Deacylative transformations of ketones via aromatization-promoted C–C bond activation

Yan Xu¹, Xiaotian Qi², Pengfei Zheng¹,³, Carlo C. Bertí¹, Peng Liu²* & Guangbin Dong¹*

Carbon–hydrogen (C–H) and carbon–carbon (C–C) bonds are the main constituents of organic matter. Recent advances in C–H functionalization technology have vastly expanded our toolbox for organic synthesis¹. By contrast, C–C activation methods that enable editing of the molecular skeleton remain limited²–⁷. Several methods have been proposed for catalytic C–C activation, particularly with ketone substrates, that are typically promoted by using either ring-strain release as a thermodynamic driving force⁶,⁷ or directing groups⁵,⁷ to control the reaction outcome. Although effective, these strategies require substrates that contain highly strained ketones or a preinstalled directing group, or are limited to more specialist substrate classes⁵. Here we report a general C–C activation mode driven by aromatization of a pre-aromatic intermediate formed in situ. This reaction is suitable for various ketone substrates, is catalysed by an iridium/phosphine combination and is promoted by a hydrazine reagent and 1,3-dienes. Specifically, the acyl group is removed from the ketone and transformed to a pyrazole, and the resulting alkyl fragment undergoes various transformations. These include the deacetylation of methyl ketones, carbenoid-free formal homologation of aliphatic linear ketones and deconstructive pyrazole synthesis from cyclic ketones. Given that ketones are prevalent in feedstock chemicals, natural products and pharmaceuticals, these transformations could offer strategic disconnections in the synthesis of complex bioactive molecules.

Aromaticity is known to be an important thermodynamic driving force⁸ for various synthetic and enzymatic transformations. For example, in the biosynthesis of oestrogens, aromatase converts testosterone to oestradiol through a multi-step oxidative C–C cleavage process⁹. The formation of aromatic compounds has also been known to promote transition-metal-mediated C–C activation since 1972¹⁰, however, this has been largely underappreciated, with only a few examples of relevant studies¹⁰–¹⁴ (Fig. 1a). These reactions use a pre-aromatic substrate to complex with a low-valent transition metal, and subsequent C–C cleavage leads to stable arene–metal species, such as Cp–metal complexes (Cp, cyclopentadienyl)¹⁰,¹¹,¹⁴. However, to use such an approach for catalytic synthetic applications, several challenges remain. First, special high-energy pre-aromatic substrates—for example, cyclopentadienes—are generally needed; therefore, it is a concern whether readily available compounds can be used as substrates. In addition, the aromatic products generated in this reaction typically coordinate strongly with metals; thus, enabling catalyst turnover could be an important issue¹⁰–¹²,¹⁴.

Moreover, given the narrow reaction scope, developing attractive and synthetically valuable transformations with aromatization-driven C–C activation represents another difficulty.

In contrast to the less-accessible carbocyclic pre-aromatics, several heterocycles prepared from readily available chemicals through 1,3-dipolar addition¹⁵ could potentially serve as precursors to form heteroarenes. We found that such a pre-aromatized heterocycle could serve as the key intermediate for aromatization-promoted C–C activation, thereby enabling deacylative transformations of common ketones (Fig. 1b). This reaction probably involves a three-component coupling of a ketone, a 1,3-diene and a substituted hydrazine to generate a dihydropyrazole intermediate (Int II) that subsequently undergoes C–C cleavage to form a pyrazole¹⁶,¹⁷ and an activated alkyl species (for example, an alkyl–Ir intermediate).

¹Department of Chemistry, University of Chicago, Chicago, IL, USA. ²Department of Chemistry, University of Pittsburgh, Pittsburgh, PA, USA. ³College of Pharmacy, Army Medical University, Chongqing, China. *e-mail: pengliu@pitt.edu; gbdong@uchicago.edu
The initial reaction mode was discovered during our exploration of rhodium-catalysed β-C–H functionalization of ketones with 1,3-buta
diene\(^\text{18}\), which unexpectedly yielded a small amount of pyrazoles (about 5%) as a side product. This reaction was further optimized using 12-phenyloxydodecan-2-one (1) as the model substrate, and iridium was found to be more reactive than rhodium (see Supplementary Information, section 3.1). After a systematic survey of reaction parameters, the ketone substrate, upon treatment with 4-methyl-2-pyridyl
hydrazine and 1,3-butadiene in toluene, underwent efficient α-C–C bond cleavage using cationic [Ir(cod)]\(2\)BArF (BArF, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; ref. \(^\text{19}\)) and 1,1-bis(diphenylphosphino)ethylen as the optimal metal/ligand combination (Fig. 2a). Pyrazole 3 was formed in 79% yield, along with deacetylation product 2 in 70% yield, as the two major products. A
minor deacylative crotylation product (2') was also observed in 9% yield, \(^\text{2} \) which arises from coupling of the alkyl fragment with 1,3-butadiene. Deacetylation of methyl ketones \(^\text{1} \) was isolated in 5% yield, which indicated site selectivity greater than 15:1 in the C–C activation step. The general trend of site selectivity in the C–C cleavage process was then examined (Fig. 2b), and the results indicated that the bond scission preferentially occurred at more substituted carbons \(^\text{20} \) or those that were \(\alpha\) to heteroatoms.

\[\text{PhCH}_2\text{Ph} \quad \text{85%} \quad \text{Me} \quad \text{65%} \quad \text{Me} \]

\[\text{Me} \quad \text{84%} \quad \text{Me} \quad \text{66%} \quad \text{Me} \]

**Fig. 2** Iridium-catalysed cleavage of unstrained ketones. a, Optimized model reaction using linear ketone 1. b, Site selectivity of this reaction. c, Deacetylation of methyl ketones. Ts, p-toluenesulfonyl; Cy, cyclohexyl; \(p\)-tol, \(p\)-tolyl; \(e.e\), enantiomeric excess; \(r.r\), regioisomeric ratio. *The reactions were conducted with 0.05 mmol 1, 0.052 mmol 4-methyl-2-(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; ref. \(^\text{19}\)) and 0.055 mmol 1,4-dioxane, 90 °C then 170 μl (20 wt% in PhMe) 3 Å molecular sieves, 160 °C for 4 days.

| Entry | \(\text{R}^1\) | \(\text{R}^2\) | A:B | Yield (\(\text{A}+\text{B}\)) |
|-------|----------------|----------------|------|-------------------------|
| 1     | Me             | Et             | 15:1 | 82%                     |
| 2     | Me             | \(c\text{-C}_2\text{H}_5\) | >20:1 | 70%                     |
| 3     | Me             | Cy             | >20:1 | 80%                     |
| 4     | Me             | \(\text{CH}_2\text{OMe}\) | >20:1 | 85%                     |
| 5     | Et             | \(n\text{-C}_2\text{H}_5\) | 1:1   | 84%                     |
| 6     | Et             | \(\text{CF}_3\) | 1:3   | 66%                     |

\[\text{PhCH}_2\text{Ph} \quad \text{85%} \quad \text{Me} \quad \text{65%} \quad \text{Me} \]

\[\text{Me} \quad \text{84%} \quad \text{Me} \quad \text{66%} \quad \text{Me} \]
Homologation of methyl ketones

Encouraged by the excellent site selectivity obtained with methyl ketones, we foresaw an opportunity to realize a redox-neutral approach to remove an acyl (particularly an acetyl) moiety from a linear ketone (Fig. 2c). The Tsuji–Wilkinson decarbonylation of aldehydes has frequently been used in natural product synthesis\(^\text{21}\), and recently a de-hydroformylation approach was reported to access unsaturated one-carbon homologation selectively at the non-methyl site of the ketone. Bpin, (pinacolato)boryl; AIBN, azobisisobutyronitrile; Bn, benzyl; Tc, thiophene-2-carboxylate; d.r., diastereometric ratio. All yields are isolated yields. aUsing the pre-formed hydrazone as the substrate. b The reaction was conducted at 170 °C. For detailed experimental procedures, see Supplementary Information.

Fig. 3 | Decyclative C–C forming reactions of linear ketones.

a, Formal ‘1,2-oxo-migration’. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, an aldehyde with a carbon chain of the same length is afforded. b, Carbenoid-free homologation of aliphatic linear ketones. With additional 2,3-dimethyl-1,3-butadiene followed by ozonolysis, the sequence offers formal 1,2-oxo-migration. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal ‘1,2-oxo-migration’ . After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal ‘1,2-oxo-migration’. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal 1,2-oxo-migration. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal 1,2-oxo-migration. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal 1,2-oxo-migration. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal 1,2-oxo-migration. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal 1,2-oxo-migration. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, formal 1,2-oxo-migration.
products\textsuperscript{22}. Hence, the related deacetylation with readily accessible methyl ketones is also expected to be synthetically valuable from a strategic viewpoint. The scope of this transformation was first explored with various structurally diverse methyl ketones. Indeed, deacetylation took place smoothly with protonation at primary or cyclic secondary positions. Notably, when two ketone carbonyl groups were present in the substrate, the C–C cleavage occurred selectively at the methyl ketone moiety (16). In addition, functional groups, such as primary sulfonamides (12), and heteroarenes, such as protected indole (20) and purine (22), were found to be compatible. This approach also holds promise for post-modification of bioactive compounds. For example, anti-inflammatory drugs—such as pentoxifylline (21) and nabumetone (23)—underwent facile C–C cleavage to generate deacetylated analogues. Furthermore, tert-amlyation of arenes is nontrivial via direct cross-coupling approaches\textsuperscript{21}, but it can be realized through first coupling of 4-phenylphenyboronic acid with 5-methylhex-4-en-2-ol using Sigman’s reox–relay oxidative Heck reaction\textsuperscript{24} followed by this deacetylation protocol. Finally, enantioselective construction of hydrocarbon quaternary stereocentres that lack nearby polar functional groups\textsuperscript{25} (28) was also achieved using a similar strategy\textsuperscript{24}.

Besides simple C–H formation, the cleaved alkyl fragment could also be trapped by 1,3-butadiene to give C-allylation products\textsuperscript{26,27} (Fig. 2a, compound 2'). The efficiency of the C-allylation products could be considerably improved by using excess 1,3-butadiene at a lower reaction temperature, and high conversion was obtained with L2 as the ligand. Upon facile ozonolysis, a formal ‘1,2-oxo-migration’—relocating the carbonyl moiety from the internal to the terminal position—was realized, providing the corresponding aldehydes in good yields (Fig. 3a). Ketones containing α (33, 38, 40) and/or β stereocentres (31, 40) could be tolerated. The transformation was not limited to methyl ketones. In particular, selective cleavage and coupling at the cyclo pentyl site (versus the ethyl site) in ketone 38 was achieved. Gratifyingly, a steroid natural product, 2H-pregnenolone (40), was also a competent substrate; the corresponding aldehyde product (41) would be non-trivial to prepare via conventional approaches.

Fig. 4 | Deconstructive pyrazole synthesis from ketones. a, Representative substrate scope. b, Further studies on pyrydyl group removal and larger-scale synthesis. Boc, tert-butoxycarbonyl; r.t., room temperature. All yields are isolated yields. *Yields refer to the key C–C activation reaction using pre-formed hydrazones as the substrates. See Extended Data Figs. 1, 2 for additional substrate scope and Supplementary Information for detailed experimental procedures.
The initial N–H oxidative addition gave rise to a mixture of Ir(III) hydride isomers (157 and 159), in which the exocyclic C–C bond of the dihydropyrazole was considerably weakened (bond dissociation energy of 39.0 kcal mol$^{-1}$ and 36.5 kcal mol$^{-1}$ for 157 and 159, respectively).

From 159, the homolytic C–C cleavage (160-TS; Gibbs energy of activation $\Delta G^\ddagger = 29.5$ kcal mol$^{-1}$ with respect to 159) yielded a transient Ir(II) species (161) and an alkyl radical, which then rapidly recombined to form 162. The computed NICS(1)$_z$ aromaticity index values revealed a substantial increase in the aromaticity of the five-membered ring that stabilizes 160-TS. As a comparison, without the driving force of aromatization, the corresponding C–C cleavage of pyrazolidine 165 requires a much higher barrier (Extended Data Fig. 3b). From 162, an alkane and the pyrazole product 3 are formed via C–H reductive elimination and subsequent ligand exchange. With understanding of the reaction mechanism, future work will focus on enhancing the reaction efficiency and discovering new transformations or applications based on this C–C activation mode.

Online content
Any methods, additional references, Nature Research reporting summaries, source data, statements of data availability and associated accession codes are available at https://doi.org/10.1038/s41586-019-0926-8.

Received: 27 August 2018; Accepted: 22 January 2019; Published online 30 January 2019.

1. Karimov, R. R. & Hartwig, J. F. Transition-metal-catalyzed selective functionalization of C(sp$^3$)-H bonds in natural products. Angew. Chem. Int. Ed. 57, 4234–4241 (2018).
2. Murakami, M. & Ito, Y. Cleavage of carbon–carbon single bonds by transition metals. Top. Organomet. Chem. 3, 97–129 (1999).
3. Chen, F., Wang, T. & Jiao, N. Recent advances in transition-metal-catalyzed functionalization of unstrained carbon–carbon bonds. Chem. Rev. 114, 8613–8661 (2014).
4. Souliart, L. & Cramer, N. Catalytic C–C bond activations via oxidative addition to transition metals. Chem. Rev. 115, 9410–9464 (2015).
5. Kim, D.-S., Park, W.-J. & Jun, C.-H. Metal–organic cooperative catalysis in C–H and C–C bond activation. Chem. Rev. 117, 8977–9015 (2017).
6. Fumagalli, G., Stanton, S. & Bower, J. F. Recent methodologies that exploit C–C single-bond cleavage of strained ring systems by transition metal complexes. Chem. Rev. 117, 9404–9432 (2017).
7. Dresi, A. & Douglas, C. in C–C Bond Activation (ed. Dong, G.) 85–110 (Springer, Berlin, 2014).
8. Schleyer, P. V. R. & Pühlhofer, F. Recommendations for the evaluation of aromatic stabilization energies. Org. Lett. 4, 2873–2876 (2002).
9. Santen, R. J., Brodie, H., Simpson, E. R., Siiteri, P. K. & Brodie, A. History of aromatase: saga of an important metabolic mediator and therapeutic target. Endocr. Rev. 30, 343–375 (2009).
10. King, R. B. & Efraty, A. Pentamethylcyclopentadienyl derivatives of transition metals. II. Synthesis of pentamethylcyclopentadienyl metal carbonyls from 5-acetyl-1,2,3,4,5-pentamethylcyclopentadiene. J. Am. Chem. Soc. 94, 3773–3779 (1972).
11. Crabtree, R. H., Dion, R. F., Gibbons, D. J., Mgrath, D. V. & Holt, E. M. Carbon–carbon bond cleavage in hydrocarbons by iridium complexes. J. Am. Chem. Soc. 108, 7222–7227 (1986).
12. Halcrow, M. A., Urbanos, F. & Chaudret, B. Aromatization of the B-ring of 5,7-dienyl steroids by the electrophilic ruthenium fragment “[CrP=]”. Organometallics 12, 955–957 (1993).
13. Youn, S. W., Kim, B. S. & Jagdale, A. R. Pf-catalyzed sequential C–C bond formation and cleavage: evidence for an unexpected generation of aryllipodium(l) species. J. Am. Chem. Soc. 133, 11308–11311 (2012).
14. Smits, G., Audic, B., Wodrich, M. D., Corminboeuf, C. & Cramer, N. A. Carbon elimination strategy for convenient in situ access to cyclopentadienyl metal complexes. Chem. Sci. 8, 7174–7179 (2017).
15. Padwa, A. & Pearson, W. H. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products (John Wiley & Sons, New York, 2003).
16. Le Fevre, G. & Hamelin, J. Existence d’une forme N–H stable de pyrazoline-4 lors de l’aromatisation de pyrazolines 3,3-disubstituées en position $\alpha$. C. R. Hebdo. Seances Acad. Sci. Ser. C 274, 821–823 (1972).
17. Youn, S. W., Kim, B. S. & Jagdale, A. R. Pf-catalyzed sequential C–C bond formation and cleavage: evidence for an unexpected generation of aryllipodium(l) species. J. Am. Chem. Soc. 133, 11308–11311 (2012).
18. Smiths, G., Audic, B., Wodrich, M. D., Corminboeuf, C. & Cramer, N. A. Carbon elimination strategy for convenient in situ access to cyclopentadienyl metal complexes. Chem. Sci. 8, 7174–7179 (2017).
19. Padwa, A. & Pearson, W. H. Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products (John Wiley & Sons, New York, 2003).
20. Le Fevre, G. & Hamelin, J. Existence d’une forme N–H stable de pyrazoline-4 lors de l’aromatisation de pyrazolines 3,3-disubstituées en pyrazole. Mécanisme de la réaction. Tetrahedron Lett. 19, 4503–4506 (1978).
21. Tian, M., Shi, X., Zhang, X. & Fan, X. Synthesis of 4-acylpyrroles from saturated ketones and hydrazones featured with multiple C(sp$^3$)-H bond functionalization and C–C bond cleavage and reorganization. J. Org. Chem. 82, 7363–7372 (2017).
22. Xu, Y., Young, M. C. & Dong, G. Catalytic coupling between unactivated aliphatic C–C bonds and alkynes via a metal–hydride pathway. J. Am. Chem. Soc. 139, 5716–5719 (2017).
23. Pan, S. & Shibata, T. Recent advances in iridium-catalyzed allylation of C–H and N–H bonds. ACS Catal. 3, 704–712 (2013).
20. Xia, Y., Lu, G., Liu, P. & Dong, G. Catalytic activation of carbon–carbon bonds in
cyclopentanones. Nature 539, 546–550 (2016).
21. Tsuji, J. & Ohno, K. Organic syntheses by means of noble metal compounds XXI. Decarbonylation of aldehydes using rhodium complex. Tetrahedron Lett. 6, 3969–3971 (1965).
22. Murphy, S. K., Park, J.-W., Cruz, F. A. & Dong, V. M. Rh-catalyzed C–C bond cleavage by transfer hydroformylation. Science 347, 56–60 (2015).
23. Zultanski, S. L. & Fu, G. C. Nickel-catalyzed carbon–carbon bond-forming reactions of unactivated tertiary alkyl halides: Suzuki arylations. J. Am. Chem. Soc. 135, 624–627 (2013).
24. Mei, T.-S., Patel, H. H. & Sigman, M. S. Enantioselective construction of remote quaternary stereocentres. Nature 508, 340–344 (2014).
25. Fessard, T. E. C., Andrews, S. P., Motoyoshi, H. & Carreira, E. M. Enantioselective preparation of 1,1-diarylethan-1-ones: aldehydes as removable steering groups for asymmetric synthesis. Angew. Chem. Int. Ed. 46, 9331–9334 (2007).
26. Chu, L., Ohto, C., Zuo, Z. & Macmillan, D. W. C. Carboxylic acids as a traceless activation group for conjugate additions: a three-step synthesis of (−)-pregabalin. J. Am. Chem. Soc. 136, 10886–10889 (2014).
27. Qin, T. et al. Nickel-catalyzed Barton decarboxylation and Giese reactions: a practical take on classic transforms. Angew. Chem. Int. Ed. 56, 260–265 (2017).
28. Canedeas, N. R., Paterna, R. & Gois, P. M. P. Homologation reaction of ketones with diazo compounds. Chem. Rev. 116, 2937–2981 (2016).
29. Karrouchi, K. et al. Synthesis and pharmacological activities of pyrazole derivatives: a review. Molecules 23, 134 (2018).
30. Hong, X. et al. Mechanism and selectivity of N-triflylphosphoramidate catalyzed (3+2) cycloaddition between hydrazones and alkenes. J. Am. Chem. Soc. 136, 13769–13780 (2014).

Acknowledgements This project was supported by NIGMS (RO1GM109054). Y.X. acknowledges financial support from a Charles H. Viol Fellowship and a William Rainey Harper Dissertation Fellowship from the University of Chicago and a Bristol-Myers Squibb Graduate Fellowship. P.Z. acknowledges a Joint PhD Student Scholarship 2016 from China Scholarship Council (file number 201603170182). PL thanks the NSF (CHE-1654122) for funding. Calculations were performed at the Center for Research Computing at the University of Pittsburgh. L. Deng is acknowledged for the donation of substrate 140. J. Zhu is acknowledged for conducting several control experiments.

Reviewer information Nature thanks Vy Maria Dong and the other anonymous reviewer(s) for their contribution to the peer review of this work.

Author contributions Y.X. discovered the reaction, Y.X., P.Z., C.C.B. and G.D. conceived and conducted the experimental investigation. X.Q. and PL. designed and conducted the density functional theory calculations. Y.X., X.Q., P.L. and G.D. wrote the manuscript. P.L. and G.D. directed the research.

Competing interests The authors declare no competing interests.
METHODS
General procedure for the deacetylation of methyl ketones. For a 0.05-mmol-scale reaction, a 1,4-dioxane (1 ml) solution of the ketone substrate (0.05 mmol, 1.0 equiv.), 2-hydrazinyl-4-methylpyridine (6.4 mg, 0.052 mmol, 1.04 equiv.) and p-TsOH·H₂O (stock solution in 1,4-dioxane; 0.05 M, 3.0 µl, 0.003 equiv.) was heated at 90 °C for 5 h under N₂ atmosphere in an 8-ml vial. After cooling to room temperature, the vial was charged first with [Ir(cod)]₂[BARF (6.4 mg, 0.005 mmol, 0.1 equiv.) and L1 (2.0 mg, 0.005 mmol, 0.1 equiv.) under air atmosphere, and then with 3 Å molecular sieves (pre-dried, 100 mg) and 1,3-butadiene (20 wt% in PhMe, 170 µl, about 10 equiv.) in a glovebox. The vial was sealed and heated at 160 °C while stirring for 72 h. After cooling to room temperature, the reaction mixture was filtered through Celite, concentrated under reduced pressure and further purified by flash column chromatography over silica to give the products. General procedures for the formal homologation of linear ketones and deconstructive pyrazole synthesis from cyclic ketones, together with full experimental details and characterization of new compounds, can be found in Supplementary Information.

Data availability
The data supporting the findings of this study are available within the article and its Supplementary Information. Additional data are available from the corresponding authors upon request. Metrical parameters for the structure of 123 are available free of charge from the Cambridge Crystallographic Data Centre (https://www.ccdc.cam.ac.uk/) under reference number CCDC 1876535.
Extended Data Fig. 1 | Additional substrate scope for deconstructive pyrazole synthesis from ketones. Ac, acetyl. MS, molecular sieves. *All yields are isolated yields. aThe yield refers to the key C–C activation reaction using pre-formed hydrazone as the substrate. For detailed experimental procedures, see Supplementary Information.
Extended Data Fig. 2 | Introducing pyrazoles into complex ketones via C–C cleavage. All yields are isolated yields. The yield refers to the key C–C activation reaction using pre-formed hydrazone as the substrate.

15 mol% Ir catalyst and 15 mol% L1 were used. For detailed experimental procedures, see Supplementary Information.
Extended Data Fig. 3 | Computational studies of the aromatization-driven C–C bond activation. a, Free-energy profiles of the aromatization-driven C–C bond activation of dihydropyrazole 165. Calculations were performed at the M06-L/6-311+G(d,p)–SDD/SMD(1,4-dioxane)/B3LYP/6-31G(d)–SDD level of theory. The less favourable β-C elimination pathways with and without pyridine coordination (168-TS and 167-TS, respectively) are shown in blue. The NICS(1)zz aromaticity index was calculated at the B3LYP/6-311+G(d,p)–SDD level of theory to describe the aromaticity of the pyrazole ring (highlighted in green) in 159, 160-TS and 161. The variation of NICS(1)zz indicates a substantial increase in aromaticity during the homolytic C–C bond cleavage. ΔG, change in Gibbs free energy; ΔH, change in enthalpy. b, Comparison between homolytic C–C bond cleavage of dihydropyrazole 165 and pyrazolidine 165ʹ (165ʹ without the driving force of aromatization). See Supplementary Information section 3.2.2 for details.