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Deacylative Transformations of Ketones via Aromatization-Promoted C–C Bond Activation

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Abstract

Carbon–hydrogen (C–H) and carbon–carbon (C–C) bonds are the main constituents of organic matter. The recent advancement of C–H functionalization technology has vastly expanded our toolbox for organic synthesis¹. In contrast, C–C activation methods that allow for editing the molecular skeleton remain limited^{2–7}. To date, a number of methods have appeared for catalytic C–C activation, particularly with ketone substrates, which are typically promoted either by ring-strain release as a thermodynamic driving force^{4,6} or using directing groups^{5,7} (DGs) to control the reaction outcome. While effective, these strategies require highly strained ketone substrates or those containing a preinstalled DG, or are limited to more specialist substrate classes⁵. Here, we report a general C–C activation mode driven by aromatization of an *in situ*-formed pre-aromatic intermediate. This reaction suitable for various ketone substrates, is catalyzed 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, 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 new strategic bond disconnections in the synthesis of complex bioactive molecules.

Aromaticity has been known as an important thermodynamic driving force⁸ for various synthetic and enzymatic transformations. For example, in the biosynthesis of estrogens, aromatase converts testosterone to estradiol through a multi-step oxidative C–C cleavage process⁹. Forming aromatic compounds has also been known to promote the transition metal-mediated C–C activation since 1972¹⁰, which unfortunately has been largely underappreciated with only scattered examples^{10–14} (Fig. 1a). These reactions use a pre-

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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 DFT calculations. Y.X., X.Q., P.L. and G.D. wrote the manuscript. P.L. and G.D. directed the research. Reprints and permissions information is available at www.nature.com/reprints.

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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 utilize such an approach for catalytic synthetic applications, a number of challenges still exist. First, special high-energy pre-aromatic substrates, e.g. cyclopentadienes, are generally needed; thus, it is concerned that 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 a significant issue^{10–12,14}. Moreover, given the narrow reaction scope, developing attractive and synthetically valuable transformations with aromatization-driven C–C activation represent another difficulty.

In contrast to the less accessible carbocyclic pre-aromatics, a number of heterocycles, prepared from readily available chemicals through 1,3-dipolar addition¹⁵, could potentially serve as precursors to form heteroarenes. We found such a pre-aromatized heterocycle could serve as the key intermediate for the aromatization-promoted C–C activation, thereby enabling deacylative transformations of common ketones (Fig. 1b). This reaction likely 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 (e.g. an alkyl-Ir intermediate).

The initial reaction mode was discovered during our exploration of the Rh-catalyzed β -C–H functionalization of ketones with 1,3-butadiene¹⁸, in which a small amount of pyrazoles (ca. 5%) were surprisingly yielded as a side product. This reaction was further optimized using 12-phenoxydodecan-2-one (**1**) as the model substrate, and iridium was found 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]BARF¹⁹ 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 should come from coupling of the alkyl fragment with 1,3-butadiene. Resulted from cleavage at the alternative methyl side, compound **3'** was isolated in 5% yield, which indicated >15:1 site-selectivity 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 prefers to occur at more substituted²⁰ or α -to-heteroatom carbons.

Encouraged by the excellent site-selectivity with methyl ketones, we foresaw an opportunity of realizing a *redox-neutral* approach to remove an acyl (particularly an acetyl) moiety from a linear ketone (Fig. 2c). It is well known that the Tsuji–Wilkinson decarbonylation of aldehydes has been frequently employed in natural product synthesis,²¹ and recently a dehydroformylation approach was reported to access unsaturated products.²² Hence, the related *deacetylation* with readily accessible methyl ketones is also expected to be synthetically valuable from the strategic viewpoint. The scope of this transformation was first explored with various structurally diverse methyl ketones. Indeed, the deacetylation took place smoothly with protonation at primary or cyclic secondary positions. Notably,

when two ketone carbonyl groups are present in the substrate, the C–C cleavage occurred selectively at the methyl ketone moiety (**16**). In addition, functional groups (FGs), such as primary sulfonamides (**12**), and heteroarenes, such as protected indole (**20**) and purine (**22**), were found 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*-arylation of arenes is nontrivial *via* direct cross coupling approaches²³, 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 reaction²⁴ followed by this deacetylation protocol. Finally, enantioselective construction of hydrocarbon quaternary stereocenters that *lack nearby polar FGs*²⁵ (**28**) was also achieved using a similar strategy²⁴.

Besides the simple C–H formation, the cleaved alkyl fragment could also be trapped by 1,3-butadiene to give C-allylation products (*vide supra*, Fig. 2a, compound **2'**)^{26,27}. The efficiency of the C-allylation products could be significantly improved 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 stereocenters (**31**, **40**) could be tolerated. The transformation is 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, i.e. *2H-pregnenolone* (**40**), was also a competent substrate; the corresponding aldehyde product (**41**) would be non-trivial to prepare via conventional approaches.

Interestingly, when the reaction was run in the presence of a second but bulkier 1,3-diene, such as 2,3-dimethyl-1,3-butadiene, the resulting C-allylation intermediate, upon ozonolysis, led to a formal one-carbon homologation product (Fig. 3b). A variety of 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. A variety of FGs, 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 allows for preparation of 1,7-ketoesters (**83**) and enantioselective synthesis of ketones with γ -stereocenters (**86**) from readily available precursors. Natural product-derived ketones, such as the one from *α -ionone* (**87**), could also be used as substrates. Compared with the classical carbenoid-mediated homologation²⁸, this method features high reactivity, excellent site- and chemo-selectivity.

On the other hand, when *cyclic ketones* were employed as substrates, a redox-neutral deconstructive pyrazole-synthesis method was realized (Fig. 4 and Extended Data Fig. 1)^{16,17}. As a highly important class of pharmacophores, pyrazoles are commonly found in bioactive compounds and approved drugs²⁹, e.g. *Celecoxib*, *Rimonabant*, *Fomepizole* and *Sildenafil*. While many methods have been developed for pyrazole synthesis²⁹, 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 same

conditions shown in Fig. 2c, a variety of cyclic ketones with different substitutions and ring-sizes were converted to the desired pyrazole products that contain rich structural diversity. Similarly, when using unsymmetrical ketones, the C–C bonds at more substituted (**101**) or benzylic positions (**99**, **127–129**), or α to a heteroatom (**107**), were activated dominantly. Note that simple acetone is a suitable substrate, and a range of different dienes, such as 1,3-butadiene, *isoprene*, *myrcene*, 1,3-pentadiene and other functionalized 1,3-dienes, could be readily coupled. The transformation tolerates a broad range of FGs. Moreover, the 2-pyridyl moiety can be readily removed using SmI_2 and water, furnishing a free pyrazole product in a high yield. Importantly, the catalyst loading could be reduced to 4 mol% on larger scales, where 0.7 gram of product **91** was isolated in 90% yield (Fig. 4b). Compared with the classical pyrazole syntheses²⁹, this approach only requires a mono-ketone FG to be used as a handle. Thus, it provides a simple and distinct strategy to introduce 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 of preparing novel pyrazole-containing analogues for pharmaceutical or agrochemical research.

Preliminary mechanistic studies have been 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 intermediate³⁰ could be isolated during the course of the reaction, and was found to undergo the C–C cleavage with similar efficiency and selectivity as the standard reaction (Fig. S2). Upon olefin migration, the dihydropyrazole species (**Int II**), which is one unsaturation degree shy of an aromatic pyrazole structure, is proposed to be the key intermediate for the following C–C activation. In contrast, no C–C cleavage was observed without the *endocyclic* double bond or the ring structure (Fig. S2c). From **Int II**, an aromatization-promoted homolytic C–C cleavage/radical recombination mechanism was suggested by the density functional theory (DFT) calculations over other C–C activation pathways (Extended Data Fig. 3a and Fig. S5). The initial N–H oxidative addition gives rise to a mixture of Ir(III) hydride isomers (**157** and **159**), in which the exocyclic C–C bond of the dihydropyrazole is significantly weakened (BDE = 39.0 and 36.5 kcal/mol for **157** and **159**, respectively). From **159**, the homolytic C–C cleavage (**160-TS**, $G^\ddagger = 29.5$ kcal/mol with respect to **159**) yields a transient Ir(II) species (**161**) and an alkyl radical, which then rapidly recombine to form **162**. The computed NICS(1)_{zz} aromaticity index values revealed a substantial increase of 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. Based on the current mechanistic understanding, future work will focus on enhancing the reaction efficiency and discovering new transformations or applications based on this C–C activation mode.

Methods

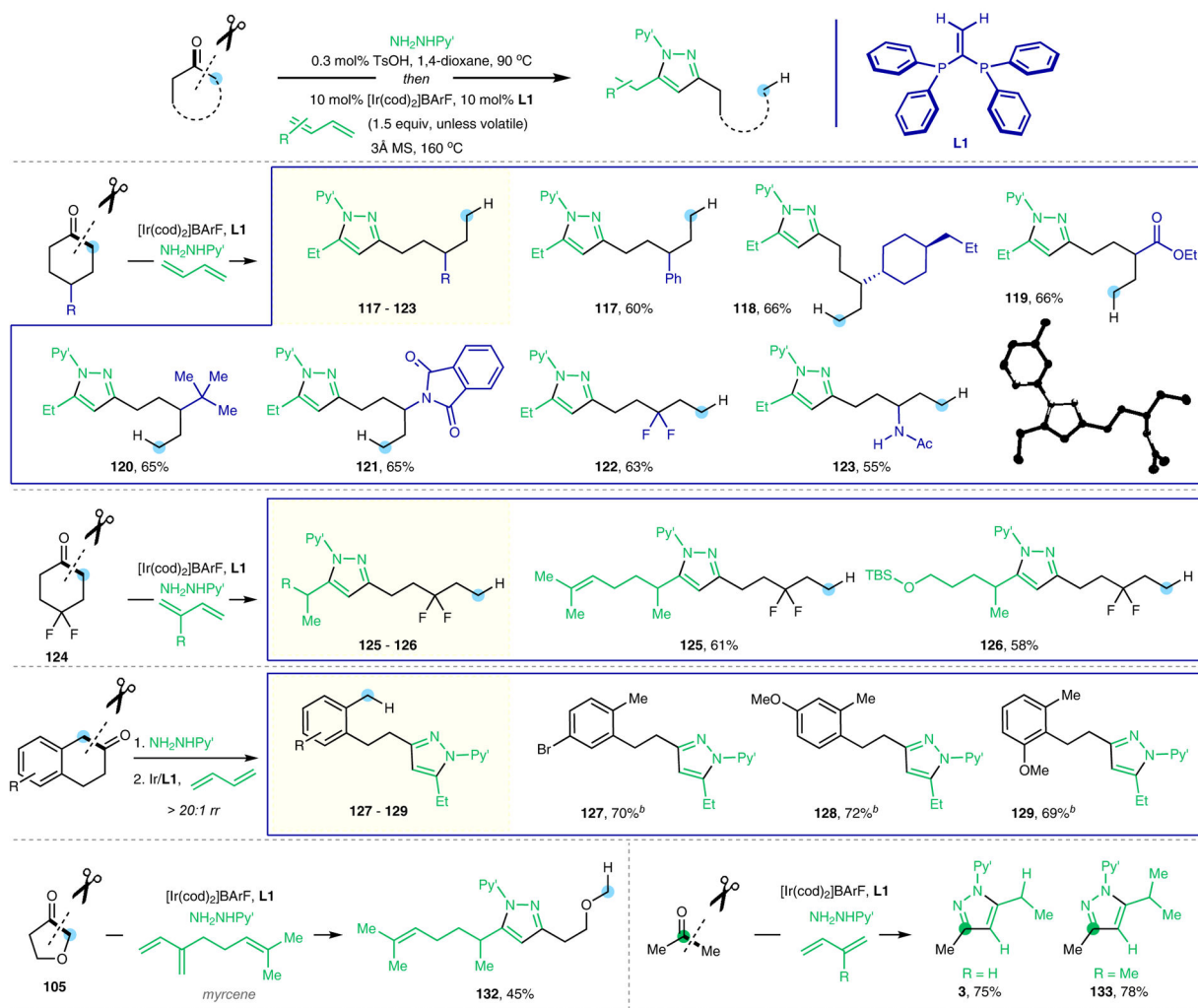
General procedure for the deacetylation of methyl ketones.

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-hydrazineyl-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 hours under N₂ atmosphere in a 8 mL vial. After cooled 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 sieve (pre-dried, 100 mg) and 1,3-butadiene (20 wt.% in PhMe, 170 μL, ca. 10 equiv) in a glovebox. The vial was sealed and heated at 160 °C under stirring for 72 hours. After cooled 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 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 the Supplementary Information.

Data availability

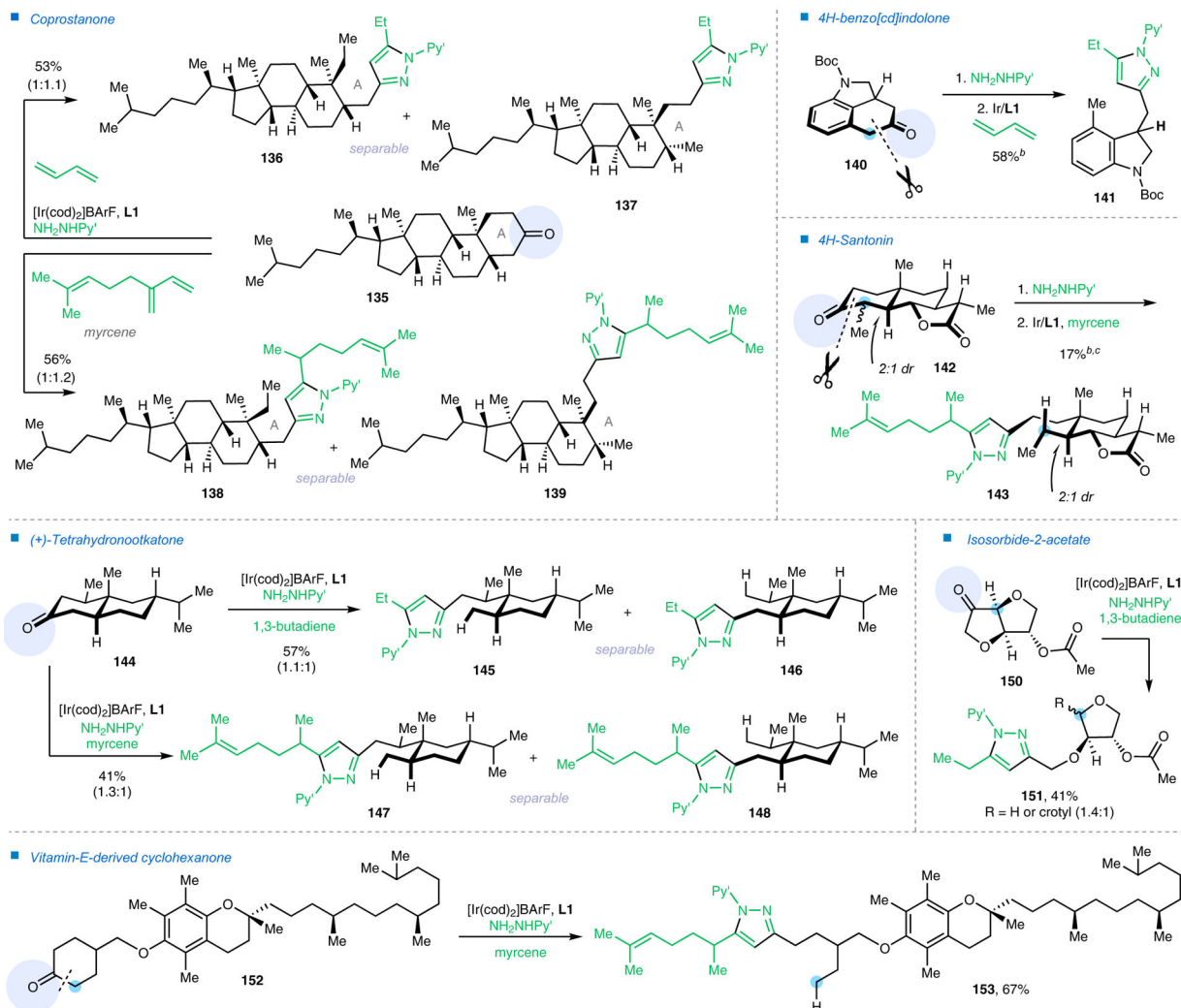
The data supporting the findings of this study are available within the article and its Supplementary Information. Additional data are available from the corresponding authors upon request. Metrical parameters for the structure of **123** are available free of charge from the Cambridge Crystallographic Data Centre (<https://www.ccdc.cam.ac.uk/>) under reference number CCDC 1876535.

Extended Data



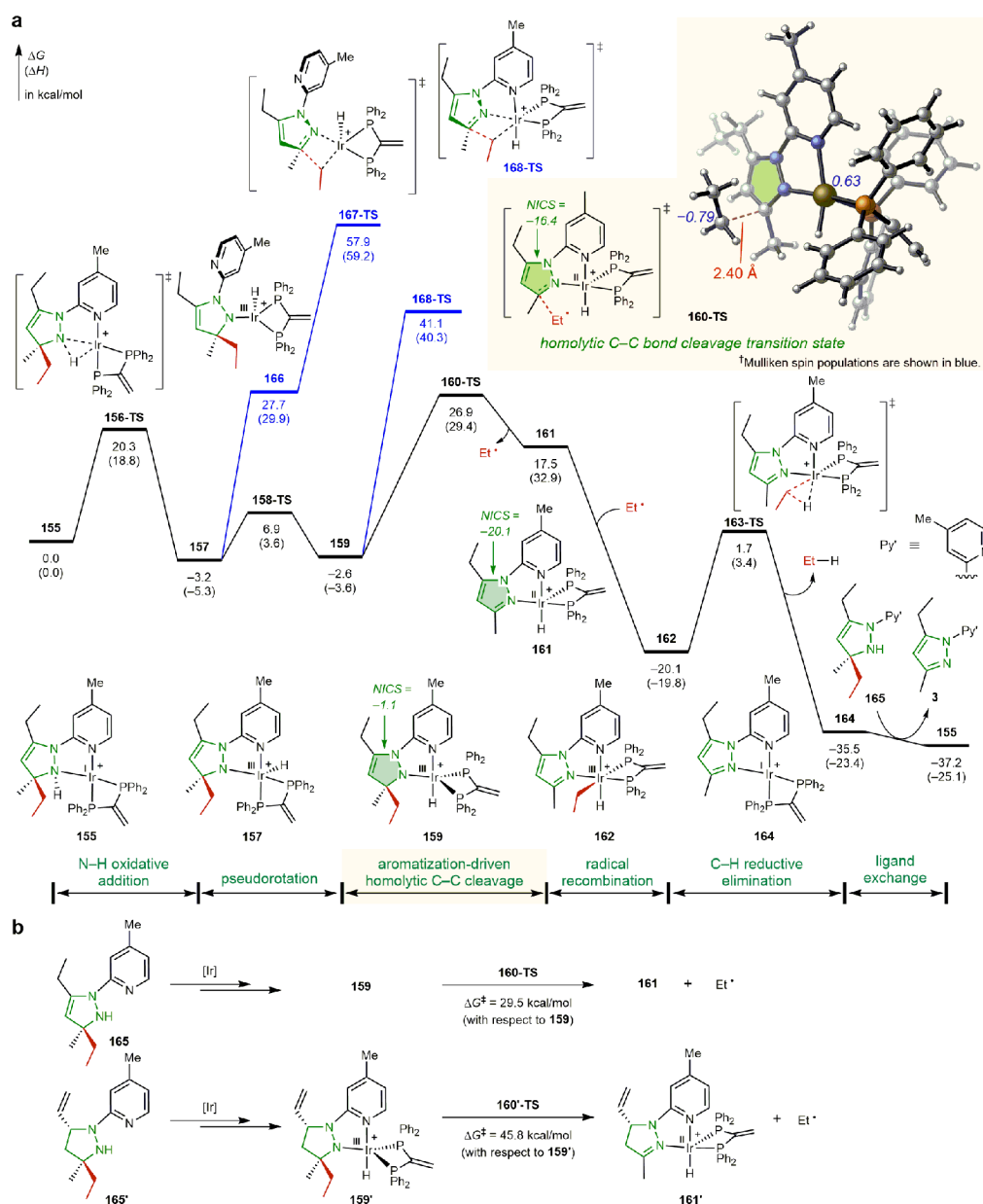
Extended Data Fig. 1 | Additional substrate scope for deconstructive pyrazole synthesis from ketones.

Py', 4-methyl-2-pyridyl; Ts, *p*-toluenesulfonyl; BARf, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; MS, molecular sieves; Ac, acetyl. ^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.

Py', 4-methyl-2-pyridyl; BARf, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; Boc, *tert*-butoxycarbonyl. ^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 favorable 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 B3LYP/6–311+G(d,p)–SDD level of theory to describe the aromaticity of pyrazole ring (highlighted in green) in **159**, **160-TS**, and **161**. The variation of NICS(1)_{zz} values indicates a significant increase of aromaticity during the homolytic C–C bond cleavage. **b**, Comparison between homolytic C–C bond cleavage of dihydropyrazole **165** and pyrazolidine **165'** (**165'** without the driving force of aromatization). See Section 3.2.2 in Supplementary Information for details.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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References:

1. Karimov RR & Hartwig JF Transition-Metal-Catalyzed Selective Functionalization of C(sp³)-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). [PubMed: 25062400]
4. Souillart L & Cramer N Catalytic C–C bond activations via oxidative addition to transition metals. *Chem. Rev* 115, 9410–9464 (2015). [PubMed: 26044343]
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). [PubMed: 28060495]
6. Fumagalli G, Stanton S & Bower JF Recent methodologies that exploit C–C single-bond cleavage of strained ring systems by transition metal complexes. *Chem. Rev* 117, 9404–9432 (2017). [PubMed: 28075115]
7. Dreis A; Douglas C In C–C Bond Activation; Dong G, Ed.; Springer: Berlin; 346, 85–110 (2014).
8. Schleyer PVR & Pühlhofer F Recommendations for the evaluation of aromatic stabilization energies. *Org. Lett* 4, 2873–2876 (2002). [PubMed: 12182577]
9. Santen RJ, Brodie H, Simpson ER, Siiteri PK & Brodie A History of aromatase: saga of an important biological mediator and therapeutic target. *Endocr. Rev* 30, 343–375 (2009). [PubMed: 19389994]
10. King RB & 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 RH, Dion RP, Gibboni DJ, Mcgrath DV & Holt EM Carbon–carbon bond cleavage in hydrocarbons by iridium complexes. *J. Am. Chem. Soc* 108, 7222–7227 (1986).
12. Halcrow MA, Urbanos F & Chaudret B Aromatization of the B-ring of 5,7-dienyl steroids by the electrophilic ruthenium fragment “[Cp**Ru*]⁺”. *Organometallics* 12, 955–957 (1993).
13. Youn SW, Kim BS & Jagdale AR Pd-catalyzed sequential C–C bond formation and cleavage: evidence for an unexpected generation of arylpalladium(II) species. *J. Am. Chem. Soc* 134, 11308–11311 (2012). [PubMed: 22721172]
14. Smits G, Audic B, Wodrich MD, Corminboeuf C & Cramer N A β-Carbon elimination strategy for convenient in situ access to cyclopentadienyl metal complexes. *Chem. Sci* 8, 7174–7179 (2017). [PubMed: 29081949]
15. Padwa A & Pearson WH Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products (John Wiley & Sons, 2003).
16. Fevre GL & Hamelin J Existence d’une forme N–H stable de pyrazoline-4 lors de l’aromatization de pyrazolidines 3,3-disubstituees en pyrazole. Mecanisme de la reaction. *Tetrahedron Lett.* 19, 4503–4506 (1978).

17. Tian M, Shi X, Zhang X & Fan X 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* 82, 7363–7372 (2017). [PubMed: 28640624]
18. Xu Y, Young MC & Dong G Catalytic coupling between unactivated aliphatic C-H bonds and alkynes via a metal-hydride pathway. *J. Am. Chem. Soc* 139, 5716–5719 (2017). [PubMed: 28387510]
19. Pan S & Shibata T Recent advances in iridium-catalyzed alkylation 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). [PubMed: 27806379]
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 SK, Park J-W, Cruz FA & Dong VM Rh-catalyzed C-C bond cleavage by transfer hydroformylation. *Science* 347, 56–60 (2015). [PubMed: 25554782]
23. Zultanski SL & Fu GC Nickel-catalyzed carbon-carbon bond-forming reactions of unactivated tertiary alkyl halides: Suzuki arylations. *J. Am. Chem. Soc* 135, 624–627 (2013). [PubMed: 23281960]
24. Mei T-S, Patel HH & Sigman MS Enantioselective construction of remote quaternary stereocentres. *Nature* 508, 340–344 (2014). [PubMed: 24717439]
25. Fessard TEC, Andrews SP, Motoyoshi H & Carreira EM Enantioselective preparation of 1,1-diarylethanes: aldehydes as removable steering groups for asymmetric synthesis. *Angew. Chem. Int. Ed* 46, 9331–9334 (2007).
26. Chu L, Ohta C, Zuo Z & Macmillan DWC Carboxylic acids as a traceless activation group for conjugate additions: a three-step synthesis of (±)-Pregabalin. *J. Am. Chem. Soc* 136, 10886–10889 (2014). [PubMed: 25032785]
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. Candeias NR, Paterna R & Gois PMP Homologation reaction of ketones with diazo compounds. *Chem. Rev* 116, 2937–2981 (2016). [PubMed: 26854865]
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). [PubMed: 25226575]

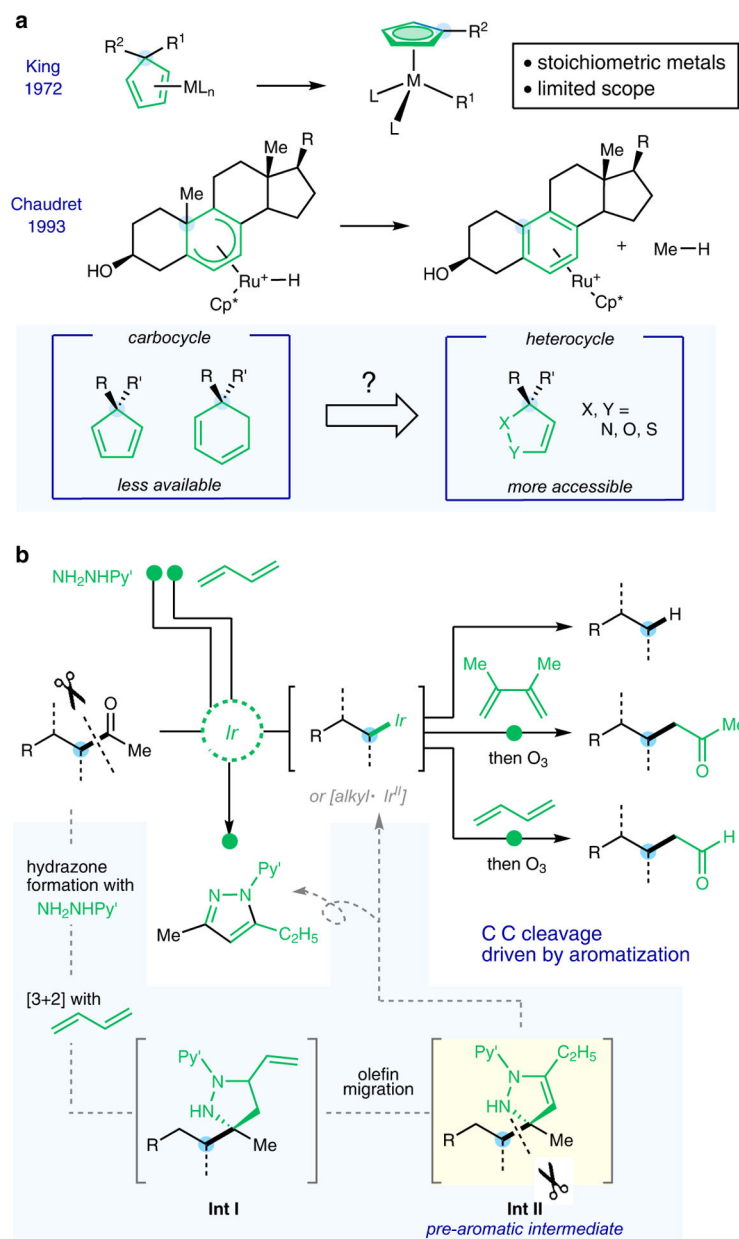


Figure 1 | C-C activation driven by aromatization.

a, Known examples of transition metal-mediated C-C cleavage driven by aromatization. **b**,

This work: catalytic deacylative transformations of common unstrained ketones. M,

transition metal; Cp*, pentamethylcyclopentadienyl; Py', 4-methyl-2-pyridyl.

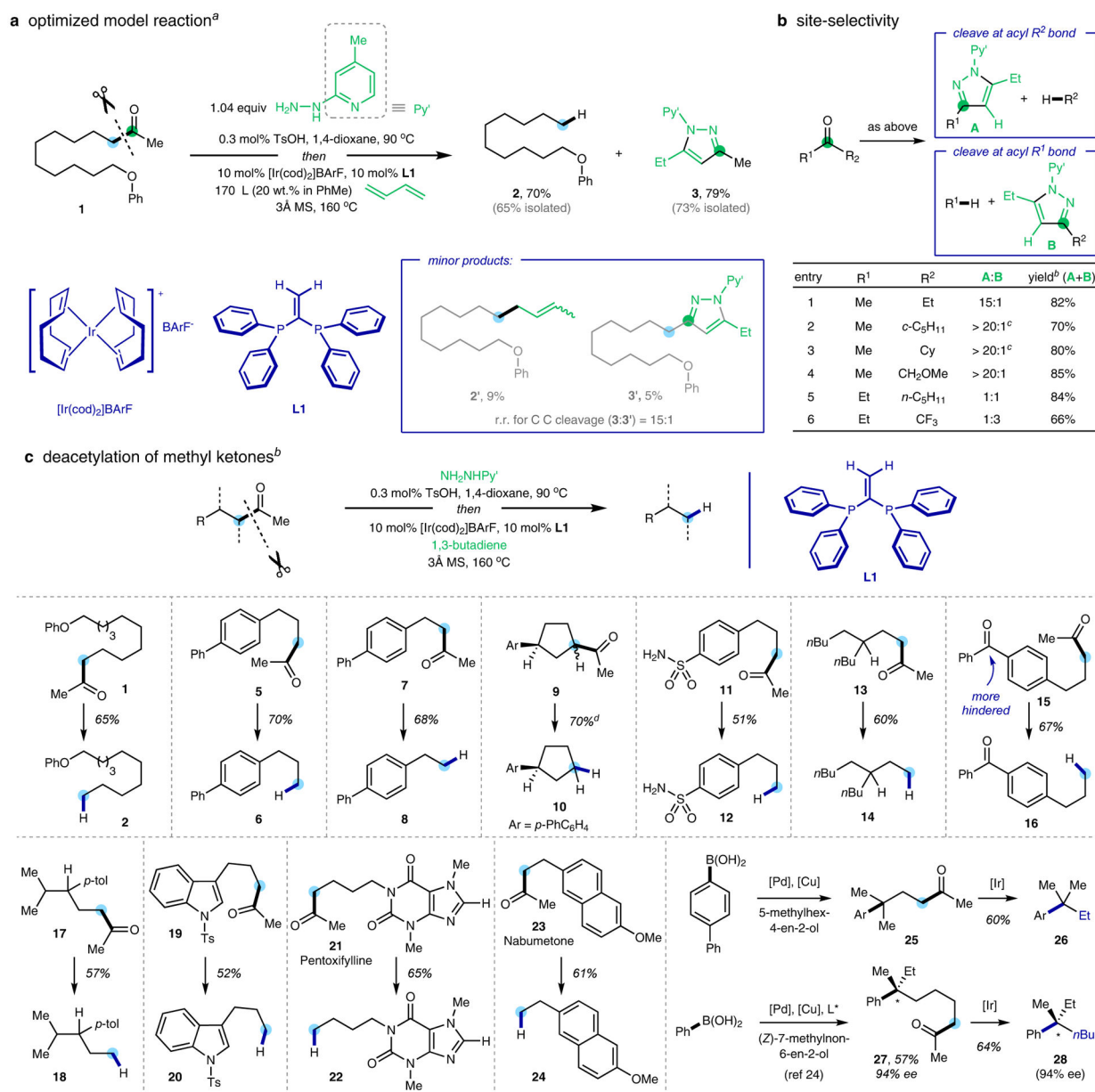


Figure 2 | Iridium-catalyzed cleavage of unstrained ketones.

a, Optimized model reaction using linear ketone **1**. **b**, Site-selectivity of this reaction. **c**, Deacetylation of methyl ketones. Ts, *p*-toluenesulfonyl; BARf, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; Cy, cyclohexyl; MS, molecular sieves; *p*-tol, *p*-tolyl. ^a The reactions were conducted with 0.05 mmol **1**, 0.052 mmol of 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.

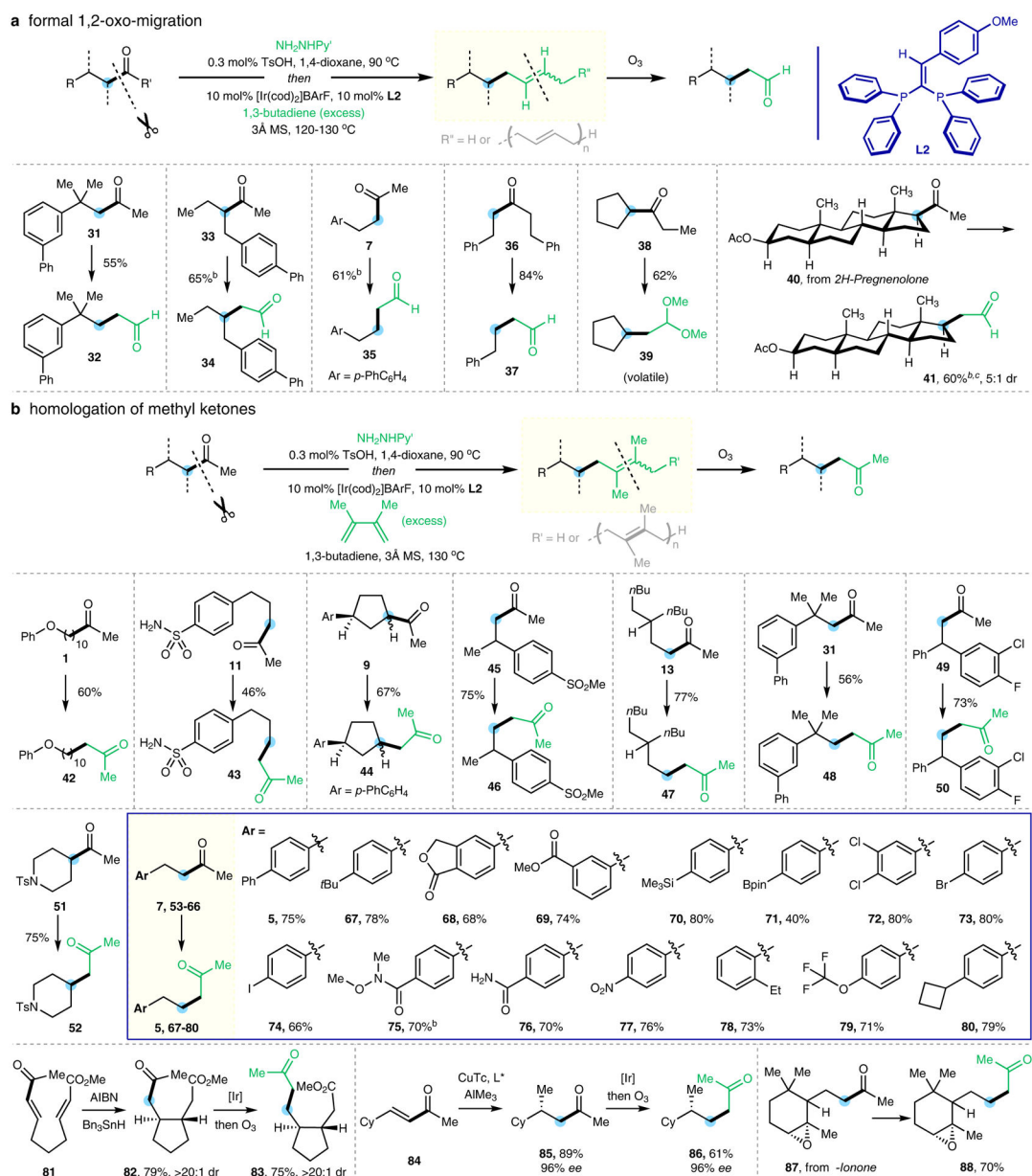


Figure 3 | Deacylative C–C forming reactions of linear ketones.

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 the same length of a carbon chain 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. Py', 4-methyl-2-pyridyl; Ts, *p*-toluenesulfonyl; BARf, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; MS, molecular sieves; Bpin, (pinacolato)boryl; AIBN, azobisisobutyronitrile; Tc, thiophene-2-carboxylate. ^a All yields are isolated yields. ^b Using the pre-formed hydrazone as the substrate. ^c The reaction was conducted at 170 °C. For detailed experimental procedures, see Supplementary Information.

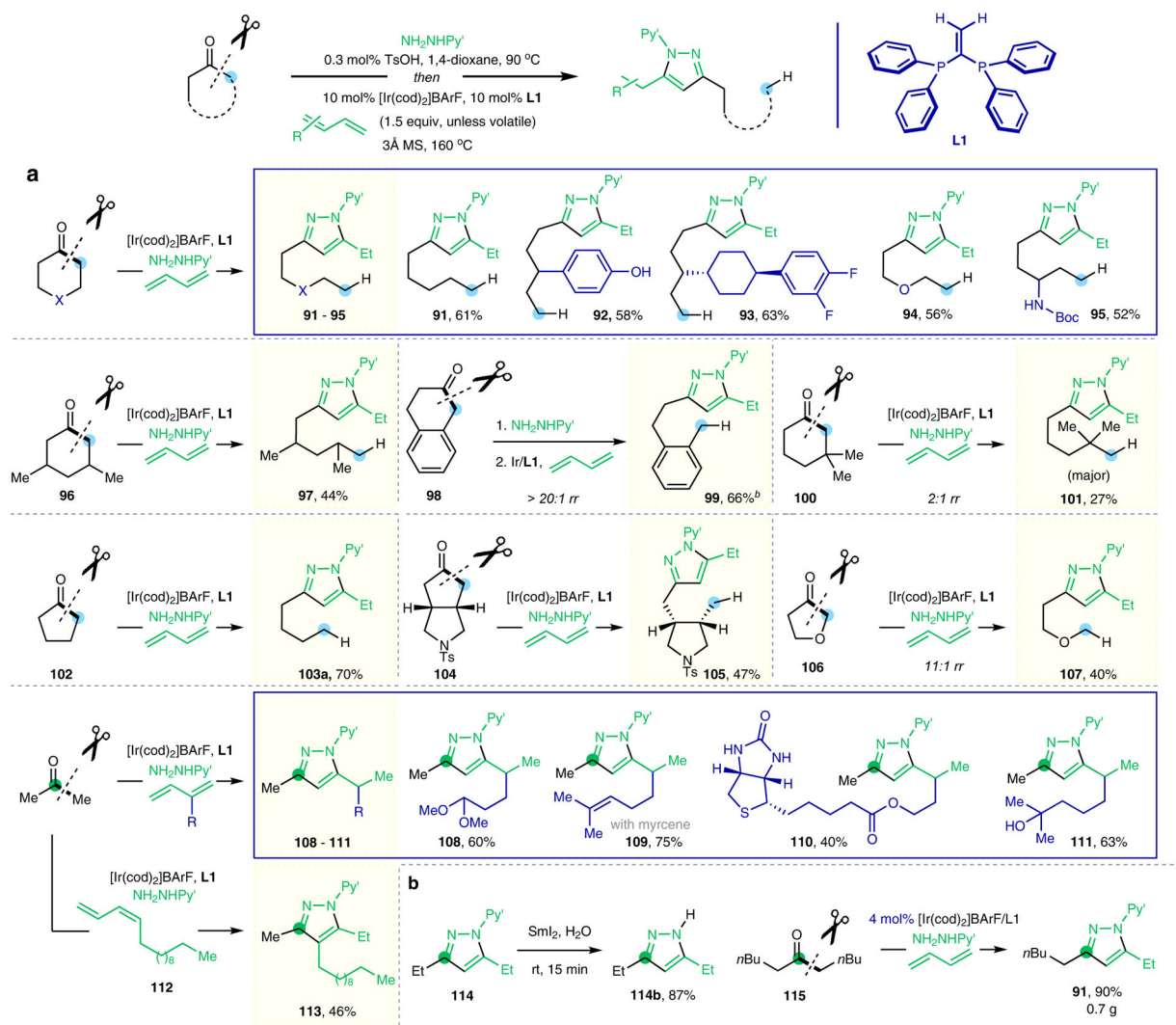


Figure 4 | Deconstructive pyrazole synthesis from ketones.

a, Representative substrate scope. **b**, Further studies on pyridyl group removal and larger scale synthesis. Py', 4-methyl-2-pyridyl; Ts, *p*-toluenesulfonyl; BARf, tetrakis(3,5-bis(trifluoromethyl)phenyl)borate; cod, 1,5-cyclooctadiene; MS, molecular sieves; Boc, *tert*-butoxycarbonyl. ^a All yields are isolated yields. ^b Yields refer to the key C–C activation reaction using pre-formed hydrazones as the substrates. See Extended Data Figs. 1 and 2 for additional substrate scope, and see Supplementary Information for detailed experimental procedures.