Deacylative Transformations of Ketones via Aromatization-Promoted Carbon−Carbon Bond Activation

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Carbon−hydrogen (C−H) and carbon−carbon (C−C) bonds are generally the most abundant bonds in organic compounds, regardless for simple feedstock chemicals or complex drugs/natural products. The recent advancement of C−H functionalization technology has vastly expanded our toolbox for efficient manipulations of specific C−H bonds on molecular surfaces[1]; in contrast, widely applicable C−C activation methods that allow for selectively editing embedded molecular skeletons remain limited[2]. 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[2d,2g] or using directing groups[2f,3] (DGs) to gain kinetic benefits. While effective, these strategies require employment of ketone substrates that are highly strained, or containing a preinstalled DG, or belonging to certain special classes[2f]. Hence, to extend the synthetic utility of C−C activation, methods that can activate a significantly broader range of unstrained substrates would be particularly desirable. Herein, we report a new C−C activation mode suitable for a wide variety of unstrained ketone substrates, which is driven by aromatization of an *in situ*-formed pre-aromatic intermediate. This reaction is catalyzed by a unique iridium/phosphine combination, and promoted by a hydrazine reagent and 1,3-dienes. Specifically, the acyl moiety is removed from the ketone substrate and transformed to a pyrazole structure, and the resulting alkyl fragment undergoes various distinct transformations. The synthetic utility is primarily demonstrated in (a) deacetylation of methyl ketones, (b) carbenoid-free formal homologation of aliphatic linear ketones, and (c) deconstructive pyrazole synthesis from cyclic ketones.

Aromaticity has been known as an important thermodynamic driving force[4] 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 process[5]. Forming aromatic compounds has also been known to promote the transition metal-mediated C−C activation since 1972[6a], which unfortunately has been largely underappreciated with only scattered examples[6] (Fig. 1a). These reactions use a pre-aromatic substrate to complex with a low-valent TM, and subsequent C−C cleavage leads to stable arene-metal species, such as CpTM complexes (Cp: cyclopentadienyl)[6b-e,6i]. 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 TMs; thus, enabling catalyst turnover could be a significant issue[6b-g,6i]. 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 addition[7], could potentially serve as precursors to form heteroarenes. Thus, if heterocyclic pre-aromatics could be employed as key intermediates for the aromatization-driven C−C activation, distinct and synthetically useful transformations would be imagined. Herein, we report a new C−C activation mode suitable for general unstrained ketone substrates, which is driven by aromatization of an *in situ*-formed pre-aromatic intermediate (Fig. 1b). This iridium-catalyzed reaction likely involves a three-component coupling among a ketone, a 1,3-diene and a substituted hydrazine to generate a dihydropyrazole intermediate (**Int II**) that could subsequently undergo C−C cleavage to form a pyrazole[8] and an activated alkyl species (e.g. an alkyl-Ir intermediate). Ultimately, a number of deacylative transformations of ketones, including C−H or C−C forming reactions, can be selectively realized under different conditions. Given that ketone moieties ubiquitously exist in feedstock chemicals, natural products and advanced pharmaceuticals, these unusual transformations could offer new strategic bond disconnections in synthesis of complex bioactive molecules.

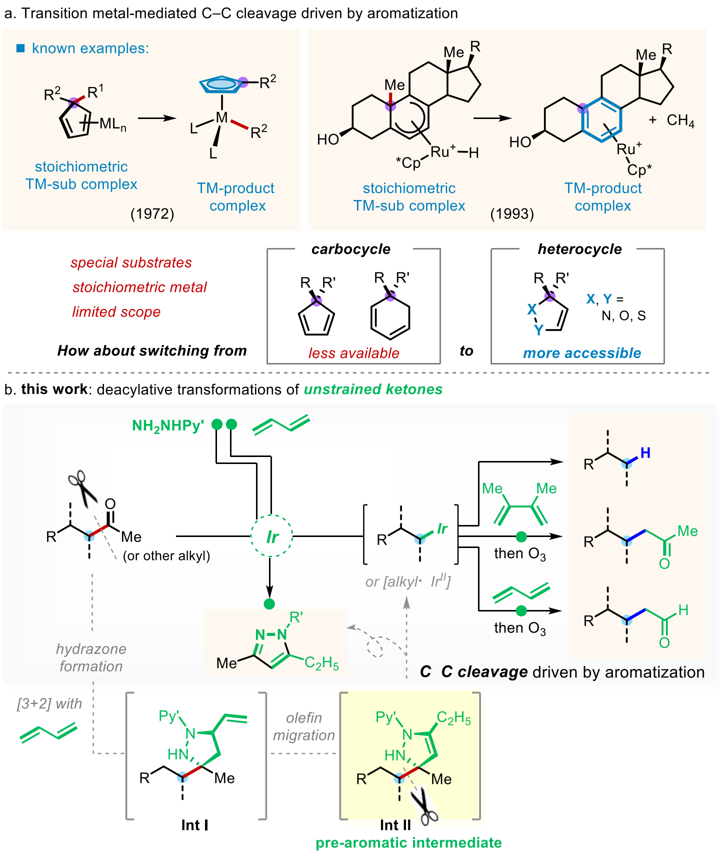
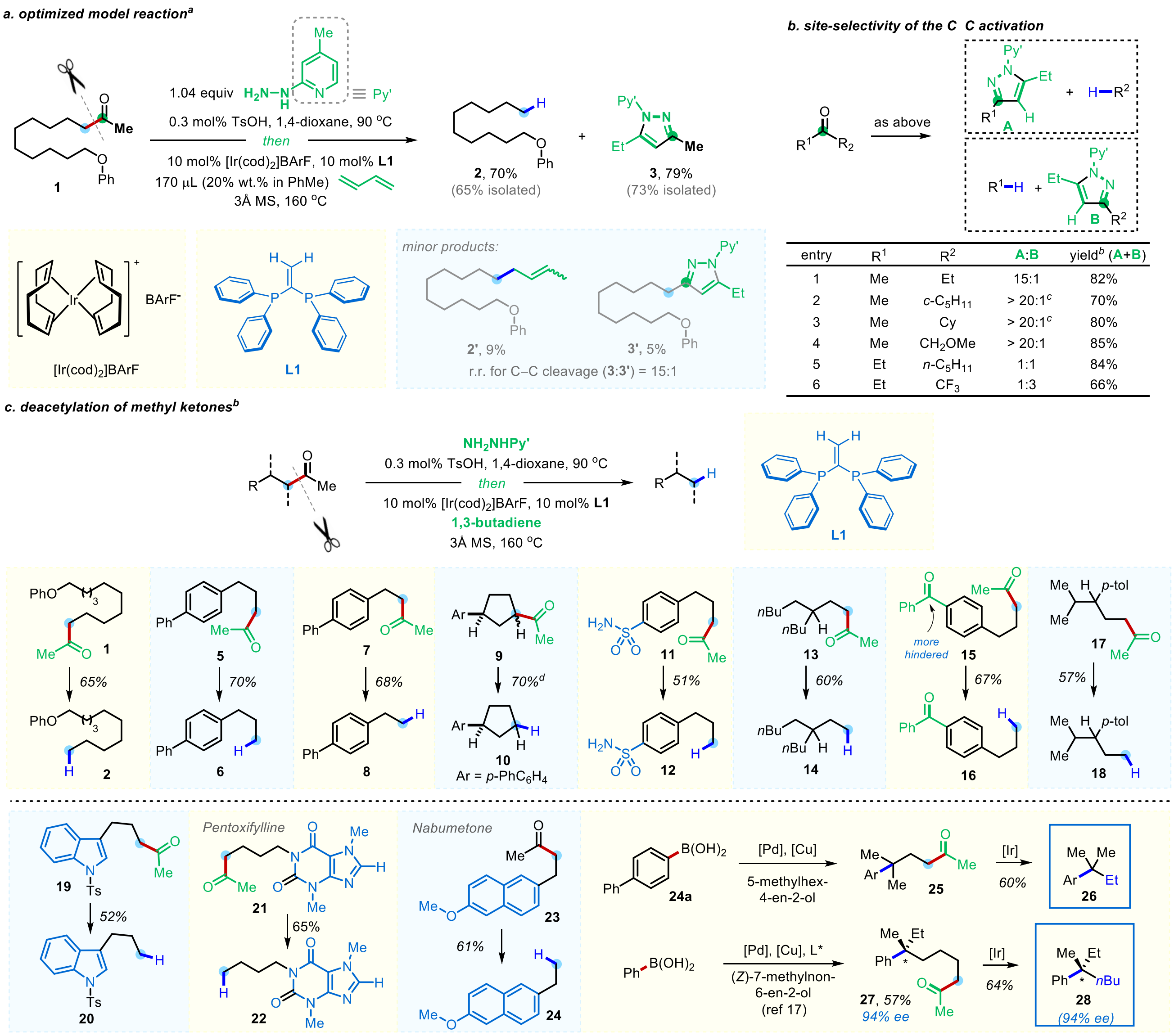


Figure 1 | C−C activation driven by aromatization. a, Transition metal-mediated C−C cleavage driven by aromatization. **b,** Deacylative transformations of common unstrained ketones.

The initial reaction mode was discovered during our exploration of the Rh-catalyzed β-C−H functionalization of ketones with 1,3-butadiene[9], 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 to offer a more active catalytic system 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 $[Ir(cod)_2]BArF$[10] 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 key 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 substituted[11] (entries 1-3) or α-to-heteroatom carbons (entry 4). An exception was found with trifluoromethyl-substituted ketones, in which cleavage of the ethyl group was more favored over the trifluoromethyl (entry 6). Unsurprisingly, no selectivity was observed between an ethyl and an *n*-pentyl group in 3-octanone (entry 5).

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,[12] and recently a de-hydroformylation approach was reported to access unsaturated products.[13] 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 while the benzophenone moiety remained untouched (**16**). In addition, FGs, such as primary sulfonamides (**12**), and heteroarenes, such as protected



entry	R^1	R^2	A:B	yield^b (A+B)
1	Me	Et	15:1	82%
2	Me	c-C_5H_{11}	> 20:1^c	70%
3	Me	Cy	> 20:1^c	80%
4	Me	CH_2OMe	> 20:1	85%
5	Et	n-C_5H_{11}	1:1	84%
6	Et	CF_3	1:3	66%

Figure 2 | Iridium-catalyzed cleavage of unstrained ketones. a, Optimized model reaction using linear ketone **1**. The reaction is redox neutral, showing high selectivity. **b,** The site-selectivity of this reaction was further explored. In general, the bond scission prefers to occur at more substituted or α-to-heteroatom carbons. **c,** Deacetylation of methyl ketones. The scope is broad and a number of FGs are tolerated. ^{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. The yields were determined by ^{1}H NMR using 1,1,2,2-tetrachloroethane as the internal standard. ^{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.

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*-amylation of arenes is nontrivial *via* direct cross coupling approaches,[14] but it can be realized through first coupling of aryl boronic acid **24a** with 5-methylhex-4-en-2-ol using Sigman's redox-relay oxidative-Heck reaction[15] followed by this deacetylation reaction. Finally, enantioselective construction of hydrocarbon quaternary stereocenters that *lack nearby polar FGs*[16] (**28**) was also achieved using a similar strategy.[15]

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'**)[17]. 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 that contain 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 effectively 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.

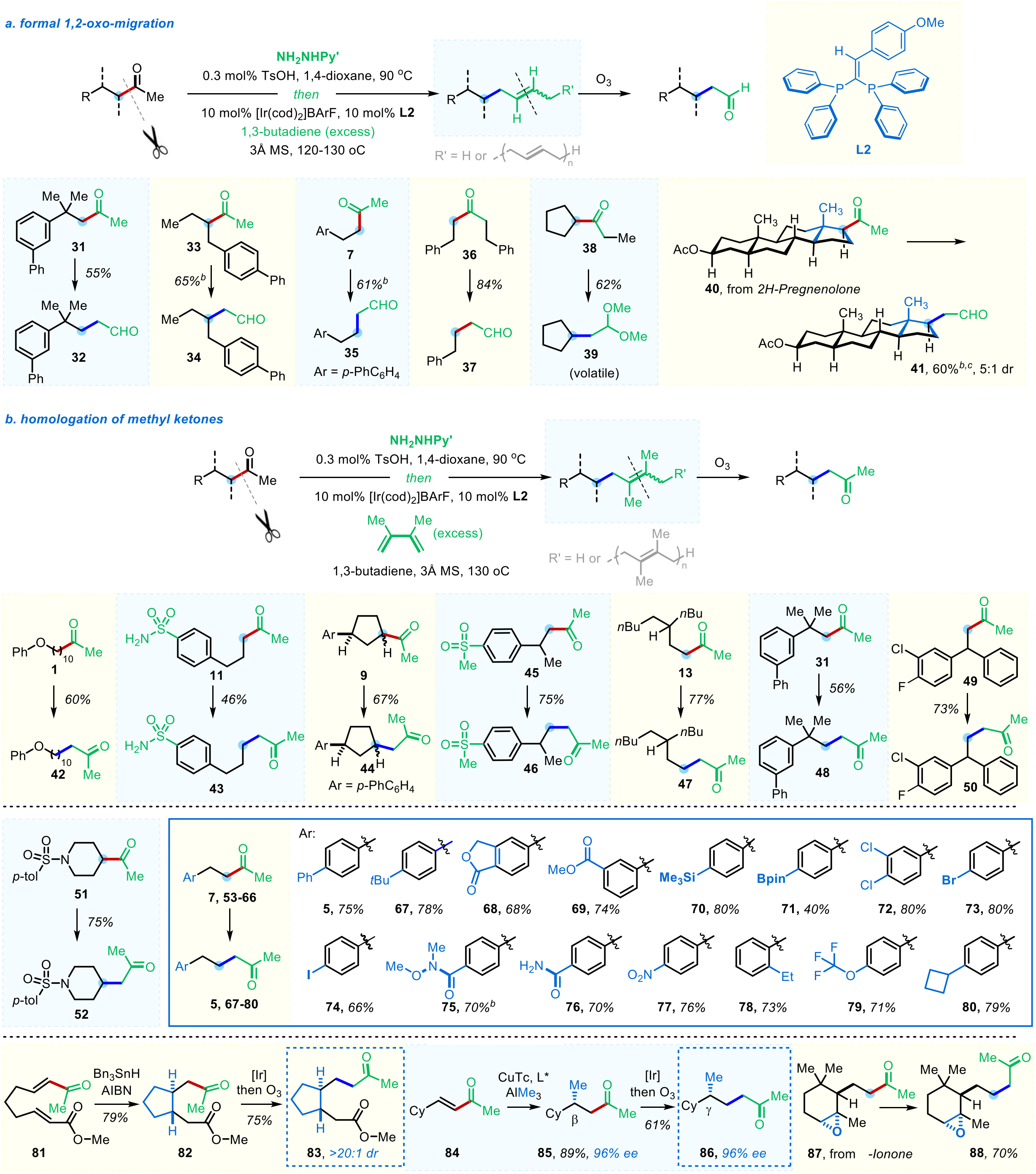


Figure 3 | Deacylative C−C forming reactions of linear ketones. a, Formal "*1,2-oxo-migration*". After C−C cleavage, through coupling the alkyl fragment with 1,3-butadiene followed by ozonolysis, an aldehyde with the same length of a carbon chain is afforded **b,** Carbenoid-free homologation of aliphatic 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. [a] All yields are isolated yields. [b] Using the pre-formed hydrazone as the substrate. [c] The reaction was conducted at 170 ºC. For detailed experimental procedures, see Supplementary Information.

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. It is noteworthy that 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 homologation[18], this method features high reactivity, excellent site- and chemo-selectivity.

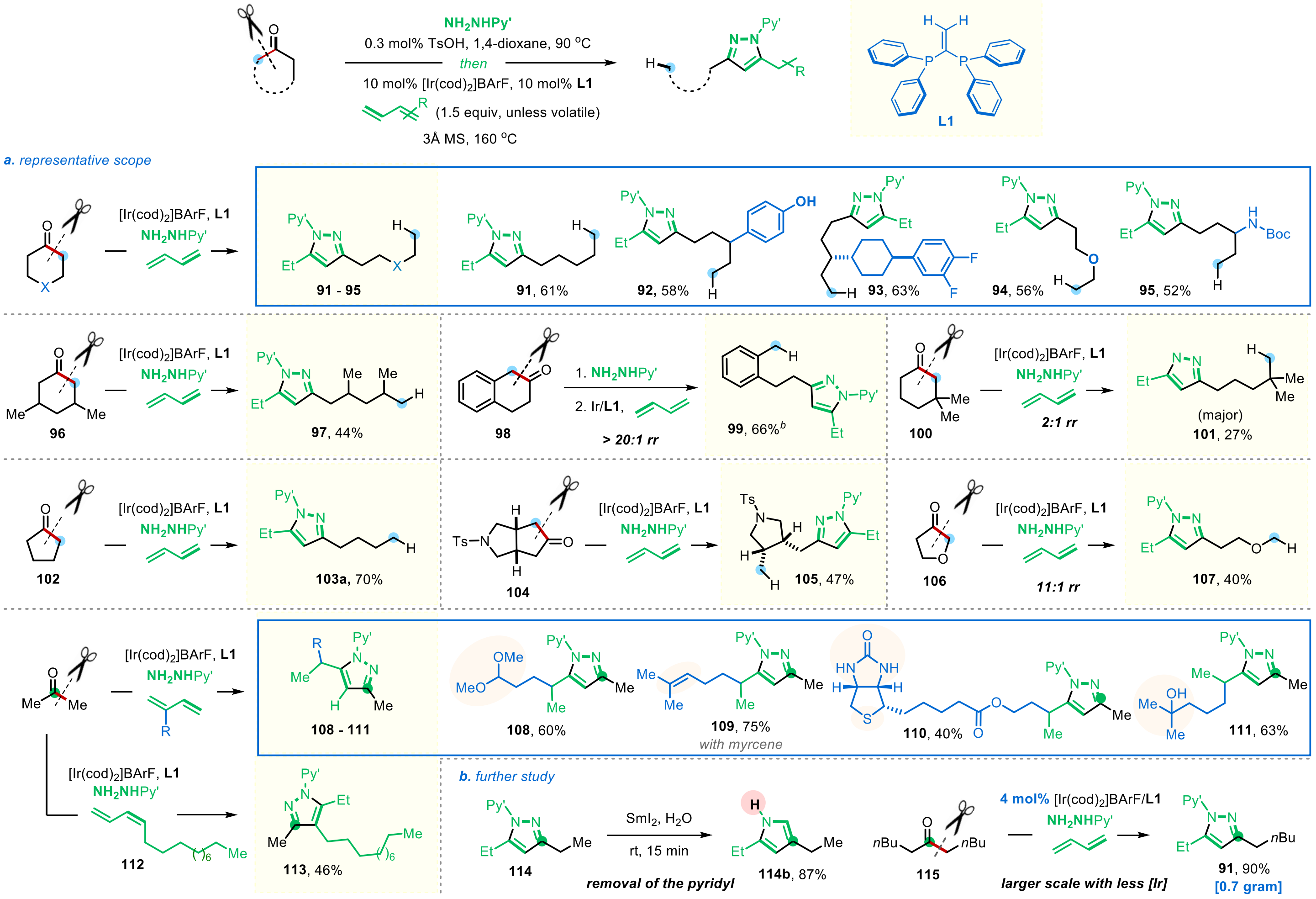
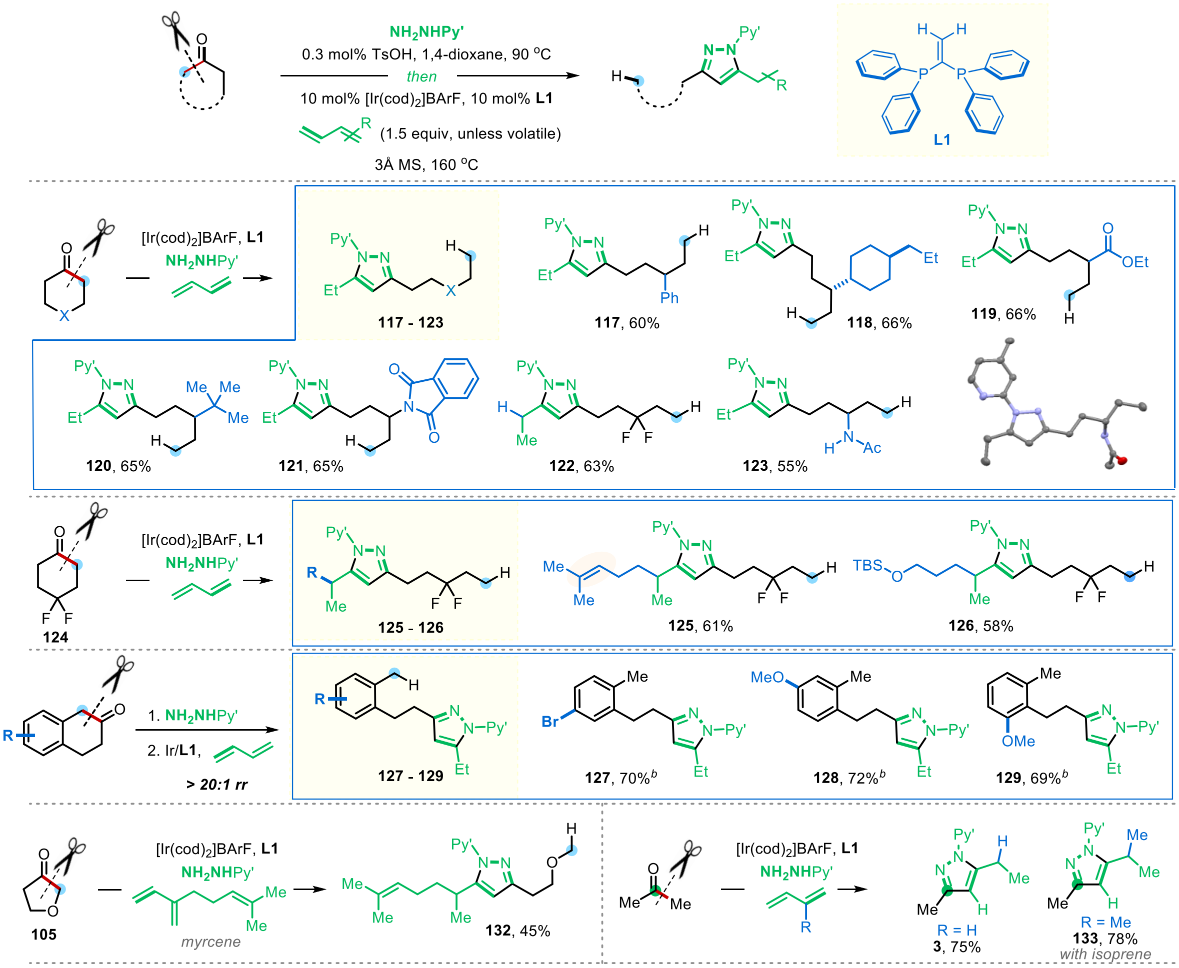


Figure 4 | Deconstructive pyrazole synthesis from ketones. **a,** Representative substrate scope. **b,** Further studies on pyridyl group removal and larger scale synthesis. [a] All yields are isolated yields. [b] Yields refer to the key C−C activation reaction using pre-formed hydrazones as the substrates.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

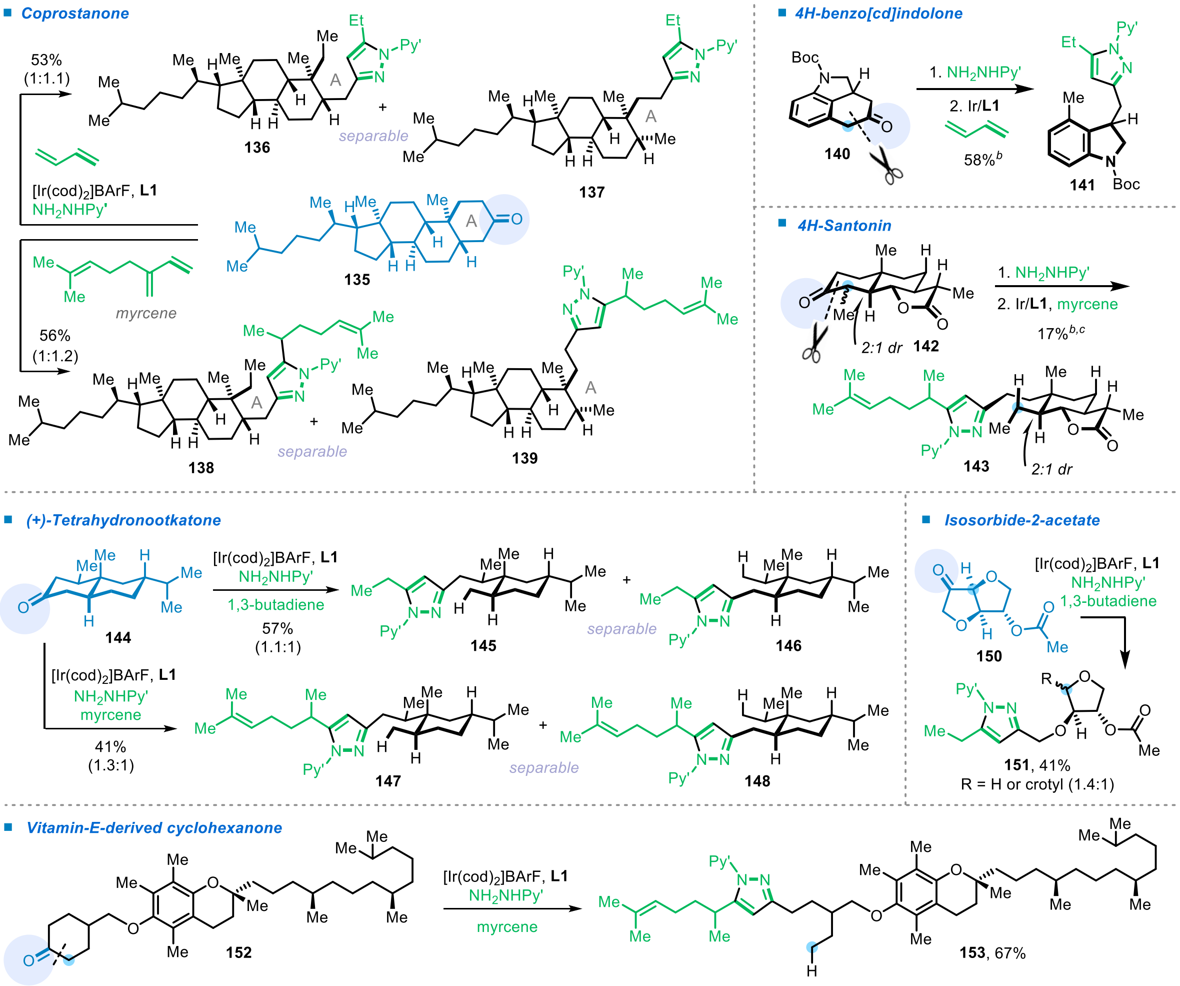
On the other hand, when *cyclic ketones* were employed as substrates, a redox-neutral deconstructive pyrazole-synthesis method was realized (Fig. 4 and Extended Data Fig. 1)[8]. As a highly important class of pharmacophores, pyrazoles are commonly found in bioactive compounds and approved drugs[19b], e.g. *Celecoxib*, *Rimonabant*, *Fomepizole* and *Sildenafi.* While many methods have been developed for pyrazole synthesis,[19] 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 through aromatization-promoted C−C activation. 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. Ketones featuring oxygen heterocycles (**94** and **107**) also reacted as well. Note that simple acetone could be used as the 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 to introduce different FGs and substitution patterns. The transformation tolerates trisubstituted olefins (**109**), aryl bromides (**127**), free and protected alcohols (**111** and **126**), free phenols (**92**), thioethers (**110**), dimethyl acetals (**108**), protected amines (**95** and **123**), phthalimides (**121**), sulfonamides (**105**), esters (**119**), ethers (**94** and **107**), aliphatic and aromatic fluorides (**93** and **122**), and ureas (**110**). 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 syntheses[19], 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 that mono-ketone moieties are prevalent in complex molecules or readily accessible from other FGs, this C−C activation method could become a useful tool of preparing novel pyrazole-containing analogues for pharmaceutical or agrochemical research.

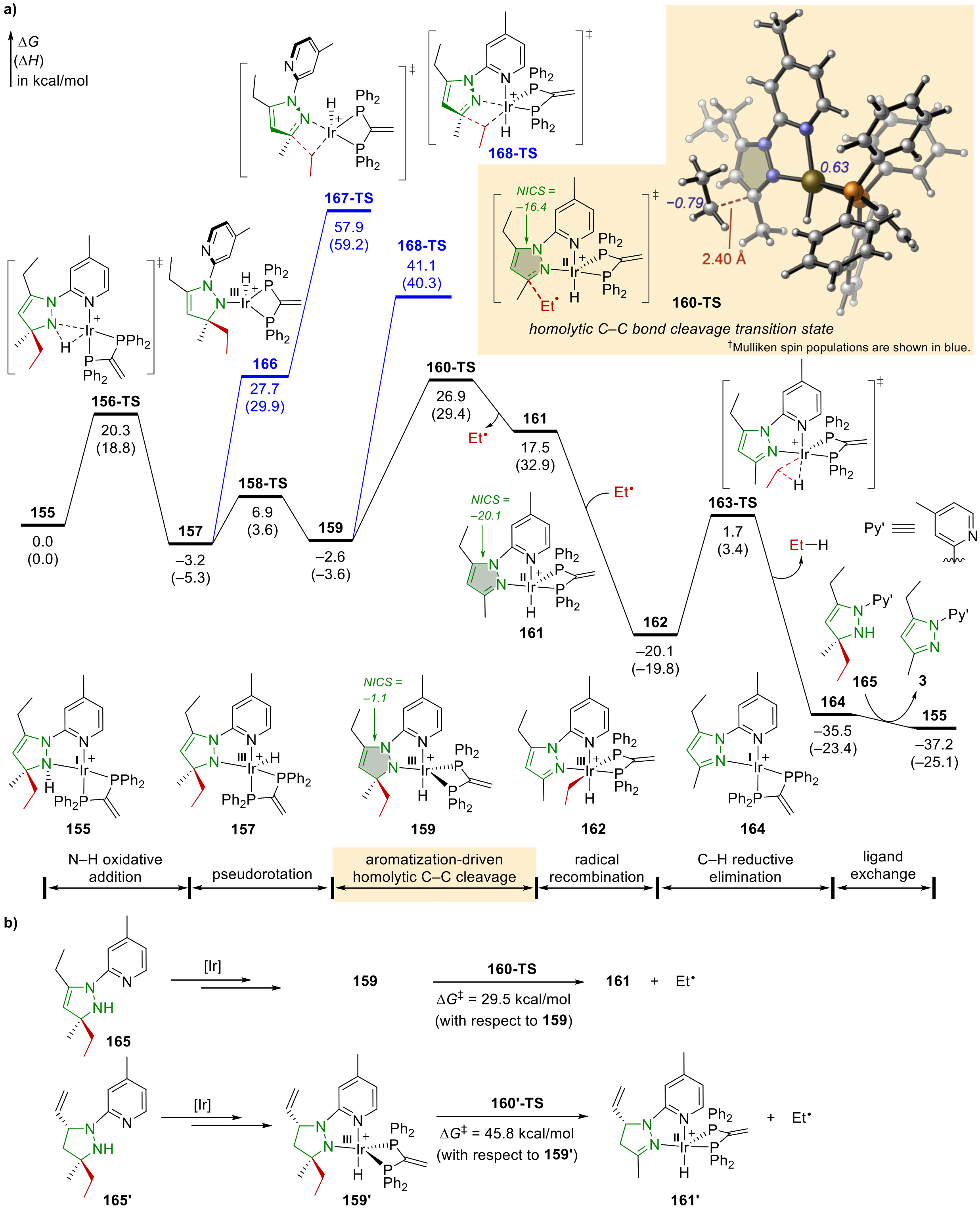
Preliminary mechanistic studies have been performed (see *Supplementary Information, Section 3.2*) to support the proposed reaction pathway depicted in Fig. 1b. First, the [3+2] cycloaddition adduct (**Int I**) between 1,3-butadiene and the hydrazone intermediate[20] could be isolated during the course 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 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**, $\Delta G^{\ddagger} = 29.5$ 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 $\text{NICS}(1)_{zz}$ 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.



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

Acknowledgements

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