LETTER

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

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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 synthesis[1]. By contrast, C–C activation methods that enable editing of the molecular skeleton remain limited[2–7]. 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 force[4,6] or directing groups[5,7] 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 classes[5]. 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 bond disconnections in the synthesis of complex bioactive molecules.

Aromaticity is known to be an important thermodynamic driving force[8] 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 process[9]. The formation of aromatic compounds has also been known to promote transition-metal-mediated C–C activation since 1972[10]; however, this has been largely underappreciated, with only a few examples of relevant studies[10–14] (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 issue[10–12,14]. 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 addition[15] 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 pyrazole[16,17] and an activated alkyl species (for example, an alkyl–Ir intermediate).

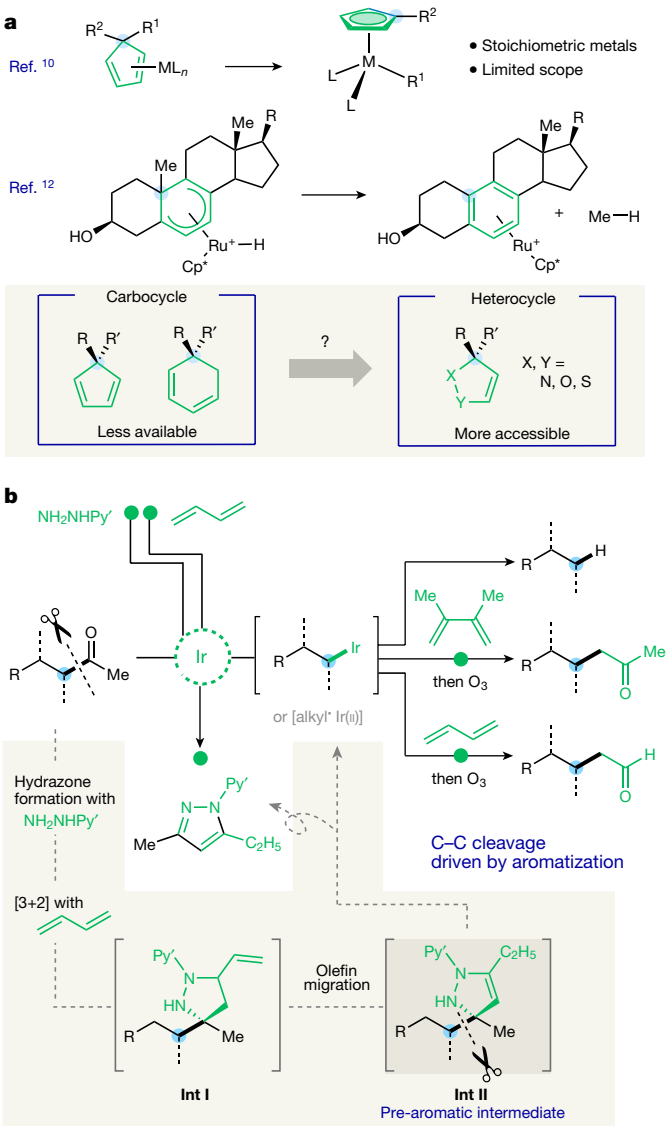

Fig. 1 | C–C activation driven by aromatization. a, Known examples of transition-metal-mediated C–C cleavage driven by aromatization[10,12]. **b**, Catalytic deacylative transformations of common unstrained ketones observed in this work. M, transition metal; Cp*, pentamethylcyclopentadienyl; Py′, 4-methyl-2-pyridyl.

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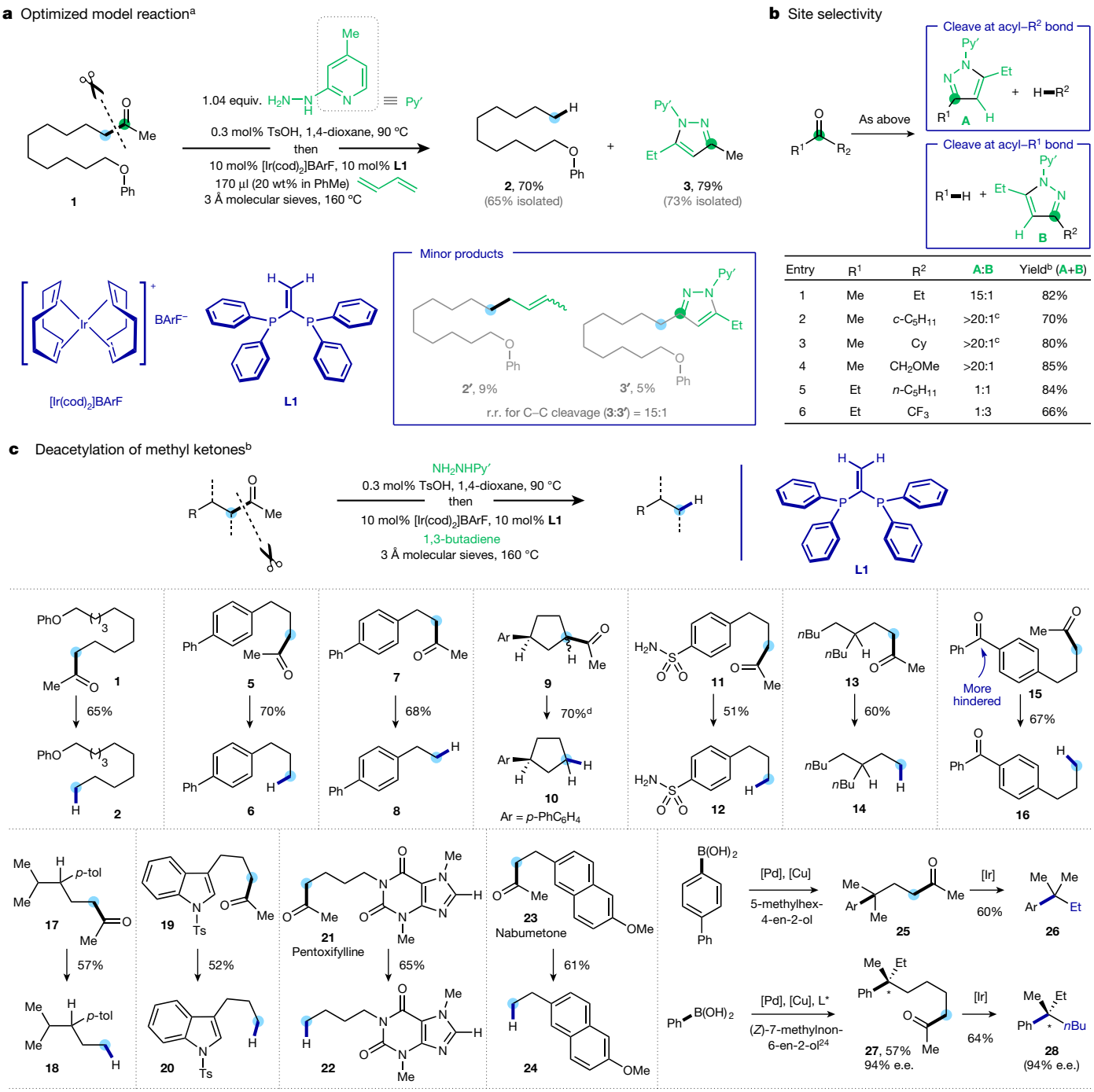

Fig. 2 | Iridium-catalysed cleavage of unstrained ketones. a, Optimized model reaction using linear ketone **1**. **b**, Site selectivity of this reaction. **c**, Deacetylation of methyl ketones. Ts, *p*-toluenesulfonyl; Cy, cyclohexyl; *p*-tol, *p*-tolyl; e.e., enantiomeric excess; r.r., regioisomeric ratio. [a]The reactions were conducted with 0.05 mmol **1**, 0.052 mmol 4-methyl-2-pyridyl hydrazine and 0.5 mmol 1,3-butadiene. [b]Isolated yield. [c]The reaction was conducted using (2-(4-methoxyphenyl)ethene-1,1-diyl) bis(diphenylphosphane) (**L2**) instead of **L1** as the ligand. [d]Using the pre-formed hydrazone as the substrate. For detailed experimental procedures, see Supplementary Information.

The initial reaction mode was discovered during our exploration of rhodium-catalysed β-C–H functionalization of ketones with 1,3-butadiene[18], which unexpectedly yielded a small amount of pyrazoles (about 5%) as a side product. This reaction was further optimized using 12-phenoxydodecan-2-one (**1**) as the model substrate, and iridium 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. [19]) and 1,1-bis(diphenylphosphino)ethylene 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, which arises from coupling of the alkyl fragment with 1,3-butadiene. Resulting from cleavage at the alternative methyl side, compound **3′** 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[20] or those that were α to heteroatoms.

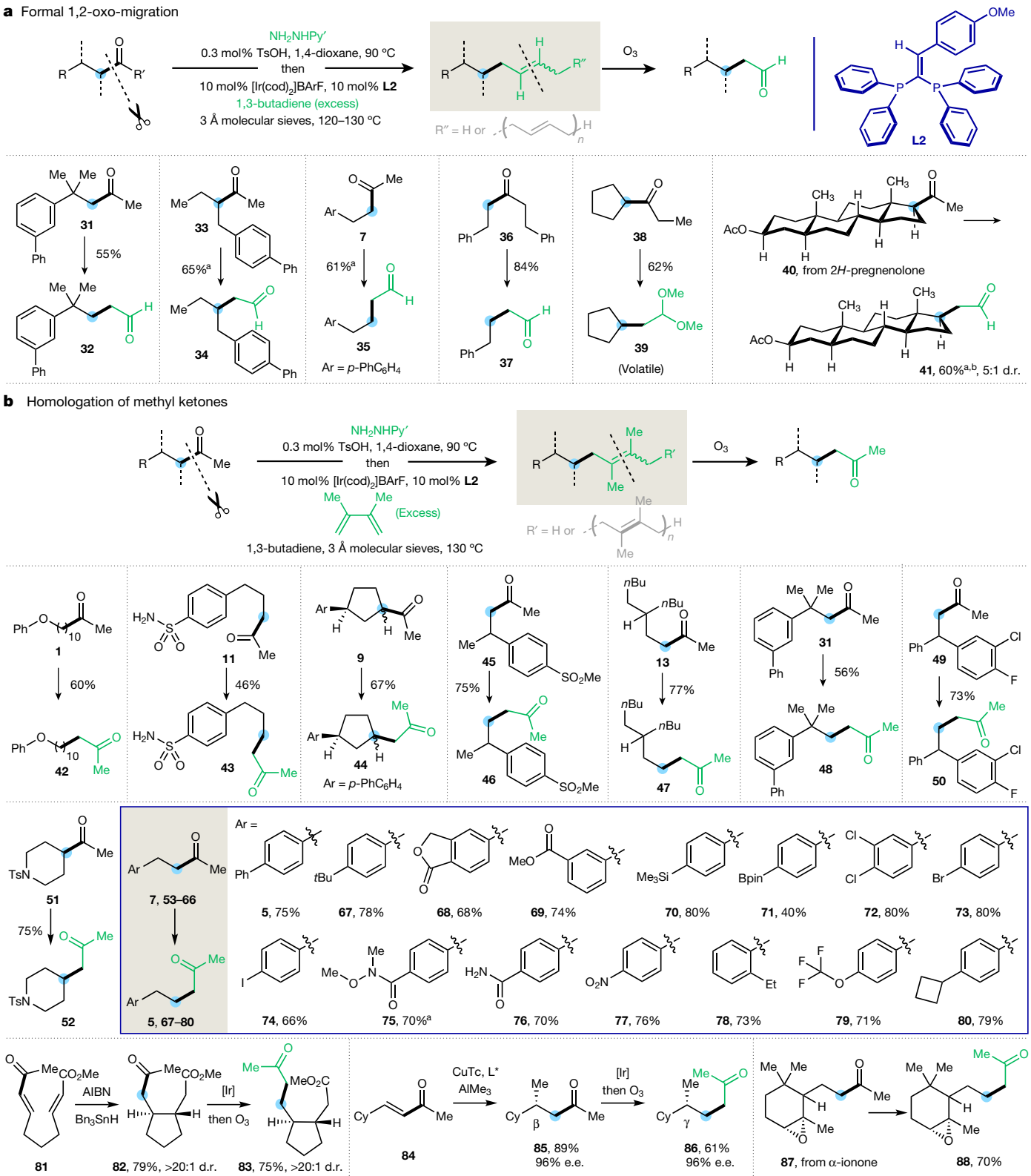

Fig. 3 | Deacylative C–C forming reactions of linear ketones. **a**, Formal '1,2-oxo-migration'. After C–C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, an aldehyde with a carbon chain of the same length is afforded. **b**, Carbenoid-free homologation of aliphatic linear ketones. With additional 2,3-dimethyl-1,3-butadiene followed by ozonolysis, the sequence offers formal 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. [a]Using the pre-formed hydrazone as the substrate. [b]The reaction was conducted at 170 °C. For detailed experimental procedures, see Supplementary Information.

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[21], and recently a de-hydroformylation approach was reported to access unsaturated

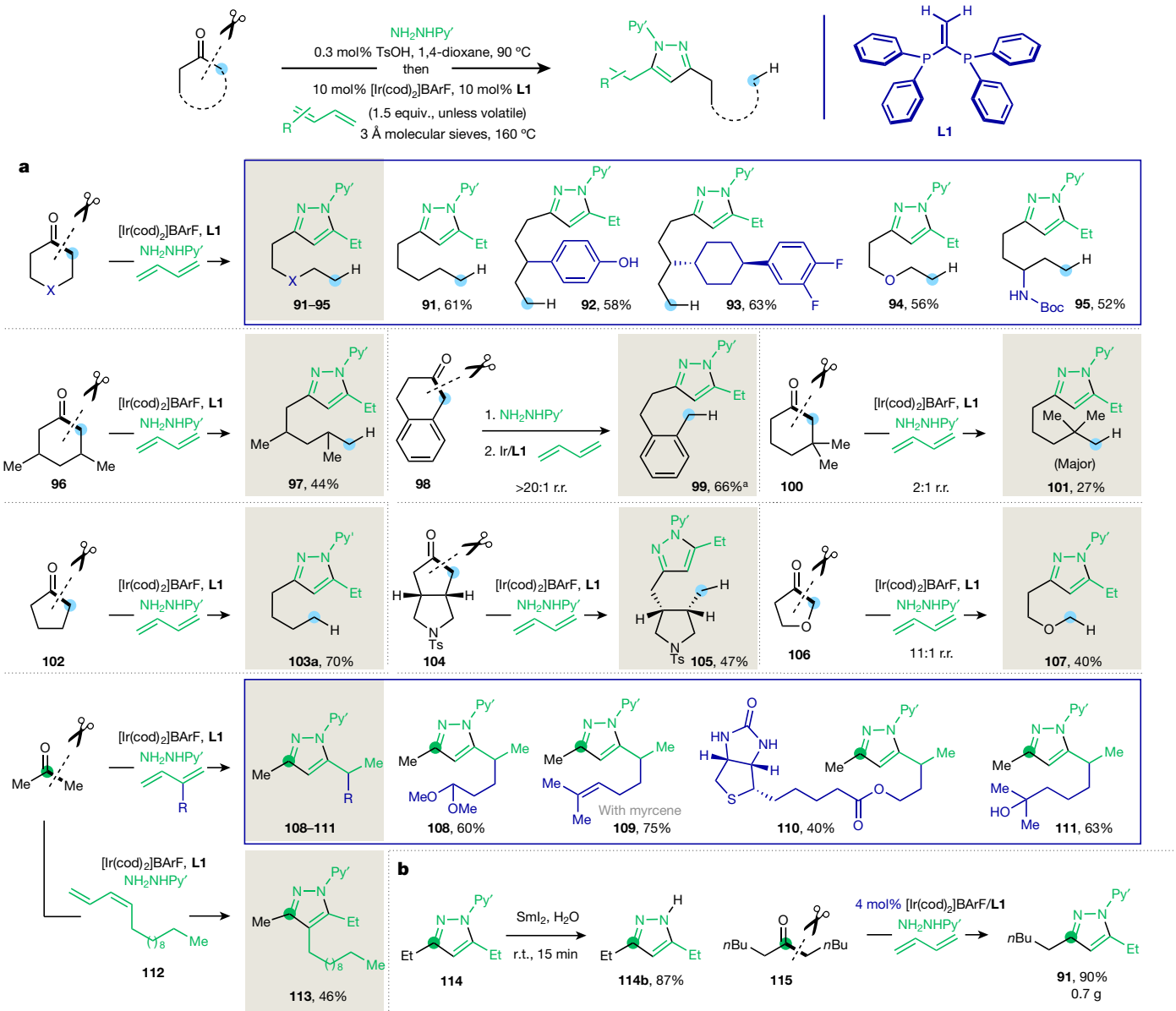

Fig. 4 | Deconstructive pyrazole synthesis from ketones. **a**, Representative substrate scope. **b**, Further studies on pyridyl group removal and larger-scale synthesis. Boc, *tert*-butoxycarbonyl; r.t., room temperature. All yields are isolated yields. [a]Yields refer to the key C–C activation reaction using pre-formed hydrazones as the substrates. See Extended Data Figs. 1, 2 for additional substrate scope and Supplementary Information for detailed experimental procedures.

products[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*-amylation of arenes is nontrivial via direct cross-coupling approaches[23], but it can be realized through first coupling of 4-phenylphenylboronic acid with 5-methylhex-4-en-2-ol using Sigman's redox–relay oxidative Heck reaction[24] followed by this deacetylation protocol. Finally, enantioselective construction of hydrocarbon quaternary stereocentres that lack nearby polar functional groups[25] (**28**) was also achieved using a similar strategy[24].

Besides simple C–H formation, the cleaved alkyl fragment could also be trapped by 1,3-butadiene to give C-allylation products[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 cyclopentyl site (versus the ethyl site) in ketone **38** was achieved. Gratifyingly, a steroid natural product, 2*H*-pregnenolone (**40**), was also a competent substrate; the corresponding aldehyde product (**41**) would be non-trivial to prepare via conventional approaches.

Notably, when the reaction was run in the presence of a second, bulkier 1,3-diene—such as 2,3-dimethyl-1,3-butadiene—the resulting C-allylation intermediate led to a formal one-carbon homologation product upon ozonolysis (Fig. 3b). Various ketones with different skeletons, including those with multiple substitutions at α and/or β positions, readily reacted and gave decent yields of the homologation products over two steps. Various functional groups—such as aryl iodides (**74**) and bromides (**73**), aryl boronic esters (**71**) and silanes (**70**), epoxides (**88**), esters (**69**, **83**), lactones (**68**), nitros (**77**), amides (**75**, **76**), sulfonamides (**43**, **52**) and sulfones (**46**)—were tolerated. The strained cyclobutane motif remained untouched (**80**). This formal-homologation approach also enabled the preparation of 1,7-ketoesters (**83**) and enantioselective synthesis of ketones with γ-stereocentres (**86**) from readily available precursors. Ketones derived from natural products, such as the one from α-ionone (**87**), could also be used as substrates. Compared with the classical carbenoid-mediated homologation[28], this method features high reactivity and excellent site- and chemoselectivity.

Conversely, when cyclic ketones were used as substrates, a redox-neutral deconstructive pyrazole synthesis method was realized[16,17] (Fig. 4, Extended Data Fig. 1). As a highly important class of pharmacophores, pyrazoles are commonly found in bioactive compounds and approved drugs[29]—for example celecoxib, rimonabant, fomepizole and sildenafil. Although many methods have been developed for pyrazole synthesis[29], it could still be attractive to devise a straightforward and oxidant-free approach to prepare complex functionalized pyrazoles from readily available ketones and 1,3-dienes. Under the conditions shown in Fig. 2c, various cyclic ketones with different substitutions and ring sizes were converted to the desired pyrazole products with rich structural diversity. Similarly, when using unsymmetrical ketones, C–C bonds at more substituted (**101**), benzylic (**99**, **127**–**129**) or α-to-heteroatom (**107**) positions were activated predominantly. We note that simple acetone is a suitable substrate, and a range of different dienes—such as 1,3-butadiene, isoprene, myrcene, 1,3-pentadecadiene and other functionalized 1,3-dienes—could be readily coupled. The transformation tolerates a broad range of functional groups. Moreover, the 2-pyridyl moiety can be readily removed using samarium(II) iodide and water, furnishing a free pyrazole product in high yield. Notably, catalyst loading could be reduced to 4 mol% on larger scales, where 0.7 g of product **91** was isolated in 90% yield (Fig. 4b). Compared with the classical pyrazole syntheses[29], this approach requires only a mono-ketone functional group to be used as a handle. Thus, it provides a simple and distinct strategy for the introduction of pyrazole moieties into complex natural products or biologically interesting scaffolds (Extended Data Fig. 2). In addition, simply by switching the 1,3-diene coupling partners, several structurally related and separable pyrazole-derived analogues could be rapidly made available in one step from a single natural product (**135** and **144**). These pyrazole products would be difficult to access via conventional approaches. Given the wide availability of mono-ketone moieties, this method could offer a useful tool for preparing new pyrazole-containing analogues for pharmaceutical or agrochemical research.

Preliminary mechanistic studies were performed (see Supplementary Information, section 3.2) to support the proposed reaction pathway depicted in Fig. 1b. First, the [3+2] cycloaddition adduct (**Int I**) between 1,3-butadiene and the hydrazone intermediate[30] could be isolated during the course of the reaction and was found to undergo C–C cleavage with efficiency and selectivity similar to those of the standard reaction (Supplementary Fig. 2).We propose that, upon olefin migration, the dihydropyrazole species (**Int II**)—which is one unsaturation degree less than that of an aromatic pyrazole structure—is the key intermediate for the following C–C activation. By contrast, no C–C cleavage was observed without the endocyclic double bond or the ring structure (Supplementary Fig. 2c). From **Int II**, an aromatization-promoted homolytic C–C cleavage/radical recombination mechanism was suggested by density functional theory calculations over other C–C activation pathways (Extended Data Fig. 3a, Supplementary Fig. 5). 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 $NICS(1)_{zz}$ 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.

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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 P.L. 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.

Additional information
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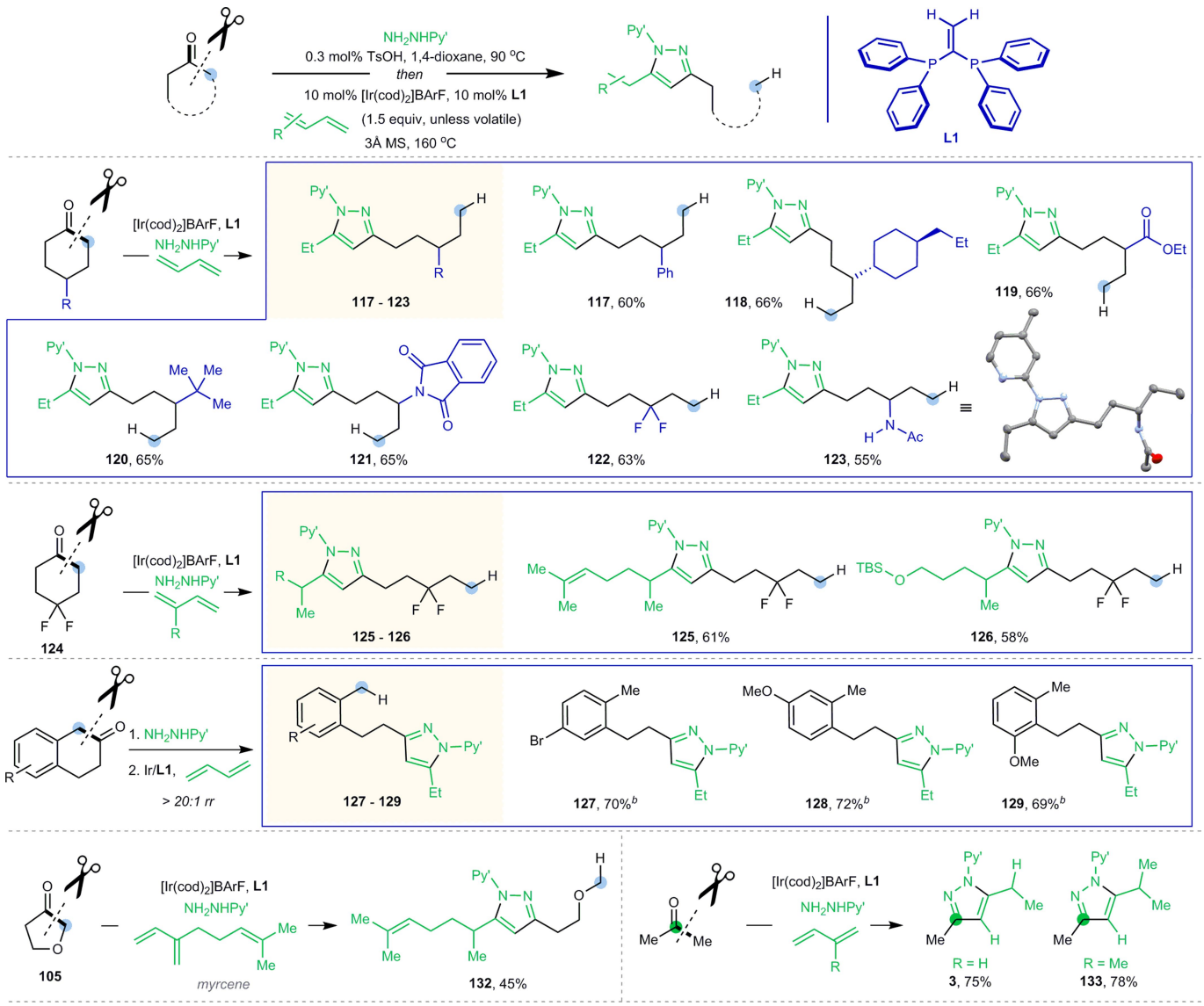
METHODS

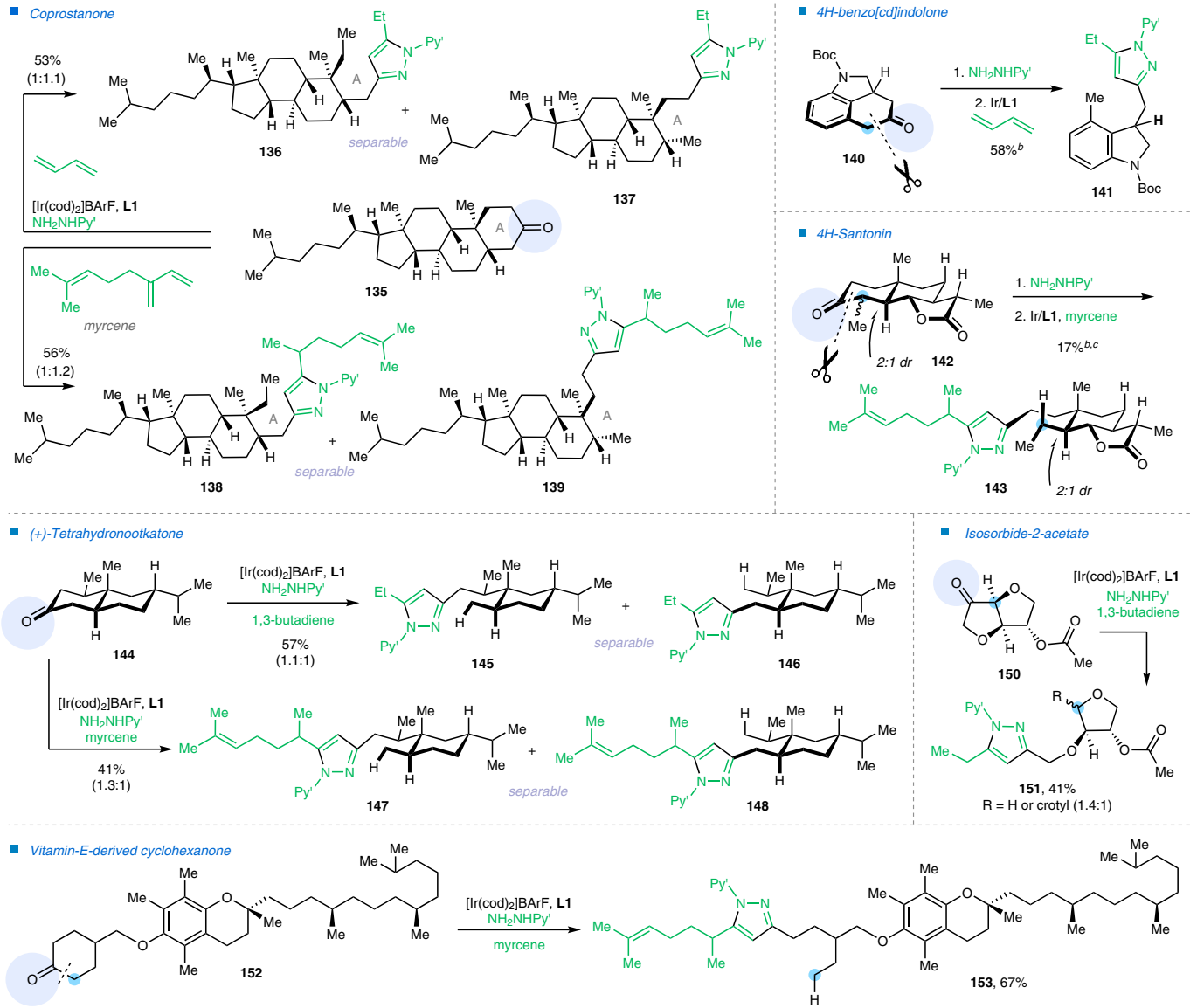
General procedure for the deacetylation of methyl ketones. For a 0.05-mmol-scale reaction, a 1,4-dioxane (1 ml) solution of the ketone substrate (0.05 mmol, 1.0 equiv.), 2-hydrazinyl-4-methylpyridine (6.4 mg, 0.052 mmol, 1.04 equiv.) and *p*-TsOH·H_2O (stock solution in 1,4-dioxane; 0.05 M, 3.0 μl, 0.003 equiv.) was heated at 90 °C for 5 h under N_2 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

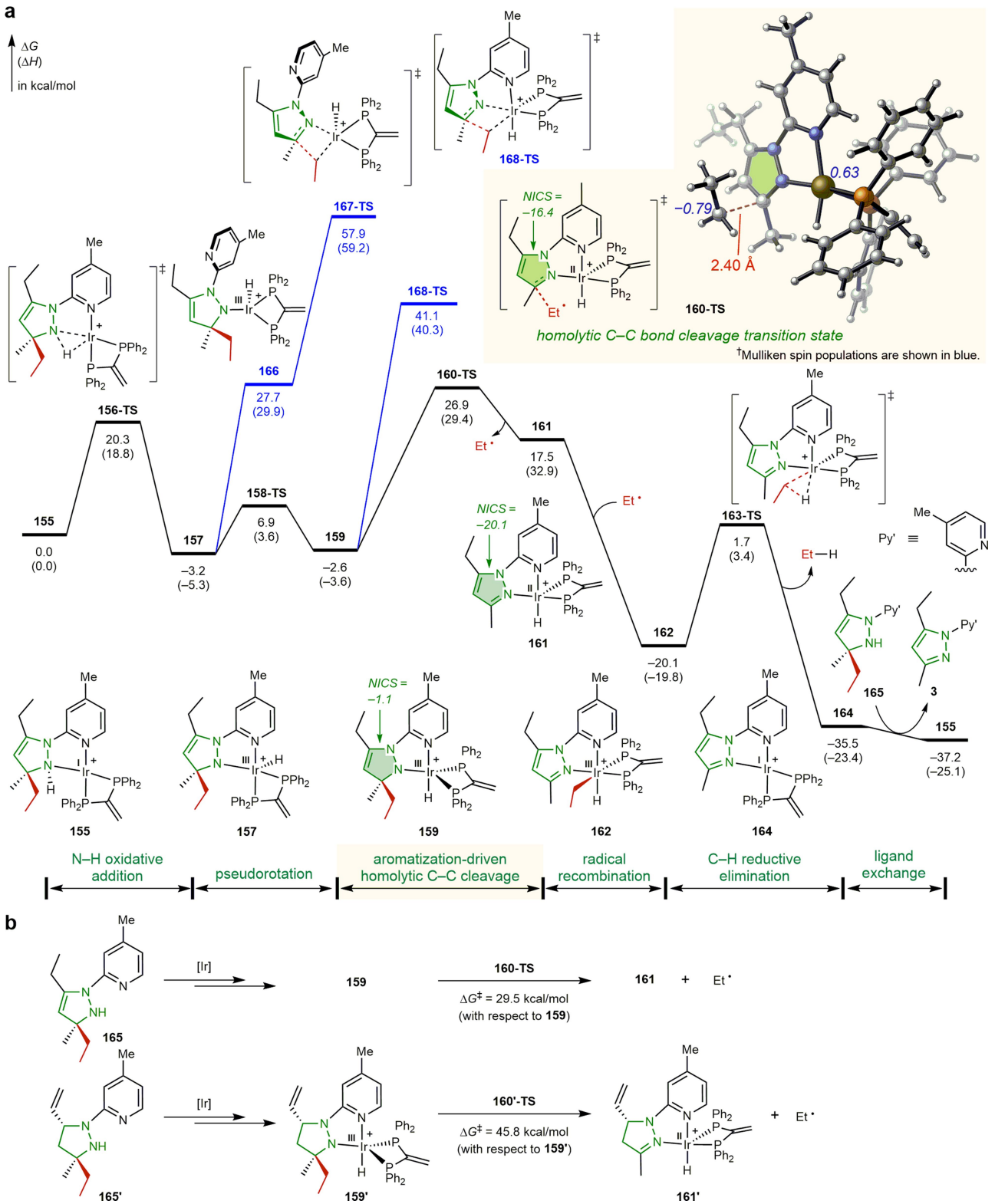
The data supporting the findings of this study are available within the article and its Supplementary Information. Additional data are available from the corresponding authors upon request. Metrical parameters for the structure of **123** are available free of charge from the Cambridge Crystallographic 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. [a]All yields are isolated yields. [b]The 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. [a]All yields are isolated yields. [b]The yield refers to the key C–C activation reaction using pre-formed hydrazone as the substrate. [c]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 **165′** (**165′** without the driving force of aromatization). See Supplementary Information section 3.2.2 for details.