Rapid syntheses of N-fused heterocycles via acyl-transfer in heteroaryl ketones

Dan Ye¹,³, Hong Lu¹,³, Yi He¹, Zhaojing Zheng², Jinghao Wu¹ & Hao Wei¹✉

The wide-ranging potencies of bioactive N-fused heterocycles inspire the development of synthetic transformations that simplify preparation of their complex, diverse structural motifs. Heteroaryl ketones are ubiquitous, readily available, and inexpensive molecular scaffolds, and are thus synthetically appealing as precursors in preparing N-fused heterocycles via intramolecular acyl-transfer. To best of our knowledge, acyl-transfer of unstrained heteroaryl ketones remains to be demonstrated. Here, we show an acyl transfer-annulation to convert heteroaryl ketones to N-fused heterocycles. Driven via aromatisation, the acyl of a heteroaryl ketone can be transferred from the carbon to the nitrogen of the corresponding heterocycle. The reaction commences with the spiroannulation of a heteroaryl ketone and an alkyl bromide, with the resulting spirocyclic intermediate undergoing aromatisation-driven intramolecular acyl transfer. The reaction conditions are optimised, with the reaction exhibiting a broad substrate scope in terms of the ketone and alkyl bromide. The utility of this protocol is further demonstrated via application to complex natural products and drug derivatives to yield heavily functionalised N-fused heterocycles.
N-fused heterocyclic compounds, such as pharmaceuticals, agrochemicals, plastics, and dyes (Fig. 1a), are integrated into everyday life1–6. Big data analysis shows that heterocycle synthesis is one of the most common reactions in the field of medicinal chemistry7–8. Among the best-selling therapeutics, almost a third contain fused heterocyclic structures9. Due to the high value of N-fused heterocycles, their novel, effective, flexible, general syntheses require investigation10–12.

Acyl transfer is a critical process in various biological transformations13. In the field of organic synthesis, acyl transfer is frequently used in formation carbonyl compounds14–18. A typical acyl transfer employs a reactive carboxylic acid derivative (e.g., an acyl chloride or a thioester) as an acyl source. However, whether relatively inert ketones may serve as acyl transfer agents remains unclear.

Ketones are ubiquitous functional groups that not only occur widely in drug molecules and natural products but also act as bulk feedstocks in the syntheses of fine chemicals and materials. They are stable, non-toxic, and simple to prepare via various methods, rendering them ideal synthetic precursors19. If intra-molecular acyl transfer of heteroaryl ketones can be realised, a stable chelate (Fig. 1c)33–36 may be employed in N-fused heterocycle preparation (Fig. 1b). However, owing to the kinetic inertness of C–C bonds, acyl transfer of ketones largely focuses on highly strained ketones20–26. For unstrained ketones27–32, the most common strategy involves using directing groups to form a stable chelate (Fig. 1c)33–40. Although effective, the use of directing groups complicates the overall synthesis and limits the scope of the accessible products. Hence, a acyl transfer of unstranned ketones for use in N-fused heterocycle synthesis is warranted.

Aromatisation, which enables delocalisation of electron density, stabilising the molecule41, is a critical thermodynamic driving force in the field of organic chemistry42–45, e.g., aromatisation-driven deacylations of ketones are prominent bond-cleavage strategies46–48. Therefore, we conceived an approach for the acyl transfer of unstrained heteroaryl ketones driven by aromatisation of a pre-aromatic intermediate (Fig. 1d). This strategy may be suitable for use in the syntheses of N-fused heterocycles, and, critically, the directing group is no longer required. The next challenge in this strategy is the in situ formation of special, high-energy, pre-aromatic substrates. Transition metal-catalysed dearomatisation is a straightforward strategy to prepare spirocyclic scaffolds49–52. The spirocyclic intermediates, which are formed in situ from readily available heteroaryl ketones via dearomatisations53–56, should serve as pre-aromatic precursors to facilitate rearrangement (Fig. 1d). This likely involves a Pd-catalysed dearomative spirocyclisation of a heteroaryl ketone with an alkyl bromide to generate a pre-aromatic intermediate (A), which is then intramolecularly trapped by the heterocyclic nitrogen57–64. The resulting intermediate (B) may subsequently lose a hydrogen, restoring aromaticity to yield the fused heterocyclic product.

Here, we report an acyl transfer-annulation of heteroaryl ketones driven by aromatisation. This method is operationally simple, scalable, and applicable to late-stage modifications of natural products and drug derivatives, which make it a valuable method for the synthesis of organic N-fused heterocycles.

**Results**

**Reaction optimisation.** To explore this strategy, we initially used a heteroaryl ketone with a tethered olefin (1), which was prepared in one step using commercially available benzimidazole and 2-vinylbenzoyl chloride, as a model substrate. Because of the unique properties of difluoromethylene group (CF2) and its critical applications in medicinal chemistry55–57, ethyl bromodifluoroacetate (BrCF2COOEt) was employed as the coupling partner. After systematic screening, the desired rearrangement product (2) is obtained in a 90% yield using PdCl2 in combination with 1,1-bis(diphenylphosphino)pentane (dpppent, L1) as the ligand and Na2CO3 as the base in dioxane/tetrahydrofuran (THF) (Table 1, entry 1). The structure of 2 was unambiguously determined by X-ray crystallography. In addition, the Pd catalyst appears to be critical in this reaction. Using Pd(OAc)2 or Pd2(dba)3 (dba = dibenzylideneacetone) as the catalyst results in much lower yields (Table 1, entries 2–3), and other metals, such as NiCl2 and FeCl2, are

---

**Fig. 1** Examples of critical fused-heterocycles and our reaction design. **a** N-fused heterocycles are ubiquitous within critical molecules, including biologically active natural and synthetic compounds and fine chemicals for use in functional materials. **b** Transfer-annulation strategy for synthesis of N-fused heterocycles. **c** Different strategies used in acyl transfer of ketones. **d** Fused heterocycle synthesis in this study via aromatisation-driven acyl transfer of heteroaryl ketones with alkyl bromides.

---

2 NATURE COMMUNICATIONS | (2022) 13:3337 | https://doi.org/10.1038/s41467-022-31063-3 | www.nature.com/naturecommunications
Table 1 Screening of reaction conditions.

| Entry | Variation from ‘standard condition’ | Yield[a]% |
|-------|------------------------------------|-----------|
| 1     | None                               | 90        |
| 2     | Pd(OAc)₂ instead of PdCl₂          | 54        |
| 3     | Pd₂(dba)₃ instead of PdCl₂         | 51        |
| 4     | NiCl₂ or FeCl₂ instead of PdCl₂    | Trace     |
| 5     | L₂-L₁₂ instead of L₁              | See right |
| 6     | Without Na₂CO₃                     | 12        |
| 7     | In toluene                         | Trace     |
| 8     | In dioxane                         | 78        |
| 9     | In THF                             | 68        |

Unless otherwise specified, all reactions were carried out using 1 (0.1 mmol) and ethyl bromodiactate (0.15 mmol, 1.5 equiv), with 10 mol% PdCl₂, 12 mol% L₁ and Na₂CO₃ (1.0 equiv) in dioxane/THF (1:2) at 130 °C for 24 h. The CCDC number of 2 is 2116750.

[a] Isolated yields after chromatography.

Fig. 2 Substrate scope of alkyl bromides. Unless otherwise specified, all the reactions were carried out using ketone 1 (0.1 mmol, 1.0 equiv) and alkyl bromide (0.15 mmol, 1.5 equiv.), PdCl₂ (10 mol%), dpppent (12 mol%) and Na₂CO₃ (1.0 equiv) in dioxane/THF (1:2) at 130 °C. Isolated yields after chromatography are shown.
Fig. 3 Substrate scope of heteroaryl ketones. Isolated yields after chromatography are shown. The CCDC number of 43 is 216753, 52 is 216752. aThe reaction was performed under optimised condition A: ketone 1 (0.1 mmol, 1.0 equiv) and ethyl bromodiﬂuoroacetate (0.15 mmol, 1.5 equiv), PdCl2 (10 mol %), dpppent (12 mol%) and Na2CO3 (1.0 equiv) in dioxane/THF (1:2) at 120 °C for 24 h. bThe reaction was conducted under optimised condition A with a slight modiﬁcation: bis(2-diphenylphosphinophenyl)ether (DPEPhos) (12 mol%) was used as ligand during the reaction. cThe reaction was performed under optimised condition B: ketone 1 (0.1 mmol, 1.0 equiv) and ethyl bromodiﬂuoroacetate (0.15 mmol, 1.5 equiv), PdCl2 (10 mol %), dppf (12 mol%) and K2CO3 (1.0 equiv) in dioxane/THF (1:1) at 130 °C for 24 h. dppf = 1,1′-bis(diphenylphosphino)ferrocene.
fully coupled with various alkyl bromides, with 5-, 6-, 7-, or 12-individually good, albeit generating slightly lower yields than that survey of different solvents reveals that dioxane and THF are tetrahydropyrane (\(\text{THP}\)).

**Mechanistic studies.** a Radical trapping study using TEMPO showing that alkyl radical species are involved in the reaction. b EPR studies also suggest that this reaction may involve alkyl radicals. c Deuterium labelling studies. d Reaction of 1 with benzyl bromide in the presence of [Ph(PPh\(_3\)]\(_2\)PdBr] (58-[Pd]). e A proposed reaction pathway.

Substrate scope. With the conditions determined, the scope of alkyl bromides was examined first (Fig. 2). Ketone 1 is successfully coupled with various alkyl bromides, with 5-, 6-, 7-, or 12-membered cycloalkyls (3–6) generating good yields of the desired coupling products. Heterocyclic bromides, with moieties such as tetrahydroprayne (7) and THF (8), react smoothly, resulting in good yields. Remarkably, the polycyclic bromide derived from the natural steroid stanolone is also amenable to coupling under the reaction conditions (9). Linear alkyl bromides are also suitable for reaction (10–12). We then investigated substrates with a CF\(_2\) group. Bromofluoroacetate, bromodifluoromethyl ketone, perfluoroalkyl bromide, bromodifluoromethyl phosphonate, and bromodifluoromethyl sulfone effectively undergo the desired annulation (13–17).

We further explored the rearrangements of various heteroaryl ketones with bromodifluoroacetate (Fig. 3). The rearrangement took place smoothly by using 2-acylimidazoles and 2-acylbenzimidazoles as substrates (18–41). Both electron-rich and deficient substrates are competent during the cyclization process. A range of functional groups are compatible, including aryl fluorides (28 and 40) and chlorides (20 and 39), trifluoromethyl (21 and 38), esters (23) and cyano (22), are all tolerated. Changing the nitrogen protecting group from methyl to isopropyl (30) and benzyl (31) did not significantly affect the reactivity.

Compared to the substrate with 4,5-diphenylimidazole (32), the reactions of 4-phenylimidazole (33) and imidazole (34) yield lower conversions, indicating that aromatisation is essential to promote the reaction. Marketed drug-derived ketones, such as ketocanazole (41), also react smoothly despite the presence of several other functional groups. Significantly, numerous substrates are synthesised via direct acylation of commercially available imidazoles or benzimidazoles, with the resulting ketones directly undergoing rearrangement, which further highlights the efficiency of this process. Further, we examined other types of heterocycles, which should yield different heterocyclic cores via rearrangement. Heterocycles such as thiazole (42), benzothiazoles (43–51), benzoazole (52), and oxazole (53) may also be incorporated, yielding pharmaceutically interesting fused-ring skeletons\(^{55,56}\).

Mechanistic considerations. A study was performed to investigate the reaction pathway. To determine whether an alkyl radical
exists during this Pd-catalysed process, a radical inhibition study was performed. When 2,2,6,6-tetramethylpiperidinooxy (TEMPO) is added to the reaction mixture, it traps alkyl radicals, indicating that the reaction involves radical species (Fig. 4a). An electron paramagnetic resonance (EPR) study of the reaction of bromocyclopentane with the spin-trapping agent phenyl-N-tert-butyl nitrotrone reveals the presence of spin adducts of the trapped alkyl radicals 56 and 57 (Fig. 4b), as indicated by the EPR spectrum (see supporting information). Deuterium labelling studies were conducted using the heteroaryl ketone D-1 (79% deuterium content) as a substrate under the optimised conditions, with a significant level of the deuterated product D-2 (76% deuterium content) detected, suggesting that there were no reversible hydro-metallation in this process (Fig. 4c)67,68. Finally, we synthesised an aryl Pd complex (58-[Pd]), with 12 produced instead of 59 in the presence of 58-[Pd], benzyl bromide, and 1 (Fig. 4d). Therefore, the alkyl group of the fused heterocyclic product is not derived from the migratory insertion of the Pd(II)
complex. The proposed reaction pathway is thus shown in Fig. 4e. The reaction may be initiated by a single electron transfer between Pd(0) and the alkyl bromide, producing hybrid alkyl Pd(I)-radical species INT I. Subsequently, radical addition to the alkene occurs, leading to the hybrid benzylic radical INT II, which then undergoes degradative-spirocyclisation to form the spiro-N-radical INT III. Aromatisation-driven intramolecular acyl transfer may then occur to form the alkyl radical INT IV. Subsequent β-H elimination at the latter yields the product with concomitant regeneration of the Pd catalyst. This proposed mechanism is also supported by X-ray photoelectron spectroscopy, which revealed the presence of three distinct Pd oxidation states (Pd(0), Pd(I), and Pd(II)) during the process, suggesting the mechanism is also supported by X-ray photoelectron spectroscopy.

Data availability

Data relating to the optimisation studies, mechanistic studies, general methods, and the characterisation data of materials and products, are available in the Supplementary Information. Crystallographic data for compounds 2, 43, 52 and 74 are available free of charge from the Cambridge Crystallographic Data Centre under CCDC 2116750 (2), 2116753 (43), 2116752 (52) and 2113840 (74). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

Received: 16 February 2022; Accepted: 30 May 2022; Published online: 09 June 2022

References

1. Taylor, R. D., MacCoss, M. & Lawson, A. D. Rings in drugs. J. Med. Chem. 57, 5845–5859 (2014).
2. Ning, J. et al. A highly sensitive and selective two-photon fluorescent probe for real-time sensing of cytochrome P450 1A1 in living systems. Mater. Chem. Front. 2, 2013–2020 (2018).
3. Kumar, S., Bawal, S. & Gupta, H. Biological activities of quinoline derivatives. Mini. Rev. Med. Chem. 9, 1648–1654 (2009).
4. Bollini, M. et al. New potent imidazolquinolinemine derivatives as anti-trypanosoma cruzi agents: Biological evaluation and structure–activity relationships. Bioorg. Med. Chem. 17, 1437–1444 (2009).
5. Cui, J. et al. A highly sensitive and selective fluorescent probe for N{sub}-H{sub} in air and living cells. J. Nat. Chem. 41, 11891–11897 (2017).
6. Hao, Y. et al. Discovery of trypanthrinis as novel antiviral and anti-phytopathogenic fungus agents. J. Agric. Food Chem. 68, 5386–5395 (2020).
7. Schneider, N., Lowe, D. M., Sayle, R. A., Tarselli, M. A. & Landrum, G. A. Big data from pharmaceutical patents: a computational analysis of medicinal chemists' bread and butter. J. Med. Chem. 59, 4385–4402 (2016).
8. Brown, D. G. & Boström, J. Analysis of past and present synthetic methodologies on medicinal chemistry: where have all the new reactions gone? J. Med. Chem. 59, 4443–4458 (2016).
9. McGrath, N. A., Brichacek, M. & Njardarson, J. T. A graphical journey of innovative organic architectures that have improved our lives. Chem. Educ. 87, 1348–1349 (2010).
10. Roeyt J. Asymmetric Synthesis of Nitrogen Heterocycles (Wiley-VCH, 2009).
11. Eicher, T., Hauptmann, S. & Speicher, A. The Chemistry of Heterocycles: Structures, Reactions, Synthesis, and Applications (Wiley-VCH, 2012).
12. Wu, X.-F. Transition Metal-Catalyzed Heterocycle Synthesis via C=H Activation (Wiley-VCH, 2015).
13. Roth, S. Y., Denu, J. M. & Allis, C. D. Histone acetyltransferases. Annu. Rev. Biochem. 70, 81–120 (2001).
14. Burke, H. M., McSweeney, L. & Scanlan, E. M. Exploring chemoselective S-to-N acyl transfer reactions in synthesis and chemical biology. Nat. Commun. 8, 15653 (2017).
15. Ramakers, B. E. L., van Hesta, J. C. M. & Löwik, D. W. P. M. Molecular tools for the construction of peptide-based materials. Chem. Soc. Rev. 43, 2743–2756 (2014).
16. Penteado, F. et al. a-Keto acids: acylating agents in organic synthesis. Chem. Rev. 19, 7113–7278 (2019).
17. Li, G. & Szostak, M. Transition-metal-free activation of amides by N–C bond cleavage. Chem. Rec. 20, 649–659 (2020).
18. Shi, S., Nolan, S. P. & Szostak, M. Well-defined palladium(II)–NHC precatalysts for cross-coupling reactions of amides and esters by selective N=O–C=O cleavage. Acc. Chem. Res. 51, 2589–2599 (2018).
19. March, J. March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (8th ed) pp 579–586, pp 891–899 (John Wiley & Sons, 2020).
20. Chen, P.-h., Billett, B. A., Tsukamoto, T. & Dong, G. "Cut and sew" transformations via transition-metal-catalyzed carbon-carbon bond activation. ACS Catal. 7, 1340–1360 (2017).

Synthetic utility. Further studies were conducted to demonstrate the viability of this acyl transfer-annulation strategy. The protocol was applied in the late-stage modifications of natural products and drug derivatives (Fig. 5a). Various complex molecules with diverse structural features, such as steroids (62 and 69), N-heteroaromatic oxazoles (63 and 64), alkaloids (65-67), halogenated (68), and carboxylic acids (72), are readily converted into the corresponding products in useful yields. This strategy provides a straightforward, versatile method of generating valuable N-fused heterocyclic moieties within complex molecules. Given the ubiquity of N-fused heterocycles in pharmaceuticals, this approach may be used in the field of medicinal chemistry.

In conclusion, a synthetically useful, mechanistically intriguing intramolecular acyl transfer of heteroaryl ketones was developed, which was suitable for use in fused-ring synthesis. The formation of a high-energy pre-aromatic spirocyclic intermediate was critical in the successful transformation, with aromatisation the driving force that facilitated C–C bond cleavage. Given the ready availability of the ketone moiety, this strategy could be used to simplify the syntheses of complex N-fused heterocyclic systems, which are privileged structures within numerous biologically active compounds. Moreover, the protocol enabled the late-stage modifications of intricate natural products and drug derivatives and may thus facilitate heterocyclic drug discovery.

Methods

General condition A for transfer-annulation of heteroaryl ketones derived from (benz)imidazoles. In a nitrogen-filled glovebox, an oven-dried 10 mL sealed tube equipped with a Teflon-coated magnetic stir bar was charged successively with heteroaryl ketone 1 (0.1 mmol), difluorobromomethyl ester (0.15 mmol, 1.5 equiv), PdCl2 (0.01 mmol, 10 mol%), dpdf (0.012 mmol, 12 mol%), K2CO3 (0.1 mmol, 1.0 equiv) and dioxane/THF (1.0 mL, 1:1). The tube then was sealed with a Teflon screw cap, moved out of the glovebox, and placed on a hotplate pre-heated to 120 °C for 24 h. After completion of the reaction, the mixture was filtered through a thin pad of silica gel. The filter cake was washed with ethyl acetate and the combined filtrate was concentrated under vacuum. The residue was purified via silica gel chromatography.

General condition B for transfer-annulation of heteroaryl ketones derived from (benzo)thiazoles and (benzo)oxazoles. In a nitrogen-filled glovebox, an oven-dried 10 mL sealed tube equipped with a Teflon-coated magnetic stir bar was charged successively with heteroaryl ketone 1 (0.1 mmol), difluorobromomethyl ester (0.15 mmol, 1.5 equiv), PdCl2 (0.01 mmol, 10 mol%), dpdf (0.012 mmol, 12 mol%), K2CO3 (0.1 mmol, 1.0 equiv) and dioxane/THF (1.0 mL, 1:1). The tube then was sealed with a Teflon screw cap, moved out of the glovebox, and placed on a hotplate pre-heated to 120 °C for 24 h. After completion of the reaction, the mixture was filtered through a thin pad of silica gel. The filter cake was washed with ethyl acetate and the combined filtrate was concentrated under vacuum. The residue was purified via silica gel chromatography.

NATURE COMMUNICATIONS | https://doi.org/10.1038/s41467-022-31063-3 | www.nature.com/naturecommunications
21. Murakami, M. & Ishida, N. Cleavage of carbon-carbon σ-bonds of four-membered rings. *Chem. Rev.* **121**, 264–299 (2021).

22. Fumagalli, G., Stanton, S. & Bower, J. F. Recent methodologies that exploit C–C single-bond cleavage of strained ring systems by transition metal complexes. *Chem. Rev.* **117**, 9404–9432 (2017).

23. Seiser, T., Saget, T., Tran, D. N. & Cramer, N. Cyclobutanes in catalysis. *Angew. Chem. Int. Ed.* **50**, 7740–7752 (2011).

24. Murakami, M., H. & Ito, Y. Selective activation of carbon–carbon bonds next to a carbonyl. *Nature* **370**, 540–541 (1994).

25. Murakami, M. & Chatani, N. Cleavage of carbon-carbon single bonds by transition metals (Wiley-VCH, 2015).

26. Bender, M., Turnbull, B. W., Ambler, B. R. & Krisha, M. J. Ruthenium-catalyzed insertion of adjacent diol carbon atoms into C–C bonds: entry to cyclobutane derivatives. *Science* **357**, 779–781 (2017).

27. Soulliart, L. & Cramer, N. Catalytic C–C bond activations via oxidative addition to transition metals. *Chem. Rev.* **115**, 9410–9464 (2015).

28. Deng, L. & Dong, G. Carbon-bond activation of ketones. *Trends Chem.* **2**, 183–198 (2020).

29. Xia, Y. & Dong, G. Temporary or removable directing groups enable activation of unstrained C–C bonds. *Nat. Rev. Chem.* **4**, 600–614 (2020).

30. Chen, F., Wang, T. & Jiao, N. Recent advances in transition-metal-catalyzed functionalization of unstrained carbon-carbon bonds. *Chem. Rev.* **114**, 8613–8661 (2014).

31. Lu, H., Yu, T.-Y., Xu, P.-F. & Wei, H. Selective decarboxylation via transition-metal-catalyzed carbon-bond cleavage. *Chem. Rev.* **121**, 365–411 (2021).

32. Song, F., Gao, T., Wang, B.-Q. & Shi, Z.-J. Catalytic activations of unstrained C–C bond involving organometallic intermediates. *Chem. Soc. Rev.* **47**, 7078–7115 (2018).

33. Dreis, A. M. & Douglas, C. J. Catalytic carbon-carbon σ bond activation: an intramolecular meta-cleavage reaction with acylaziridines. *J. Am. Chem. Soc.* **131**, 412–413 (2009).

34. Jun, C.-H. & Lee, H. Catalytic carbon-carbon bond activation of unstrained ketone by soluble transition-metal complex. *J. Am. Chem. Soc.* **121**, 880–881 (1999).

35. Xia, Y. et al. Catalytic activation of carbon-carbon bonds in cyclopentanones. *Nature* **539**, 546–550 (2016).

36. Rong, Z. Q. et al. Intramolecular acetyl transfer to olefins by catalytic C–C bond activation of unstrained ketones. *Angew. Chem. Int. Ed.* **57**, 475–479 (2018).

37. Xia, Y. et al. Two-carbon ring expansion of 1-indanones via insertion of ethylene into carbon-bonded indanones. *J. Am. Chem. Soc.* **141**, 13038–13042 (2019).

38. Shao, P., Yu, T., Lu, H., Xu, P.-F. & Wei, H. Regioselective access to 2- or 3-substituted indanones: catalyst-controlled carboacylation via C–C bond activation. *CCS Chem.* **2**, 1862–1871 (2020).

39. Zhang, R., Xia, Y. & Dong, G. Intermolecular [5+2] annihilation between 1-indanones and internal alkenes by rhodium-catalyzed C–C C bond activation. *Angew. Chem. Int. Ed.* **60**, 20476–20482 (2021).

40. Huang, J., Zhang, R., Wu, X., Dong, G. & Xia, Y. Intramolecular one-carbon homologation of unstrained ketones via C–C activation-enabled 1,1-insertion of alkynes. *Org. Lett.* **24**, 2436–2440 (2022).

41. Schleyer, P. V. R. & Pühlofer, F. Recommendations for the evaluation of aromatic stabilization energies. *Org. Lett.* **4**, 2873–2876 (2002).

42. King, R. B. & Efraty, A. Pentamethylene cyclopentadienyl derivatives of transition metals. II. Synthesis of pentamethylene cyclopentadienyl metal carbonyls from 5-acetyl-1,2,3,4,5-pentamethylcyclopentadiene. *J. Am. Chem. Soc.* **94**, 3773–3779 (1972).

43. Crabtree, R. H., Dion, R. P., Gibboni, D. J., Mcgrath, D. V. & Holt, E. M. Carbon–carbon bond cleavage in hydrocarbons by iridium complexes. *J. Am. Chem. Soc.* **108**, 7222–7227 (1986).

44. Youn, S. W., Kim, B. S. & Jagdal, A. R. 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).

45. Smith, G., Audic, B., Wodrich, L. M., Corninnhout, C. & Cramer, N. A β-carbon elimination strategy for convenient in situ access to cyclopentadienyl metal complexes. *Chem. Sci.* **8**, 7174–7179 (2017).

46. Xu, Y. et al. Deacetylative transformations of ketones via aromatization-promoted C–C bond activation. *Nature* **567**, 573–578 (2019).

47. Zhou, X., Xu, Y. & Dong, G. Deacylation-aided C–H alklylation annihilation through C–C cleavage of unstrained ketones. *Nat. Catal.* **4**, 703–710 (2021).

48. Zhou, X., Xu, Y. & Dong, G. Olefination via Cu-mediated dehydroacylation of unsaturated ketones. *J. Am. Chem. Soc.* **143**, 20042–20048 (2021).

49. Roche, S. P. & Porco, J. A. Jr. Deaoromatization strategies in the synthesis of complex natural products. *Angew. Chem. Int. Ed.* **50**, 4068–4093 (2011).

50. Zhou, C.-X., Zhang, W. & You, S.-L. Catalytic asymmetric deaoromatization reactions. *Angew. Chem. Int. Ed.* **51**, 12662–12686 (2012).
