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Deacylation-aided C–H alkylative annulation through C–C cleavage of unstrained ketones

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Arene- and heteroarene-fused rings are pervasive in biologically active molecules. Direct annulation between a C–H bond on the aromatic core and a tethered alkyl moiety provides a straightforward approach to access these scaffolds; however, such a strategy is often hampered by the need of special reactive groups and/or less compatible cyclization conditions. It would be synthetically appealing if a common native functional group can be used as a handle to enable a general C–H annulation with diverse aromatic rings. Here, we show a deacylative annulation strategy for preparing a large variety of aromatic-fused rings from linear simple ketone precursors. The reaction starts with homolytic cleavage of the ketone α C–C bond via a pre-aromatic intermediate, followed by a radical-mediated dehydrogenative cyclization. Using widely available ketones as the robust radical precursors, this deconstructive approach allows streamlined assembly of complex polycyclic structures with broad functional group tolerance.

Arenes and heteroarene-fused rings are commonly found in structures of drugs, natural products and other bioactive compounds (Fig. 1a)[1–4]. Among many possible synthetic approaches, the direct intramolecular C–H alkylation of the aromatic core from a linear precursor, namely C–H alkylative annulation, provides a straightforward approach to access these fused scaffolds, as prefunctionalization of arenes could be avoided (Fig. 1b)[5–8]. However, a long-standing challenge of this strategy arises from limited choices of reactive moieties at the alkyl terminus, regardless of whether this is through either a polar- or radical-addition pathway[9–20]. The typical alkylative annulation relies on the use of special or very reactive coupling partners, such as alkyl halides[9–13], xanthates[14,15], phenyl selenides[16], allyl sulfones[17], redox-active esters[18,19] and so on; it is generally not a trivial task to introduce these high-energy functional groups (FGs) with tolerating FGs that exist in the molecule[21,22]. In addition, carrying out multi-step operations with these sensitive FGs could also be difficult, which hinders implementation of convergent synthetic approaches. Hence, from the viewpoint of synthetic efficiency, it would be attractive to employ common, stable, native FGs as a handle for C–H alkylative annulation, as this should minimize FG manipulations or the usage of protecting groups. Recently, successes on mild radical annulations have been achieved with unactivated olefins through metal-hydride hydrogen atom transfer[23,24] or with carboxylic acids through oxidative decarboxylation[25–29]. Tolerance of FGs that are sensitive to atom-transfer processes or oxidants in complex settings can be a concern. Additionally, primary radicals are hard to generate via the metal-hydride hydrogen atom transfer pathway[30,31].

Complementary to the prior arts in the C–H alkylative annulation, a deacylation-aided C–H annulation could serve as a promising alternative strategy for preparing aromatic-fused rings. Ketone is among one of the most versatile FGs in organic synthesis: they can be readily prepared from various other FGs and are derivable at the α or β positions[32,33]. If site-selective C–C cleavage of alkyl ketones can be realized to generate an active alkyl terminus[33–42], such as a carbon-centred radical[43–46], for cyclization, a two-phase annulation strategy could be imagined from simple arene and alkyl substrates (Fig. 1c). Herein, we report a deacylation-aided C–H alkylative annulation of a wide array of arenes and heteroarenes, in which better step-economy and FG compatibility are realized using unstrained ketones as robust and native radical precursors under reductant/oxidant-free and near pH-neutral conditions.

Results

Initial considerations. Homolytic cleavage of ketone α-C–C bonds has been achieved through the Norrish–Young reaction under ultraviolet light irradiation[47]; alternatively, it can be elegantly realized by converting ketones into the corresponding oxime esters[48–54]/activated ethers[55–58] or tertiary alcohols followed by β-scission[59–61]. In our ongoing efforts to develop new C–C activation methods, we recently reported an iridium-catalysed cleavage of the α-C–C bonds of unstrained common ketones using aromatization as the driving force (Fig. 2)[62]. The reaction involves the formation of a pre-aromatic intermediate (**A**) between the ketone substrate and two activating reagents (hydrazine and 1,3-diene), which then undergoes the Ir(III)-mediated C–C cleavage driven by pyrazole formation to generate a carbon-centred radical and an odd-electron metal-hydride species (**B**). The radical–metal recombination can be facile, as shown previously, leading to the deacylation products via C–H reductive elimination. However, we hypothesize that, in the presence of an adjacent arene or heteroarene, the transient carbon-centred radical could be trapped intramolecularly; the resulting delocalized radical intermediate (**C**) could then lose a hydrogen and restore aromaticity to afford the fused bicyclic product.

Reaction discovery and optimization. To test this hypothesis, 5-(anthracenyl)pentan-2-one (**1**), prepared in one step from the corresponding aryl bromide and homoallyl alcohol, was selected as a model substrate. 4-Methyl-2-pyridylhydrazine (**D1**) and 1,3-butadiene were employed as the activating reagents to allow in situ formation of the pre-aromatic intermediate. On optimization, we were delighted to observe the formation of the desired annulation product (**2**) in 62% yield using $[Ir(cod)_2]$BArF (where cod is 1,5-cyclooctadiene and BArF is tetrakis[3,5-bis(trifluoromethyl)

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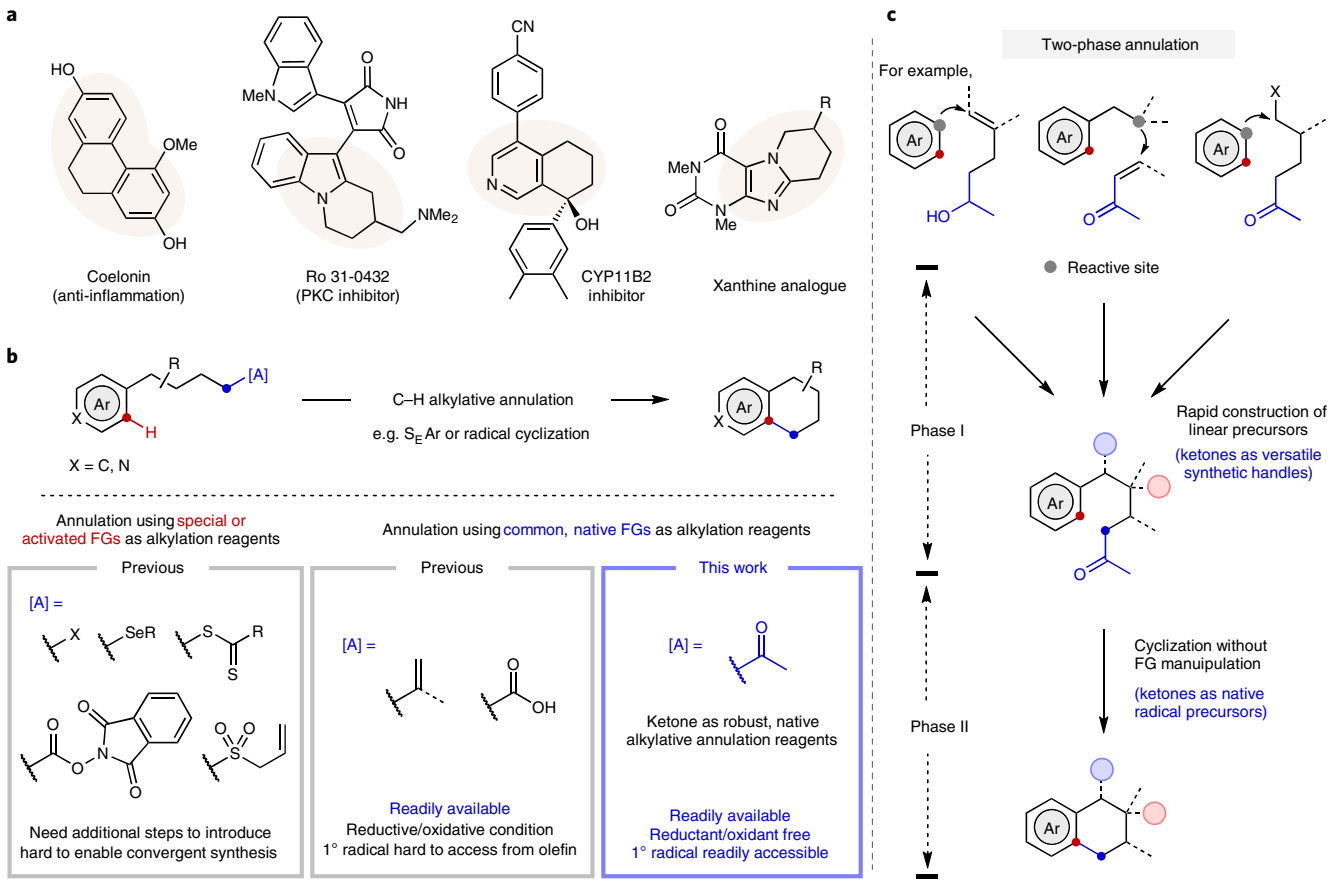


Fig. 1 | Alkylative annulation of aromatic C(sp^2)–H bonds. a, Arene- and heteroarene-fused rings are commonly found in bioactive compounds. **b**, Different alkylation approaches used in the alkylative annulation of aromatic C–H bonds. **c**, A two-phase annulation strategy using ketones as both a versatile synthetic handle and a native radical precursor. Ar, arene or heteroarene; PKC, protein kinase C; S_E, electrophilic aromatic substitution.

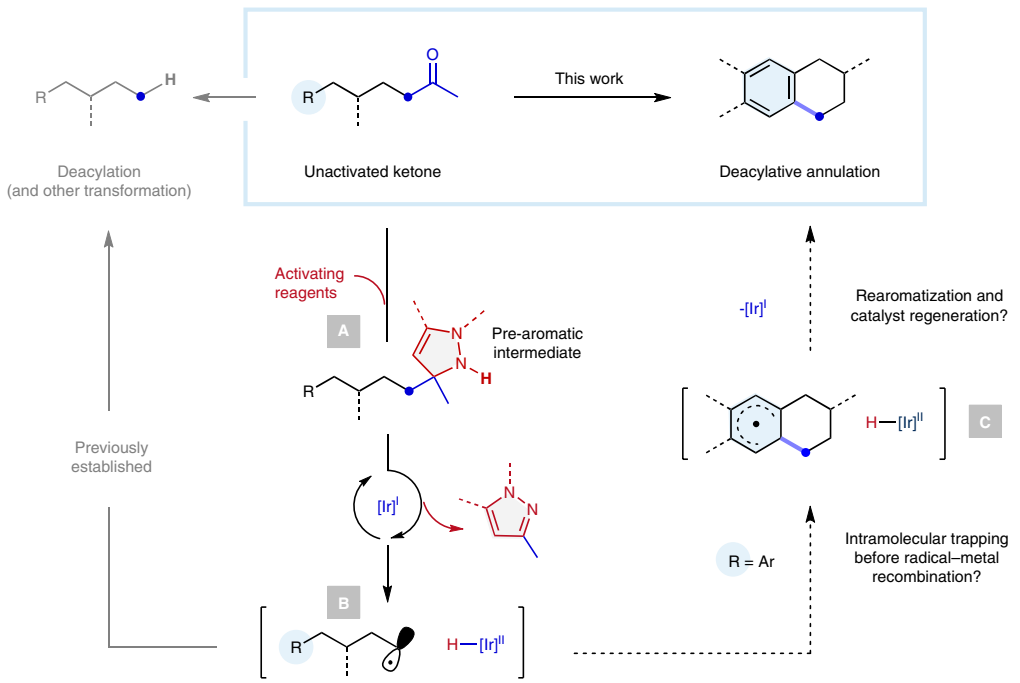
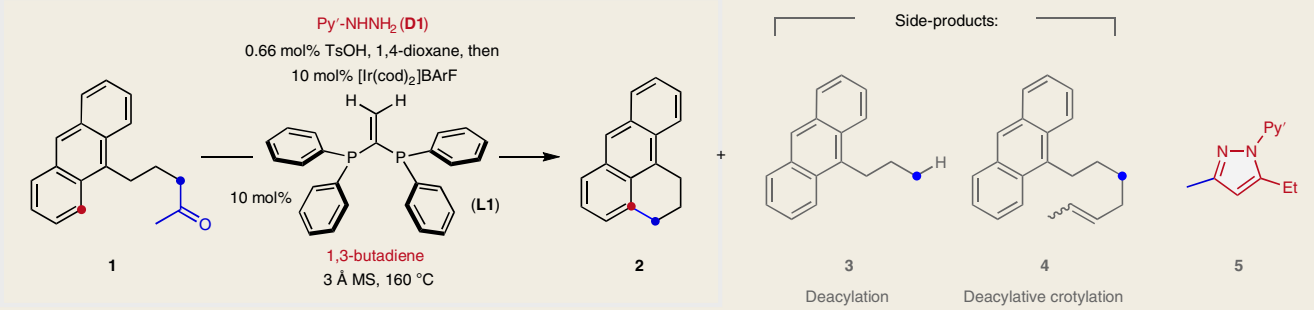
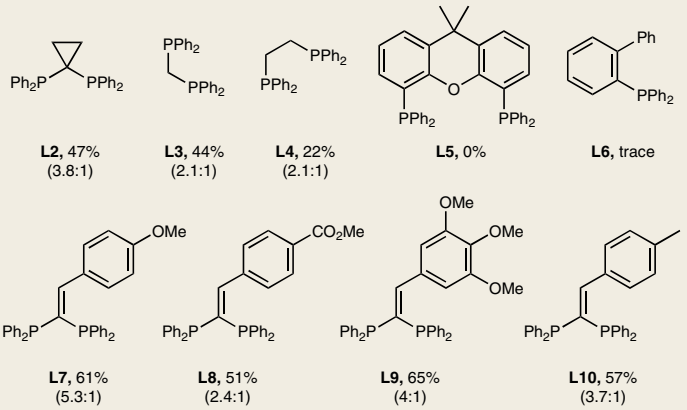


Fig. 2 | Reaction design. A working mechanistic hypothesis of deacylative C–H annulation through aromatization-driven C–C cleavage.

Table 1 | Optimal condition and control experiments



Entry	Variation from the standard condition	Total yield (%)	Selectivity **2**:(**3** + **4**)
1	None	68	10:1
2	$[Ir(cod)_2]BF_4$ instead of $[Ir(cod)_2]BArF$	trace	N/A
3	$[Ir(cod)_2]Cl$ instead of $[Ir(cod)_2]BArF$	trace	N/A
4	Without 3Å MS	15	3.2:1
5	2-MeTHF instead of 1,4-dioxane	57	2.1:1
6	DME instead of 1,4-dioxane	36	2.3:1
7[a]	**L2**-**L10** instead of **L1**	See right	



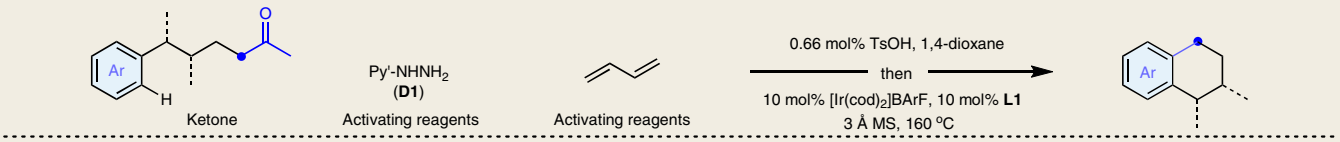
The reactions were conducted with **1** (0.05 mmol), 4-methyl-2-pyridylhydrazine (0.052 mmol) and 1,3-butadiene (0.54 mmol). The total yield and selectivity were determined by ^{1}H NMR analysis of the crude products using 1,1,2,2-tetrachloroethane as an internal standard. [a]The reaction was conducted using different ligands (**L2**-**L10**) instead of **L1** and a preformed hydrazone as the substrate. For detailed experimental procedures, see Supplementary Methods. Et, ethyl; Py′, 4-methyl-2-pyridyl.

phenyl]borate) and **L1** as an effective catalyst–ligand combination in 1,4-dioxane (Table 1, entry 1). A very small amount of TsOH (0.66 mol%, where Ts is *p*-toluenesulfonyl) was used together with molecular sieves to ensure complete condensation between the hydrazine and the ketone substrate (entry 4). The counter anion of the Ir catalysts appears to play a pivotal role in determining the reactivity (entries 2 and 3). While the site selectivity of the C–C cleavage was high (>15:1), major side-products came from other competing deacylative transformations, such as hydrogen termination and crotylation, which are expected to be influenced by the solvent and choice of ligands. For example, much lower cyclization selectivity was achieved in 2-methyl tetrahydrofuran (2-MeTHF) or 1,2-dimethoxyethane (DME) despite a comparable total yield (entries 5 and 6). A study of the ligand effect further suggested that large bite-angle bisphosphines (**L5**) or monophosphines (**L6**) were not effective, whereas bidentate ligands with small bite angles (**L1**–**L3**, **L7**–**L10**, ref. [63]) generally worked better, with **L1** giving both the optimal yield and selectivity (entry 7).

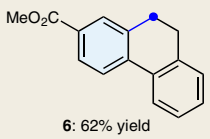
Substrate scope. With the optimal conditions in hand, the scope of the substrates was next explored (Table 2). A wide variety of single- and multi-arenes, including benzene, naphthalene (**26**), phenanthrene (**27**), anthracene (**28**) and even pyrene (**30**), can effectively undergo the desired alkylative annulation. Both electron-rich and deficient aromatic substrates are competent during the cyclization process. In all cases, the formation of six-membered rings was strongly favoured[9,14–18], and the possible five-membered ring side-product (for example, in the case of **14**) was essentially negligible. When the formation of six-membered rings was not realizable, five- and seven-membered rings (**24**, **25** and **35**) can still be constructed, albeit in lower efficiency due to competing hydrogen termination and crotylation. Moreover, a double annulation (**16**) proved to be feasible, directly affording a symmetrical tetracycle from a simple biaryl precursor. On the other hand, various FGs, such as Weinreb amides (**10**), esters (**6**), nitriles (**11**) and aryl halides (**17**, **21** and **22**), can all be tolerated in this transformation. It is worth noting that the carbon skeletons of many substrates were forged through either 1,4-additions with methyl vinyl ketone or migrative oxidative Heck reactions with enols; the resulting ketones were directly subjected to the annulation process, further highlighting the efficiency of the two-phase approach. Further, heteroarenes such as indoles (**31**), quinolines (**41**), dibenzofurans (**37**), benzothiophenes (**38**), imidazoles (**39**) and quinazolinones (**35** and **36**) can also be incorporated, providing pharmaceutically interesting fused-ring skeletons that are non-trivial to prepare otherwise[64]. Interestingly, when the cyclization took place on thiophenes or isoquinolinones, a dearomative annulation pathway competed with the re-aromatization process, showing the potential to access partially saturated heterocycles (**42′**–**44′**)[65,66].

Mechanistic considerations. While the detailed mechanism of the deacylative annulation reaction remains to be uncovered, a proposed reaction pathway is depicted in Fig. 3a. Based on our previous experimental and computational mechanistic studies of the deacylative functionalization[62], this reaction may be initiated from hydrazone formation between the ketone and hydrazine **D1**, followed by an Ir-catalysed [3+2] cycloaddition with 1,3-diene and alkene migration to form the pre-aromatic intermediate (**Int 2**). Subsequently, a directed N–H oxidative addition with the Ir(I) catalyst could take place to give an Ir(III)-hydride intermediate (**Int 3**),

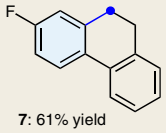
Table 2 | Scope of the substrates



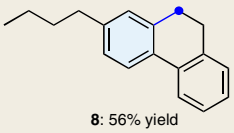
Simple arene



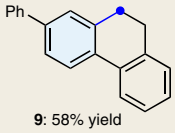
6: 62% yield



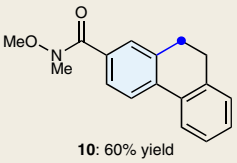
7: 61% yield



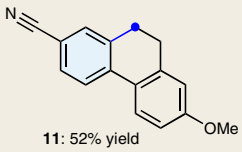
8: 56% yield



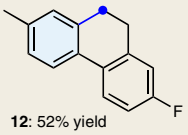
9: 58% yield



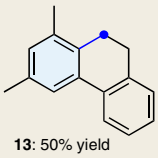
10: 60% yield



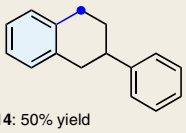
11: 52% yield



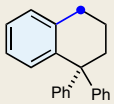
12: 52% yield



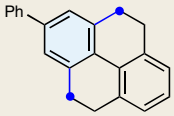
13: 50% yield



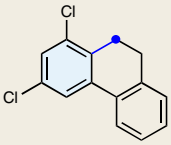
14: 50% yield



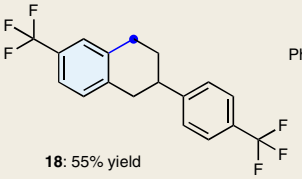
15: 43% yield



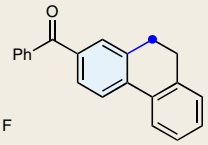
16: 44% yield[a]



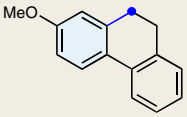
17: 52% yield



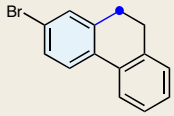
18: 55% yield



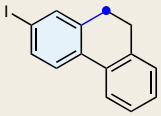
19: 48% yield[b]



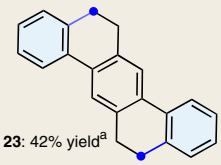
20: 43% yield



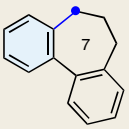
21: 52% yield



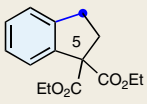
22: 32% yield



23: 42% yield[a]

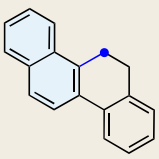


24: 21% yield

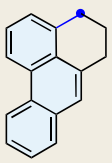


25: 32% yield

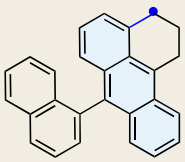
Multi-arene



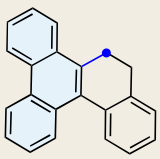
26: 70% yield, 4:1



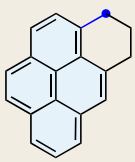
27: 64% yield



28: 52% yield

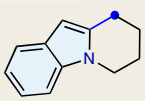


29: 50% yield

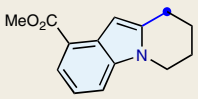


30: 36% yield

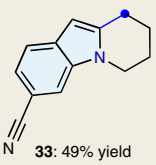
Heteroarene



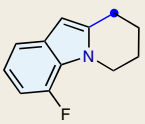
31: 57% yield



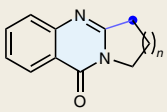
32: 50% yield



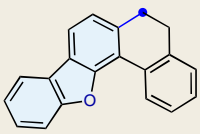
33: 49% yield



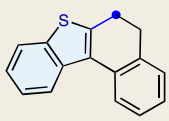
34: 60% yield



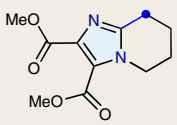
35: $n = 1$, 48% yield
36: $n = 2$, 53% yield



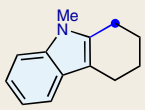
37: 44% yield



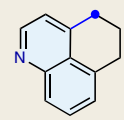
38: 49% yield



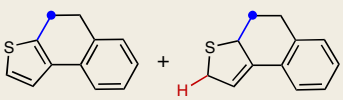
39: 52% yield[b]



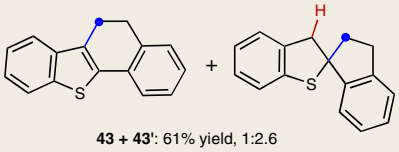
40: 47% yield



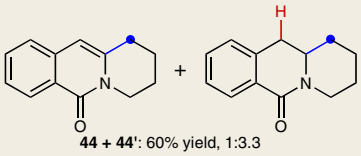
41: 42% yield



42 + 42': 65% yield, 1:1



43 + 43': 61% yield, 1:2.6



44 + 44': 60% yield, 1:3.3

The reactions were conducted on a 0.05 mmol scale. The reported isolated yields of the desired products were based on an average of two runs. [a]Ketone condensation with **D1** (2 equiv.) at 90 °C for 15 h. [b]Ketone condensation with **D1** at 60 °C for 18 h. For detailed experimental procedures, see Supplementary Methods.

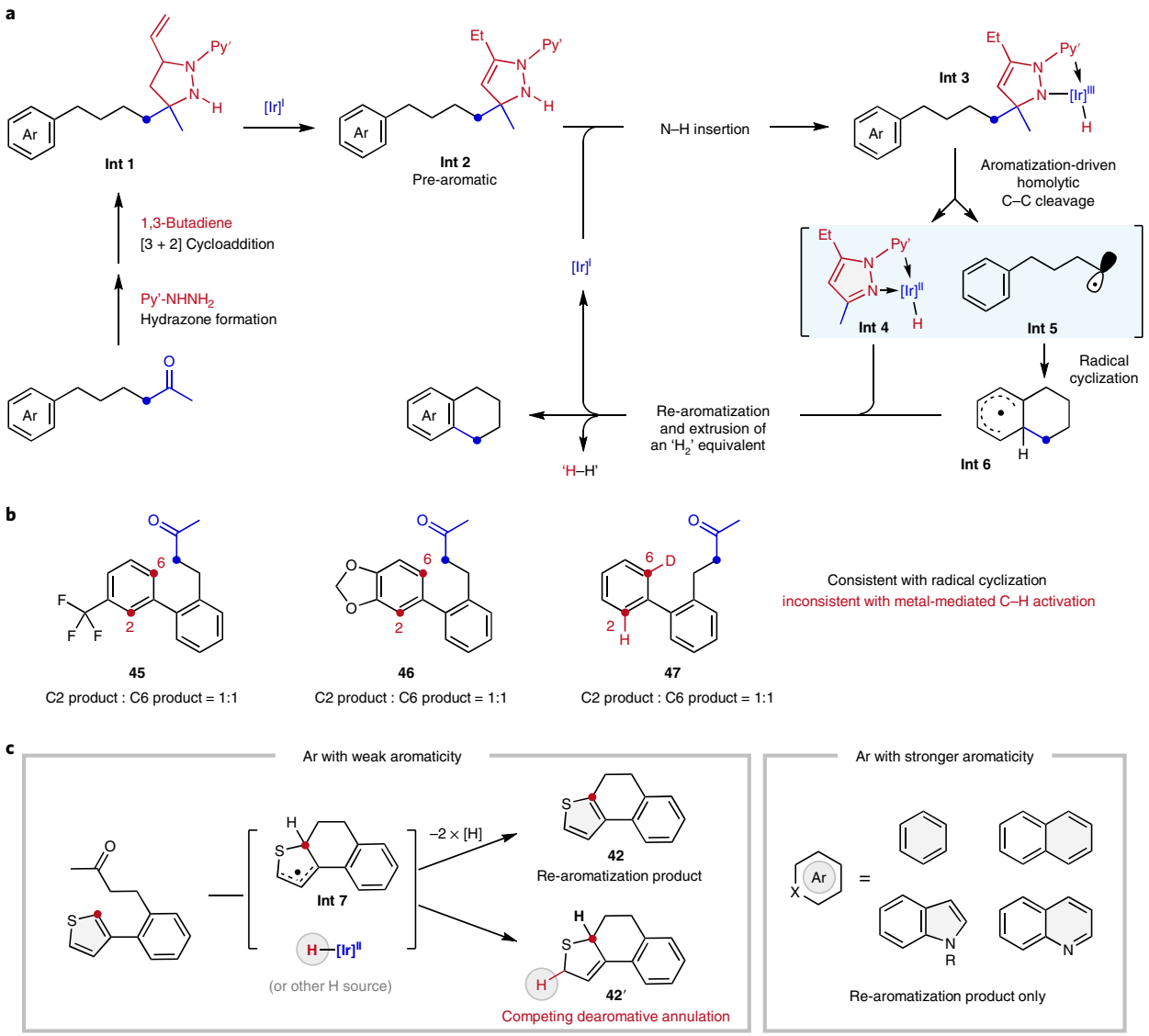


Fig. 3 | Preliminary mechanistic consideration. a, A proposed reaction pathway. **b**, A radical-based cyclization was suggested by the lack of steric influence and intramolecular kinetic isotope effect. **c**, Dearomative annulation was observed with heteroarenes having relatively weak aromaticity.

which then undergoes aromatization-driven homolytic C–C cleavage to form a pyrazole-coordinated Ir(II) hydride (**Int 4**) and an alkyl radical (**Int 5**). While facile radical–metal recombination was observed in the previous study, the alkyl radical is intercepted by a tethered arene in the current system. In line with the proposed pathway, the site selectivity of the cyclization appears to be less sensitive to the steric environment on the arene (for example, in **45** and **46**), which argues against a metal-mediated C–H activation pathway (Fig. 3b). In addition, no intramolecular kinetic isotope effect was observed in substrate **47**, which is also consistent with a radical-cyclization mechanism. While it is not completely clear how the re-aromatization occurs from **Int 6** at this stage, a plausible pathway may involve H-atom abstraction or radical trapping by the Ir(II) hydride intermediate. The resulting Ir(III) dihydride could eventually regenerate the Ir(I) catalyst, for example using a sacrificial 1,3-diene as the H_2 acceptor. For instance, when a heavier 1.3-diene, myrcene, was used in place of 1,3-butadiene, partially reduced myrcene with a molecular mass increased by 2 Da was observed. On the other hand, the oxidation of **Int 6** into a carbocation intermediate by the Ir(II), followed by deprotonation, cannot be ruled out. Nevertheless, the potential involvement of the Ir(II) hydride species could be supported by the formation of these partially aromatic products (**42′**–**44′**) from thiophenes or isoquinolinones. For example, due to the relatively weak aromaticity in thiophene, the radical-cyclization intermediate (**Int 7**) suffers from a slow re-aromatization process; an alternative pathway that involves coupling with the Ir(II) hydride intermediate to form a C–H bond can compete or even dominate (Fig. 3c). In contrast, no partial aromatic products were observed for arenes or heteroarenes with high aromaticity. Note that, at this stage, an Ir-triggered radical chain mechanism cannot be fully excluded.

Synthetic utility. Further study was carried out to show the utility of the deacylative annulation strategy in streamlined two-phase syntheses of aromatic-fused rings (Fig. 4). For example, the bicyclic dicarboxylate **49**, the key intermediate towards synthesis of anticonvulsant-active **50**, was readily prepared in two steps through 1,4-addition (phase I) followed by deacylative annulation (phase II); for comparison, the conventional synthesis required a five-step sequence (Fig. 4a)[67]. In another study, xanthine analogue **54**

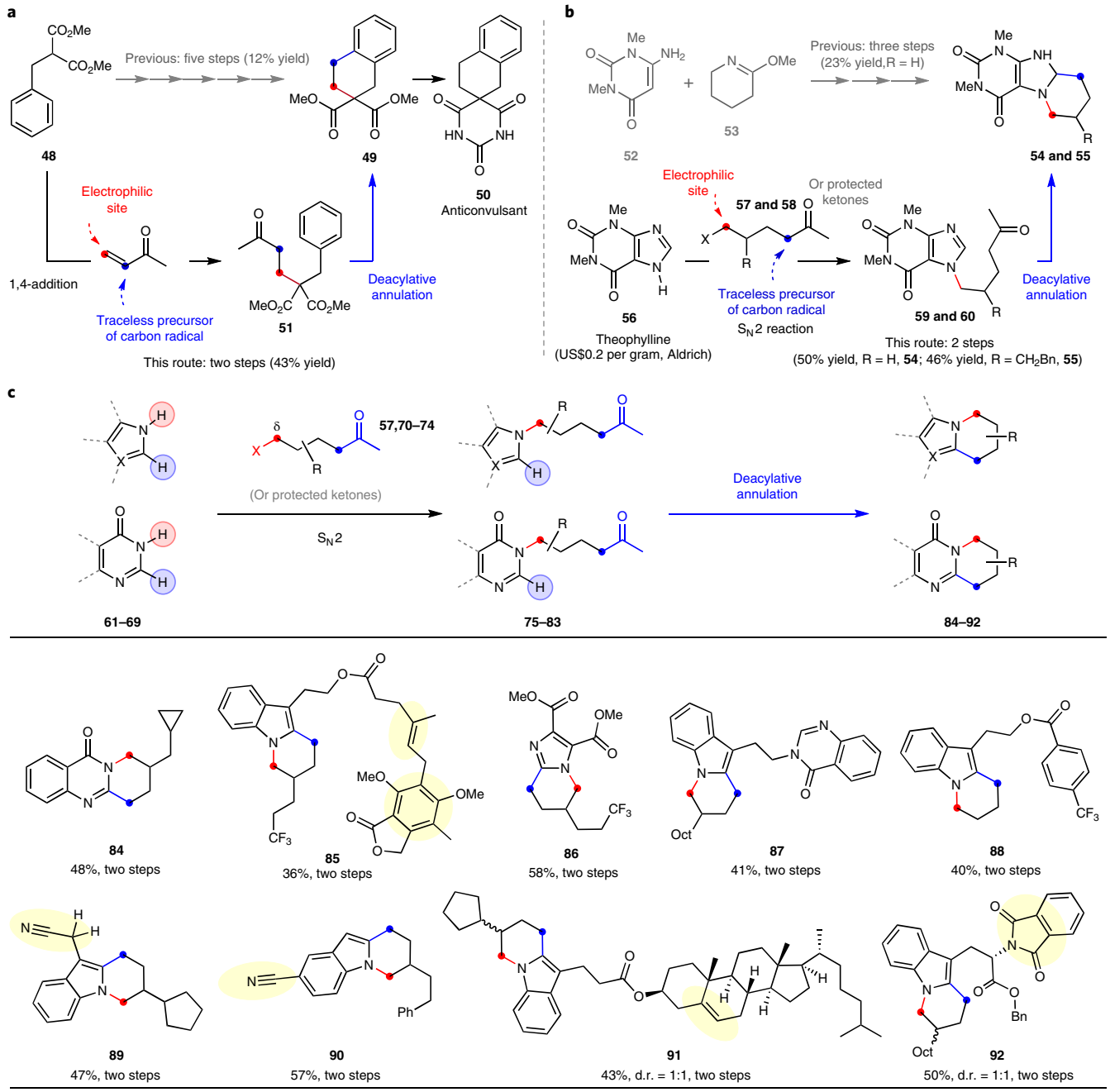


Fig. 4 | Synthetic applications of the deacylative C–H annulation. a, Synthesis of bicyclic dicarboxylate **49** was achieved in two steps, which required five steps previously. **b**, Improved synthesis of xanthine analogue **54** with a shortened route and doubled overall yield. **c**, Examples of using the two-phase annulation strategy for the late-stage construction of complex *N*-heteroarene polycyclic compounds. For detailed experimental procedures, see Supplementary Methods. d.r., diastereomeric ratio; S_N2, bimolecular nucleophilic substitution.

was previously made through a three-step sequence, while our approach only needs a two-step operation with doubled overall yield (Fig. 4b)[68]. Encouraged by these results, the two-phase annulation strategy was further applied to the late-stage construction of complex *N*-heteroarene-based polycyclic compounds (Fig. 4c)[19]. This process requires consecutive and orthogonal N–H and C–H alkylations in the presence of multiple FGs including olefins, nitriles, electron-rich arenes and reactive carbonyls, which is difficult to achieve under strongly Lewis acidic, oxidative or reductive conditions. Here, using *δ*-halo ketones as the linchpin, heterocycles, for example, indoles, imidazoles and quinazolinones, could all undergo the desired annulation to afford various fused-ring structures despite the complexity of the substrates. Given the ubiquity of *N*-heterocycle moieties in pharmaceuticals, this approach may find use in medicinal chemistry.

Conclusions. In summary, we have disclosed a distinct C–H alkylative annulation strategy for preparing diverse arene- and heteroarene-fused scaffolds. This strategy capitalized on the use of simple unstrained ketones as an unusual but native annulation reagent; through the Ir-catalysed aromatization-driven C–C cleavage, a deacylation process generates a reactive alkyl radical that undergoes subsequent C–H annulation with the tethered arene in good efficiency. Owing to the wide availability of the ketone

moiety and reductant/oxidant/strong acid-free reaction conditions, this deacylative annulation approach exhibits high FG tolerance and provides streamlined access to complex fused-ring systems. The general approach of generating alkyl radicals from ketones could have broad implications and further applications beyond this work.

Methods

General procedure for the deacylation-aided C–H alkylative annulation. For a 0.05-mmol scale reaction, a 1,4-dioxane (1 ml) solution of the ketone substrate (0.05 mmol, 1.0 equiv.), **D1** (6.4 mg, 0.052 mmol, 1.04 equiv.) and *p*-TsOH·H_2O (stock solution in 1,4-dioxane; 0.05 M, 6.6 µl, 0.0066 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 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, transferred into a glove box and further charged with a 3-Å molecular sieve (predried, 100 mg) and 1,3-butadiene (20 wt% in toluene, 180 µl, about 10.8 equiv.). 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 a short plug of Celite, concentrated and purified by flash column chromatography over silica to provide the product.

Data availability

Details about materials and methods, experimental procedures and characterization data are available in the Supplementary Information. Additional data are available from the corresponding authors upon request.

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Author contributions

X.Z, Y.X. and G.D. conceived and designed the experiments. X.Z. and Y.X. performed the experiments. X.Z., Y.X. and G.D. co-wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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