converted to CE, which is further converted to CF. CF is then converted to CG, which is further converted to CH. CH is then converted to CI, which is further converted to CJ. CJ is then converted to CK, which is further converted to CL. CL is then converted to CM, which is further converted to CN. CN is then converted to CO, which is further converted to CP. CP is then converted to CQ, which is further converted to CR. CR is then converted to CS, which is further converted to CT. CT is then converted to CU, which is further converted to CV. CV is then converted to CW, which is further converted to CX. CX is then converted to CY, which is further converted to CZ. CZ is then converted to DA, which is further converted to DB. DB is then converted to DC, which is further converted to DD. DD is then converted to DE, which is further converted to DF. DF is then converted to DG, which is further converted to DH. DH is then converted to DI, which is further converted to DJ. DJ is then converted to DK, which is further converted to DL. DL is then converted to DM, which is further converted to DN. DN is then converted to DO, which is further converted to DP. DP is then converted to DQ, which is further converted to DR. DR is then converted to DS, which is further converted to DT. DT is then converted to DU, which is further converted to DV. DV is then converted to DW, which is further converted to DX. DX is then converted to DY, which is further converted to DZ. DZ is then converted to EA, which is further converted to EB. EB is then converted to EC, which is further converted to ED. ED is then converted to EE, which is further converted to EF. EF is then converted to EG, which is further converted to EH. EH is then converted to EI, which is further converted to EJ. EJ is then converted to EK, which is further converted to EL. EL is then converted to EM, which is further converted to EN. EN is then converted to EO, which is further converted to EP. EP is then converted to EQ, which is further converted to ER. ER is then converted to ES, which is further converted to ET. ET is then converted to EU, which is further converted to EV. EV is then converted to EW, which is further converted to EX. EX is then converted to EY, which is further converted to EZ. EZ is then converted to FA, which is further converted to FB. FB is then converted to FC, which is further converted to FD. FD is then converted to FE, which is further converted to FF. FF is then converted to FG, which is further converted to FH. FH is then converted to FI, which is further converted to FJ. FJ is then converted to FK, which is further converted to FL. FL is then converted to FM, which is further converted to FN. FN is then converted to FO, which is further converted to FP. FP is then converted to FQ, which is further converted to FR. FR is then converted to FS, which is further converted to FT. FT is then converted to FU, which is further converted to FV. FV is then converted to FW, which is further converted to FX. FX is then converted to FY, which is further converted to FZ. FZ is then converted to GA, which is further converted to GB. GB is then converted to GC, which is further converted to GD. GD is then converted to GE, which is further converted to GF. GF is then converted to GG, which is further converted to GH. GH is then converted to GI, which is further converted to GJ. GJ is then converted to GK, which is further converted to GL. GL is then converted to GM, which is further converted to GN. GN is then converted to GO, which is further converted to GP. GP is then converted to GQ, which is further converted to GR. GR is then converted to GS, which is further converted to GT. GT is then converted to GU, which is further converted to GV. GV is then converted to GW, which is further converted to GX. GX is then converted to GY, which is further converted to GZ. GZ is then converted to HA, which is further converted to HB. HB is then converted to HC, which is further converted to HD. HD is then converted to HE, which is further converted to HF. HF is then converted to HG, which is further converted to HH. HH is then converted to HI, which is further converted to HJ. HJ is then converted to HK, which is further converted to HL. HL is then converted to HM, which is further converted to HN. HN is then converted to HO, which is further converted to HP. HP is then converted to HQ, which is further converted to HR. HR is then converted to HS, which is further converted to HT. HT is then converted to HU, which is further converted to HV. HV is then converted to HW, which is further converted to HX. HX is then converted to HY, which is further converted to HZ. HZ is then converted to IA, which is further converted to IB. IB is then converted to IC, which is further converted to ID. ID is then converted to IE, which is further converted to IF. IF is then converted to IG, which is further converted to IH. IH is then converted to II, which is further converted to IJ. IJ is then converted to IK, which is further converted to IL. IL is then converted to IM, which is further converted to IN. IN is then converted to IO, which is further converted to IP. IP is then converted to IQ, which is further converted to IR. IR is then converted to IS, which is further converted to IT. IT is then converted to IU, which is further converted to IV. IV is then converted to IW, which is further converted to IX. IX is then converted to IY, which is further converted to IZ. IZ is then converted to JA, which is further converted to JB. JB is then converted to JC, which is further converted to JD. JD is then converted to JE, which is further converted to JF. JF is then converted to JG, which is further converted to JH. JH is then converted to JI, which is further converted to JJ. JJ is then converted to JK, which is further converted to JL. JL is then converted to JM, which is further converted to JN. JN is then converted to JO, which is further converted to JP. JP is then converted to JQ, which is further converted to JR. JR is then converted to JS, which is further converted to JT. JT is then converted to JU, which is further converted to JV. JV is then converted to JW, which is further converted to JX. JX is then converted to JY, which is further converted to JZ. JZ is then converted to KA, which is further converted to KB. KB is then converted to KC, which is further converted to KD. KD is then converted to KE, which is further converted to KF. KF is then converted to KG, which is further converted to KH. KH is then converted to KI, which is further converted to KJ. KJ is then converted to KK, which is further converted to KL. KL is then converted to KM, which is further converted to KN. KN is then converted to KO, which is further converted to KP. KP is then converted to KQ, which is further converted to KR. KR is then converted to KS, which is further converted to KT. KT is then converted to KU, which is further converted to KV. KV is then converted to KW, which is further converted to KX. KX is then converted to KY, which is further converted to KZ. KZ is then converted to LA, which is further converted to LB. LB is then converted to LC, which is further converted to LD. LD is then converted to LE, which is further converted to LF. LF is then converted to LG, which is further converted to LH. LH is then converted to LI, which is further converted to LJ. LJ is then converted to LK, which is further converted to LL. LL is then converted to LM, which is further converted to LN. LN is then converted to LO, which is further converted to LP. LP is then converted to LQ, which is further converted to LR. LR is then converted to LS, which is further converted to LT. LT is then converted to LU, which is further converted to LV. LV is then converted to LW, which is further converted to LX. LX is then converted to LY, which is further converted to LZ. LZ is then converted to MA, which is further converted to MB. MB is then converted to MC, which is further converted to MD. MD is then converted to ME, which is further converted to MF. MF is then converted to MG, which is further converted to MH. MH is then converted to MI, which is further converted to MJ. MJ is then converted to MK, which is further converted to ML. ML is then converted to MM, which is further converted to MN. MN is then converted to MO, which is further converted to MP. MP is then converted to MQ, which is further converted to MR. MR is then converted to MS, which is further converted to MT. MT is then converted to MU, which is further converted to MV. MV is then converted to MW, which is further converted to MX. MX is then converted to MY, which is further converted to MZ. MZ is then converted to NA, which is further converted to NB. NB is then converted to NC, which is further converted to ND. ND is then converted to NE, which is further converted to NF. NF is then converted to NG, which is further converted to NH. NH is then converted to NI, which is further converted to NJ. NJ is then converted to NK, which is further converted to NL. NL is then converted to NM, which is further converted to NN. NN is then converted to NO, which is further converted to NP. NP is then converted to NQ, which is further converted to NR. NR is then converted to NS, which is further converted to NT. NT is then converted to NU, which is further converted to NV. NV is then converted to NW, which is further converted to NX. NX is then converted to NY, which is further converted to NZ. NZ is then converted to OA, which is further converted to OB. OB is then converted to OC, which is further converted to OD. OD is then converted to OE, which is further converted to OF. OF is then converted to OG, which is further converted to OH. OH is then converted to OI, which is further converted to OJ. OJ is then converted to OK, which is further converted to OL. OL is then converted to OM, which is further converted to ON. ON is then converted to OO, which is further converted to OP. OP is then converted to OQ, which is further converted to OR. OR is then converted to OS, which is further converted to OT. OT is then converted to OU, which is further converted to OV. OV is then converted to OW, which is further converted to OX. OX is then converted to OY, which is further converted to OZ. OZ is then converted to PA, which is further converted to PB. PB is then converted to PC, which is further converted to PD. PD is then converted to PE, which is further converted to PF. PF is then converted to PG, which is further converted to PH. PH is then converted to PI, which is further converted to PJ. PJ is then converted to PK, which is further converted to PL. PL is then converted to PM, which is further converted to PN. PN is then converted to PO, which is further converted to PP. PP is then converted to PQ, which is further converted to PR. PR is then converted to PS, which is further converted to PT. PT is then converted to PU, which is further converted to PV. PV is then converted to PW, which is further converted to PX. PX is then converted to PY, which is further converted to PZ. PZ is then converted to QA, which is further converted to QB. QB is then converted to QC, which is further converted to QD. QD is then converted to QE, which is further converted to QF. QF is then converted to QG, which is further converted to QH. QH is then converted to QI, which is further converted to QJ. QJ is then converted to QK, which is further converted to QL. QL is then converted to QM, which is further converted to QN. QN is then converted to QO, which is further converted to QP. QP is then converted to QQ, which is further converted to QR. QR is then converted to QS, which is further converted to QT. QT is then converted to QU, which is further converted to QV. QV is then converted to QW, which is further converted to QX. QX is then converted to QY, which is further converted to QZ. QZ is then converted to RA, which is further converted to RB. RB is then converted to RC, which is further converted to RD. RD is then converted to RE, which is further converted to RF. RF is then converted to RG, which is further converted to RH. RH is then converted to RI, which is further converted to RJ. RJ is then converted to RK, which is further converted to RL. RL is then converted to RM, which is further converted to RN. RN is then converted to RO, which is further converted to RP. RP is then converted to RQ, which is further converted to RR. RR is then converted to RS, which is further converted to RT. RT is then converted to RU, which is further converted to RV. RV is then converted to RW, which is further converted to RX. RX is then converted to RY, which is further converted to RZ. RZ is then converted to SA, which is further converted to SB. SB is then converted to SC, which is further converted to SD. SD is then converted to SE, which is further converted to SF. SF is then converted to SG, which is further converted to SH. SH is then converted to SI, which is further converted to SJ. SJ is then converted to SK, which is further converted to SL. SL is then converted to SM, which is further converted to SN. SN is then converted to SO, which is further converted to SP. SP is then converted to SQ, which is further converted to SR. SR is then converted to SS, which is further converted to ST. ST is then converted to SU, which is further converted to SV. SV is then converted to SW, which is further converted to SX. SX is then converted to SY, which is further converted to SZ. SZ is then converted to TA, which is further converted to TB. TB is then converted to TC, which is further converted to TD. TD is then converted to TE, which is further converted to TF. TF is then converted to TG, which is further converted to TH. TH is then converted to TI, which is further converted to TJ. TJ is then converted to TK, which is further converted to TL. TL is then converted to TM, which is further converted to TN. TN is then converted to TO, which is further converted to TP. TP is then converted to TQ, which is further converted to TR. TR is then converted to TS, which is further converted to TT. TT is then converted to TU, which is further converted to TV. TV is then converted to TW, which is further converted to TX. TX is then converted to TY, which is further converted to TZ. TZ is then converted to UA, which is further converted to UB. UB is then converted to UC, which is further converted to UD. UD is then converted to UE, which is further converted to UF. UF is then converted to UG, which is further converted to UH. UH is then converted to UI, which is further converted to UJ. UJ is then converted to UK, which is further converted to UL. UL is then converted to UM, which is further converted to UN. UN is then converted to UO, which is further converted to UP. UP is then converted to UQ, which is further converted to UR. UR is then converted to US, which is further converted to UT. UT is then converted to UY, which is further converted to UZ. UZ is then converted to VA, which is further converted to VB. VB is then converted to VC, which is further converted to VD. VD is then converted to VE, which is further converted to VF. VF is then converted to VG, which is further converted to VH. VH is then converted to VI, which is further converted to VJ. VJ is then converted to VK, which is further converted to VL. VL is then converted to VM, which is further converted to VN. VN is then converted to VO, which is further converted to VP. VP is then converted to VQ, which is further converted to VR. VR is then converted to VS, which is further converted to VT. VT is then converted to VY, which is further converted to VZ. VZ is then converted to WA, which is further converted to WB. WB is then converted to WC, which is further converted to WD. WD is then converted to WE, which is further converted to WF. WF is then converted to WG, which is further converted to WH. WH is then converted to WI, which is further converted to WJ. WJ is then converted to WK, which is further converted to WL. WL is then converted to WM, which is further converted to WN. WN is then converted to WO, which is further converted to WP. WP is then converted to WQ, which is further converted to WR. WR is then converted to WS, which is further converted to WT. WT is then converted to WY, which is further converted to WZ. WZ is then converted to XA, which is further converted to XB. XB is then converted to XC, which is further converted to XD. XD is then converted to XE, which is further converted to XF. XF is then converted to XG, which is further converted to XH. XH is then converted to XI, which is further converted to XJ. XJ is then converted to XK, which is further converted to XL. XL is then converted to XM, which is further converted to XN. XN is then converted to XO, which is further converted to XP. XP is then converted to XQ, which is further converted to XR. XR is then converted to XS, which is further converted to XT. XT is then converted to XY, which is further converted to XZ. XZ is then converted to YA, which is further converted to YB. YB is then converted to YC, which is further converted to YD. YD is then converted to YE, which is further converted to YF. YF is then converted to YG, which is further converted to YH. YH is then converted to YI, which is further converted to YJ. YJ is then converted to YK, which is further converted to YL. YL is then converted to YM, which is further converted to YN. YN is then converted to YO, which is further converted to YP. YP is then converted to YQ, which is further converted to YR. YR is then converted to YS, which is further converted to YT. YT is then converted to YZ, which is further converted to ZA. ZA is then converted to ZB. ZB is then converted to ZC. ZC is then converted to ZD. ZD is then converted to ZE. ZE is then converted to ZF. ZF is then converted to ZG. ZG is then converted to ZH. ZH is then converted to ZI. ZI is then converted to ZJ. ZJ is then converted to ZK. ZK is then converted to ZL. ZL is then converted to ZM. ZM is then converted to ZN. ZN is then converted to ZO. ZO is then converted to ZP. ZP is then converted to ZQ. ZQ is then converted to ZR. ZR is then converted to ZS. ZS is then converted to ZT. ZT is then converted to ZY. ZY is then converted to ZZ.

Scheme 6 Proposed mechanism for the deconstruction/functionalization of unstrained primary cycloalkanamines.

Then radical **M** undergoes the tandem 1,5-hydrogen atom shift/further oxidation/annulation process to form the key pre-aromatic heterocycle **N**, which could be isolated. The spiro heterocycle **N** tends to be oxidized by air to afford the cyclic amino radical intermediate **O** which appears in many N-containing heteroaryl migration reactions.¹⁹ Then aromatization serves as a driving force to promote the radical C–C bond cleavage to furnish the aromatic 1,2,4-triazole. The generated distal alkyl radical **P** linking aromatic 1,2,4-triazole is immediately intercepted by TEMPO to give the ring-opening product **Q**. The final acyclic carbonyl compounds **23** and **24** carrying 1,2,4-triazole could be obtained by the treatment of *m*CPBA via the oxidation/Cope-elimination sequence.

Conclusions

The C–C bond disconnection is of significant importance for editing the molecular skeleton in organic synthesis, especially for the cleavage of ubiquitous unstrained aliphatic rings. Aromatization as both dynamic and thermodynamic driving forces for promoting C–C bond cleavage could compensate for the chemical inertness of unstrained aliphatic rings. We have highlighted the aromatization-driven homolytic C–C bond cleavage of common unstrained rings promoted by the *in situ* generated pre-aromatic fused spiro cycles, which featured (1) simple operation via a convenient one-pot reaction and (2) broad scope of various ring systems which do not require pre-activation. From our viewpoint, the aromatization-driven deconstruction/refunctionalization of organic molecules would be a powerful toolbox for modifying molecular skeletons and enriching the diversity of molecules.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- (a) P. V. R. Schleyer and F. Pühlhofer, Recommendations for the evaluation of aromatic stabilization energies, *Org. Lett.*, 2002, **4**, 2873–2876; (b) M. A. Halcrow, F. Urbanos and B. Chaudret, Aromatization of the B-ring of 5,7-dienyl steroids by the electrophilic ruthenium fragment “[Cp*Ru]”, *Organometallics*, 1993, **12**, 955–957.
- (a) M. Murakami and Y. Ito, Cleavage of carbon–carbon single bonds by transition metals, *Top. Organomet. Chem.*, 1999, **3**, 97–129; (b) F. Chen, T. Wang and N. Jiao, Recent advances in transition-metal-catalyzed functionalization of unstrained carbon-carbon bonds, *Chem. Rev.*, 2014, **114**, 8613–8661; (c) D.-S. Kim, W.-J. Park and C.-H. Jun, Metal-organic cooperative catalysis in C–H and C–C bond activation, *Chem. Rev.*, 2017, **117**, 8977–9015; (d) F. Song, T. Gou, B.-Q. Wang and Z.-J. Shi, Catalytic activations of unstrained C–C bond involving organometallic intermediates, *Chem. Soc. Rev.*, 2018, **47**, 7078–7115; (e) X. Wu and C. Zhu, Recent advances in radical-mediated C-C bond fragmentation of non-strained molecules, *Chin. J. Chem.*, 2019, **37**, 171–182; (f) *C–C bond activation*, Top. Curr. Chem., ed. G. Dong, Springer, Berlin, 2014, vol. 346, pp. 1–262; (g) P.-h. Chen, B. A. Billett, T. Tsukamoto and G. Dong, “Cut and Sew” Transformations via transition-metal-catalyzed carbon–carbon bond activation, *ACS Catal.*, 2017, **7**, 1340–1360; (h) L. Deng and G. Dong, Carbon-Carbon bond activation of ketones, *Trends Chem.*, 2020, **2**, 183–198.
- R. B. King and A. Efraty, Pentamethylcyclopentadienyl derivatives of transition metals. II. Synthesis of pentamethylcyclopentadienyl metal carbonyls from 5-acetyl-1,2,3,4,5-pentamethylcyclopentadiene, *J. Am. Chem. Soc.*, 1972, **94**, 3773–3779.
- (a) R. H. Crabtree, R. P. Dion, D. J. Gibboni, D. V. McGrath and E. M. Holt, Carbon-carbon bond cleavage in hydrocarbons by iridium complexes, *J. Am. Chem. Soc.*, 1986, **108**, 7222–7227; (b) G. Smits, B. Audic, M. D. Wodrich, C. Corminboeuf and N. Cramer, A β -Carbon elimination strategy for convenient *in situ* access to cyclopentadienyl metal complexes, *Chem. Sci.*, 2017, **8**, 7174–7179.
- (a) J. Guin, C. Muck-Lichtenfeld, S. Grimme and A. Studer, Radical transfer hydroamination with aminated cyclohexadienes using polarity reversal catalysis: scope and limitations, *J. Am. Chem. Soc.*, 2007, **129**, 4498–4503; (b) S. W. Youn, B. S. Kim and A. R. Jagdale, Pd-Catalyzed sequential C–C bond formation and cleavage: evidence for an unexpected generation of arylpalladium(II) species, *J. Am. Chem. Soc.*, 2012, **134**, 11308–11311.
- (a) L. Buzzetti, A. Prieto, S. R. Roy and P. Melchiorre, Radical-based C-C bond-forming processes enabled by the photoexcitation of 4-alkyl-1,4-dihydropyridines, *Angew. Chem.*, 2017, **129**, 15235–15239; (b) á. Gutierrez-Bonet, C. Remeur, J. K. Matsui and G. A. Molander, Late-stage C–H alkylation of heterocycles and 1,4-quinones via oxidative homolysis of 1,4-dihydropyridines, *J. Am. Chem. Soc.*, 2017, **139**, 12251–12258; (c) X. Chen, F. Ye, X. Luo, X. Liu, J. Zhao, S. Wang, Q. Zhou, G. Chen and P. Wang, Histidine-specific peptide modification via visible-light-promoted C–H alkylation, *J. Am. Chem. Soc.*, 2019, **141**, 18230–18237.

- 7 (a) Y. Qiu, D. Ma, W. Kong, C. Fu and S. Ma, Regiocontrolled 1,2-migration in cyclization of 1-(indol-2-yl)-3-alkyn-1-ols: (Ph₃P)Au+vs. PtCl₄, *Org. Chem. Front.*, 2014, **1**, 62–67; (b) W. Kong, Y. Qiu, X. Zhang, C. Fu and S. Ma, Exclusive 1,2-aryl shift in platinum(II) chloride-catalyzed cyclization of 1-(Indol-2-yl)-2,3-allenols, *Adv. Synth. Catal.*, 2012, **354**, 2339–2347; (c) W. Kong, C. Fu and S. Ma, Efficient synthesis of carbazoles via PtCl₂-catalyzed RT cyclization of 1-(indol-2-yl)-2,3-allenols: scope and mechanism, *Org. Biomol. Chem.*, 2012, **10**, 2164–2173; (d) W. Kong, C. Fu and S. Ma, General Au-catalyzed benzannulation towards naturally occurring carbazole alkaloids from methoxypropadiene, *Chem. – Eur. J.*, 2011, **17**, 13134–13137; (e) W. Kong, C. Fu and S. Ma, An efficient synthesis of carbazoles from PtCl₂-catalyzed cyclization of 1-(indol-2-yl)-2,3-allenols, *Chem. Commun.*, 2009, 4572–4574; (f) X. Zhang and S. Ma, Transition metal-catalyzed benzannulation towards naturally occurring carbazole alkaloids, *Isr. J. Chem.*, 2018, **58**, 608–621.
- 8 (a) Y. Wang, C. Zheng and S.-L. You, Iridium-catalyzed asymmetric allylic dearomatization by a desymmetrization strategy, *Angew. Chem., Int. Ed.*, 2017, **56**, 15093–15097; (b) Q.-F. Wu, C. Zheng and S.-L. You, Enantioselective synthesis of spiro cyclopentane-1,3'-indoles and 2,3,4,9-tetrahydro-1H-carbazoles by Iridium-catalyzed allylic dearomatization and stereospecific migration, *Angew. Chem., Int. Ed.*, 2012, **51**, 1680–1683; (c) C.-X. Zhuo, Q. Cheng, W.-B. Liu, Q. Zhao and S.-L. You, Enantioselective synthesis of pyrrole-based spiro- and polycyclic derivatives by Iridium-catalyzed asymmetric allylic dearomatization and controllable migration reactions, *Angew. Chem., Int. Ed.*, 2015, **54**, 8475–8479; (d) C.-X. Zhuo, Y. Zhou, Q. Cheng, L. Huang and S.-L. You, Enantioselective construction of spiroindolines with three contiguous stereogenic centers and chiral tryptamine derivatives via reactive spiroindolenine intermediates, *Angew. Chem., Int. Ed.*, 2015, **54**, 14146–14149; (e) C. Zheng, Z.-L. Xia and S.-L. You, Unified mechanistic understandings of Pictet-Spengler reactions, *Chem*, 2018, **4**, 1952–1966; (f) V. Gobé, V. Gandon and X. Guinchard, Reactions involving tryptamines and δ -allenyl aldehydes: competition between Pictet-Spengler reaction and cyclization to 1-aminotetralins, *Adv. Synth. Catal.*, 2018, **360**, 1280–1288; (g) G. Bai, F. Dong, L. Xu, Y. Liu, L. Wang and S.-S. Li, Controllable syntheses of spiroindolenines and senzazepinoindoles via hexafluoroisopropanol-mediated Redox-Neutral cascade process, *Org. Lett.*, 2019, **21**, 6225–6230.
- 9 (a) M. Yoshida, T. Nozaki, T. Nemoto and Y. Hamada, Formal meta-specific intramolecular Friedel-Crafts allylic alkylation of phenols through a spirocyclization-dienone-phenol rearrangement cascade, *Tetrahedron*, 2013, **69**, 9609–9615; (b) R. A. Bauer, T. A. Wenderski and D. S. Tan, Biomimetic diversity-oriented synthesis of benzannulated medium rings via ring expansion, *Nat. Chem. Biol.*, 2013, **9**, 21–29.
- 10 (a) *Biologically Active Natural Products: Pharmaceuticals*, ed. J. C. Stephen and H. G. Cutler, CRC Press, Boca Raton, FL, 2000; (b) *Comprehensive natural products II: Chemistry and Biology*, ed. L. Mander and H.-W. Liu, Elsevier, Amsterdam, 2010.
- 11 For reviews on ring-opening of strained rings, see: (a) G. Fumagalli, S. Stanton and J. F. Bower, Recent methodologies that exploit C–C single-bond cleavage of strained ring systems by transition metal complexes, *Chem. Rev.*, 2017, **117**, 9404–9432; (b) M. Murakami and N. Ishida, Potential of metal-catalyzed C–C single bond cleavage for organic synthesis, *J. Am. Chem. Soc.*, 2016, **138**, 13759–13769; (c) L. Souillart and N. Cramer, Catalytic C–C bond activations via oxidative addition to transition metals, *Chem. Rev.*, 2015, **115**, 9410–9464; (d) F. Wang, S. Yu and X. Li, Transition metal-catalysed couplings between arenes and strained or reactive rings: combination of C–H activation and ring scission, *Chem. Soc. Rev.*, 2016, **45**, 6462–6477.
- 12 C.-H. Jun, H. Lee and S.-G. Lim, The C–C bond activation and skeletal rearrangement of cycloalkanone imine by Rh (I) catalysts, *J. Am. Chem. Soc.*, 2001, **123**, 751–752.
- 13 (a) M. Wang, M. Li, S. Yang, X.-S. Xue, X. Wu and C. Zhu, Radical-mediated C-C cleavage of unstrained cycloketones and DFT study for unusual regioselectivity, *Nat. Commun.*, 2020, **11**, 672–678; (b) H. M. Ko and G. Dong, Cooperative activation of cyclobutanones and olefins leads to bridged ring systems by a catalytic [4+2] coupling, *Nat. Chem.*, 2014, **6**, 739–744; (c) Y. Xia, G. Lu, P. Liu and G. Dong, Catalytic activation of carbon-carbon bonds in cyclopentanones, *Nature*, 2016, **539**, 546–550; (d) Y. Xia, J. B. Wang and G. Dong, Distal-Bond-Selective C–C activation of ring-fused cyclopentanones: an efficient access to spiroindanones, *Angew. Chem., Int. Ed.*, 2017, **56**, 2376–2380; (e) Y. Xia, J. B. Wang and G. Dong, Suzuki-Miyaura coupling of simple ketones via activation of unstrained carbon-carbon bonds, *J. Am. Chem. Soc.*, 2018, **140**, 5347–5351.
- 14 Y. Xu, X. Qi, P. Zheng, C. C. Berti, P. Liu and G. Dong, Deacylative transformations of ketones via aromatization-promoted C–C bond activation, *Nature*, 2019, **567**, 373–378.
- 15 M. Tian, X. Shi, X. Zhang and X. Fan, Synthesis of 4-acylpyrazoles from saturated ketones and hydrazones featured with multiple C(sp³)-H bond functionalization and C–C bond cleavage and reorganization, *J. Org. Chem.*, 2017, **82**, 7363–7372.
- 16 For representative works on ring-opening of strained cycloalkanamines, see: (a) S. Maity, M. Zhu, R. S. Shinabery and N. Zheng, Intermolecular [3+2] cycloaddition of cyclopropylamines with olefins by visible-light photocatalysis, *Angew. Chem., Int. Ed.*, 2012, **51**, 222–226; (b) Y. Cai, J. Wang, Y. Zhang, Z. Li, D. Hu, N. Zheng and H. Chen, Detection of fleeting amine radical cations and elucidation of chain processes in visible-light-mediated [3+2] annulation by online mass spectrometric techniques, *J. Am. Chem. Soc.*, 2017, **139**, 12259–12266; (c) J. Wang and N. Zheng, The Cleavage of a C-C bond in cyclobutylanilines by visible-light photoredox catalysis: development of a [4+2] annulation method, *Angew. Chem., Int. Ed.*, 2015, **54**, 11424–

- 11427; (d) S. A. Morris, J. Wang and N. Zheng, The prowess of photogenerated amine radical cations in cascade reactions: from carbocycles to heterocycles, *Acc. Chem. Res.*, 2016, **49**, 1957–1968; (e) M.-M. Wang and J. Waser, 1,3-difunctionalization of aminocyclopropanes via dielectrophilic intermediates, *Angew. Chem., Int. Ed.*, 2019, **58**, 13880–13884.
- 17 (a) J. H. Horner, F. N. Martinez, O. M. Musa, M. Newcomb and H. E. Shahin, Kinetics of dialkylammonium cation radical reactions: radical clocks, solvent effects, acidity constants, and rate constants for reactions with hydrogen atom donors, *J. Am. Chem. Soc.*, 1995, **117**, 11124–11133; (b) O. M. Musa, J. H. Horner, H. Shahin and M. Newcomb, A kinetic scale for dialkylaminyl radical reactions, *J. Am. Chem. Soc.*, 1996, **118**, 3862–3868; (c) W. R. Bowman, C. F. Bridge and P. Brookes, Radical cyclisation onto nitriles, *Tetrahedron Lett.*, 2000, **41**, 8989–8994; (d) J. Jin and M. Newcomb, Rate constants and arrhenius functions for ring opening of a cyclobutylcarbinyl radical clock and for hydrogen atom transfer from the Et3B–t3Bical cloc, *J. Org. Chem.*, 2008, **73**, 4740–4742.
- 18 J.-W. Zhang, Y.-R. Wang, J.-H. Pan, Y.-H. He, W. Yu and B. Han, Deconstructive oxygenation of unstrained cycloalk-anamines, *Angew. Chem.*, 2020, **59**, 3900–3904.
- 19 For the representative works on N-containing heteroaryl migration via a cyclic amino radical intermediate, see: (a) X. Wu, M. Wang, L. Huan, D. Wang, J. Wang and C. Zhu, Tertiary-alcohol-directed functionalization of remote C(sp³)-H bonds by sequential hydrogen atom and heteroaryl migrations, *Angew. Chem., Int. Ed.*, 2018, **57**, 1640–1644; (b) J. Yu, Z. Wu and C. Zhu, Efficient docking–migration strategy for selective radical difluoromethylation of alkenes, *Angew. Chem., Int. Ed.*, 2018, **57**, 17156–17160; (c) M. Wang, Z. Wu, B. Zhang and C. Zhu, Azidoheteroarylation of unactivated olefins through distal heteroaryl migration, *Org. Chem. Front.*, 2018, **5**, 1896–1899; (d) D. Chen, Z. Wu, Y. Yao and C. Zhu, Phosphinoyl-functionalization of unactivated alkenes through phosphinoyl radical-triggered distal functional group migration, *Org. Chem. Front.*, 2018, **5**, 2370–2374; (e) H. Zhang, X. Wu, Q. Zhao and C. Zhu, Copper-catalyzed heteroarylsilylation of unactivated olefins through distal heteroaryl migration, *Chem. - Asian J.*, 2018, **13**, 2453–2457.