Cleaving arene rings for acyclic alkenylnitrile synthesis

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Xu Qiu[1,6], Yueqian Sang[3,6], Hao Wu[1,4,6], Xiao-Song Xue[2,3], Zixi Yan[1], Yachong Wang[1], Zengrui Cheng[1], Xiaoyang Wang[1], Hui Tan[1], Song Song[1], Guisheng Zhang[4], Xiaohui Zhang[1], K. N. Houk[2] ✉ & Ning Jiao[1,5] ✉

Synthetic chemistry is built around the formation of carbon–carbon bonds. However, the development of methods for selective carbon–carbon bond cleavage is a largely unmet challenge[1–6]. Such methods will have promising applications in synthesis, coal liquefaction, petroleum cracking, polymer degradation and biomass conversion. For example, aromatic rings are ubiquitous skeletal features in inert chemical feedstocks, but are inert to many reaction conditions owing to their aromaticity and low polarity. Over the past century, only a few methods under harsh conditions have achieved direct arene-ring modifications involving the cleavage of inert aromatic carbon–carbon bonds[7,8], and arene-ring-cleavage reactions using stoichiometric transition-metal complexes or enzymes in bacteria are still limited[9–11]. Here we report a copper-catalysed selective arene-ring-opening reaction strategy. Our aerobic oxidative copper catalyst converts anilines, arylboronic acids, aryl azides, aryl halides, aryl triflates, aryl trimethylsiloxanes, aryl hydroxamic acids and aryl diazonium salts into alkenyl nitriles through selective carbon–carbon bond cleavage of arene rings. This chemistry was applied to the modification of polycyclic aromatics and the preparation of industrially important hexamethylenediamine and adipic acid derivatives. Several examples of the late-stage modification of complex molecules and fused ring compounds further support the potential broad utility of this methodology.

Since the discovery of benzene by Faraday nearly 200 years ago[12], the substitution of arenes has rapidly developed[13,14]; however, the activation of aromatic carbon–carbon (C–C) bonds[1–6] via ring-expansion or ring-opening reactions remains even now a challenging and largely unexplored area due to the difficulty in breaking aromaticity and the high bond dissociation energy of an aromatic C=C bond (calculated bond dissociation energy 147 kcal mol^{-1}). In addition, the thermodynamic and kinetic limitations block the conversion of arene rings surrounded by the C–H bonds. To achieve the preparation of useful value-added acyclic compounds from arenes, as well as coal liquefaction and biomass conversion, researchers have studied the selective cutting open of arene rings[7,8]. In industry, the naphtha hydrocracking process of benzene performed at high temperature, producing methylcyclopentane and acyclic saturated hydrocarbons, suffers from a mixture of products (Fig. 1a)[8]. Although the preparation of useful C6 synthons and more complex acyclic fragments from benzenes is attractive, catalytic methods to cleave widely available arene rings under mild conditions with good selectivity are still unknown.

In recent decades, several strategies have been reported for such reactions. (1) The cleavage of arene rings in bacteria transforms benzene into muconic acid via a multistep oxidizing pathway[4] catalysed by two key dioxygenases (Fig. 1b)[15], but the enzymatic process is hard to mimic[11,16]. (2) Transition-metal complexes have also been developed for dearomative C–C bond cleavage of arenes[9,10,17] or *ortho*-phenylenediamines[18–20]. The groups of Parkin[9] and Crimmin[17] realized the C–C bond cleavage of quinoxaline heteroarene and biphenylene by a tungsten complex and a aluminium(I) complex, respectively. A titanium-mediated C–C bond cleavage and rearrangement of benzene was disclosed by Hou and co-workers[10]. (3) Alternatively, the ring expansion of arenes by carbene[21], nitrene[22,23] or phosphinidene[24] species have been reported for the preparation of seven-membered ring compounds. Despite the importance of these strategies, the preparation of acyclic products from benzenes is rarely applied in chemical synthesis.

It is reported that 1,2-diazidobenzene yields 1,4-dicyano-1,3-butadiene through a thermal decomposition process[18,25–27], which indicates that the 1,2-phenylene bis-nitrene intermediate can lead to benzene ring-opening. Inspired by the enzymatic process in bacteria (Fig. 1b), we hypothesized that a biomimetic cascade activation strategy for general arenes could incorporate two active nitrogen cofactors that would work like the catechol to target the intradiol ring-cleaving dioxygenase for the subsequent arene ring-opening, thus converting arene derivatives into alkenyl nitriles. We demonstrate a novel copper-catalysed aerobic oxidative arene ring-opening transformation that affords selective arene-ring C–C bond cleavage. A broad range of arene derivatives,

[1]State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Sciences, Peking University, Beijing, China. [2]Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, CA, USA. [3]State Key Laboratory of Elemento-organic Chemistry, College of Chemistry, Nankai University, Tianjin, China. [4]Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, China. [5]State Key Laboratory of Organometallic Chemistry, Chinese Academy of Sciences, Shanghai, China. [6]These authors contributed equally: Xu Qiu, Yueqian Sang, Hao Wu. ✉e-mail: houk@chem.ucla.edu; jiaoning@pku.edu.cn

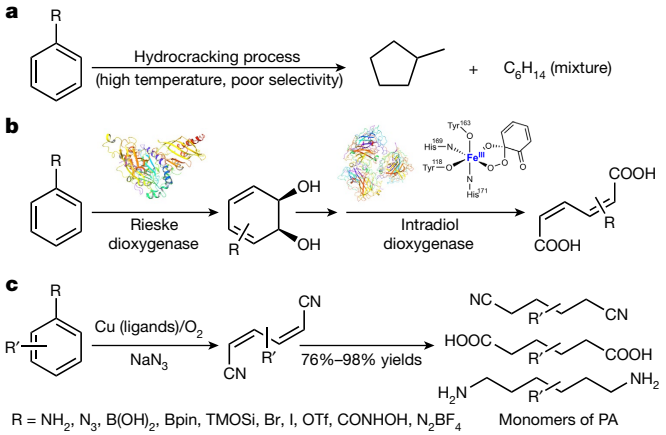

Fig. 1 | Cleaving arene rings. a, The industrial hydrocracking process for the arene ring-opening transformation. **b**, The cleavage of arene rings in bacteria with Rieske dioxygenase (Protein Data Bank 3EN1) and intradiol dioxygenase (Protein Data Bank 4WHR). **c**, Copper catalysed arene ring-opening reactions for the preparation of alkenyl nitriles and adiponitrile, hexamethylenediamine and adipic acid derivatives. FG, functional group; pin, pinacolate; TMO, trimethoxy; OTf, trifluoromethanesulfonate; PA, polyamide.

including anilines, arylboronic acids, aryl azides, aryl halides, aryl triflates, aryl trimethylsiloxanes, aryl hydroxamic acids and aryl diazonium salts can now be efficiently converted into alkenyl nitriles, and easily transformed into the industrially important adiponitrile, hexamethylenediamine and adipic acid derivatives (Fig. 1c).

The investigation began with naphthalen-1-amine as the substrate. We initially selected azides as the proposed active nitrogen cofactor, because of their high reactivity and their importance in chemistry and chemical biology, such as click chemistry[28–32], C–H functionalization[33–35], C–C functionalization[36–38] and other synthetic chemistry[39,40]. The extensive screening demonstrated that the present hypothesis was achieved by an aerobic oxidative copper catalyst, which successfully delivered (*Z*)-2-(2-cyanovinyl)benzonitrile (**2**) with high stereoselectivity (Supplementary Section 4.1). The further broad screening of catalysts and ligands indicated that the $Cu(NO_3)_2{\cdot}3H_2O$ with ligand 2,2′-bipyridine has the key role in the C–C cleavage of the benzene ring with air as the oxidant. Inspired by these results, we also achieved the cleavage of naphthalen-1-ylboronic acid. In this case, the screening results showed that the $Cu(hfacac)_2{\cdot}H_2O$ performed much better than other copper salts (Supplementary Section 4.2.2).

Modification of the skeleton of polycyclic aromatic compounds substantially alters their physical and chemical properties[41–43]. Naphthylamine and naphthylboronic acid derivatives readily give the aromatic ring-opening products (Fig. 2a); the cleavage of naphthylboronic acids better tolerates electron-withdrawing groups than naphthylamines (**15**–**20**). The transformation is not limited to naphthalene, and quinoline (**18** and **19**), isoquinoline (**20**) and some larger conjugated arene rings (**29**–**36**) can be cleaved in these reactions with moderate to good yields.

It is noteworthy that other common aromatic chemicals, including aryl hydroxamic acids, aryl azides, aryl trimethylsiloxanes, aryl halides, aryl triflates and aryl diazonium salts, can be efficiently converted into alkenyl nitriles by the present cascade activation strategy (Fig. 2b). Among them, 1-naphthohydroxamic acid **37**, 1-azidonaphthalene **38** and 1-naphthyldiazonium tetrafluoroborate **43** afforded the alkenyl nitrile product **2** with yields of 50% to 70%. Furthermore, benzene, alkyl benzenes and benzyl alcohols, which are common in bulk chemicals, could also be transformed into dearomative ring-cleavage products via modified procedures (Supplementary Section 4.4.3). These results demonstrate the broad prospects of the further development of dearomative C–C bond cleavage.

Owing to the importance of C6 synthons in polymers[44,45], the scope of different alkyl-side-chain-substituted benzene substrates was investigated (Fig. 3a). Substrates bearing amide (**58**), SMe (**59**), OMe (**60**–**62**), olefin (**63**), phenyl (**64** and **65**) and substituted aryl groups (**66**–**76** and **83**), and cyclic aliphatic rings (**77**, **78** and **84**) underwent cleavage reaction with moderate to good yields. It is noteworthy that the cleavage of conjugated aromatic heterocycles, including furan (**79**), benzofuran (**80**), benzothiophene (**81**) and indole (**82**), offers new heterocycles with cyano and cyanovinyl substituents.

These approaches also hold promise for the late-stage modification of complex molecules (Fig. 3b). Alkenes, amides, Boc-protecting groups, ethers and esters (**85**–**91**) are well tolerated, with good chirality retention. Although anilines substituted with strong electron-donating groups, such as 3,4-dimethoxyaniline, cannot undergo the cleavage process, the corresponding arylboronic acids substituted with strong electron-donating groups underwent cleavage well (**62**), which demonstrates the excellent complementary protocol for these two kinds of substrate.

Notably, the formed cyanoalkene products can be easily reduced to industrially important acrylonitrile and adiponitrile derivatives with Pd/C and H_2, and can be further transformed into corresponding substituted hexamethylenediamine **98** and adipic acid derivative **99** with good efficiencies (Extended Data Fig. 1a). In addition, the influence of the ring-cleavage transformation on the optical properties of the aromatic compounds was studied, as the introduction of a flexible alkenyl nitrile chain might improve the aggregation-induced emission property of the conjugated aryl-ring chemicals (Supplementary Section 4.4.5).

To understand the mechanism, we subjected benzene-1,2-diamine (**100**), 2-azidoaniline (**101**), 1,2-diazidobenzene (**102**), in-situ-generated benzyne (**103**) and azobenzene (**104**) to the standard conditions used for the cleavage of anilines; in no case was a ring-cleaved alkenylnitrile product formed, excluding these intermediates from being involved in this transformation (Extended Data Fig. 1b). The corresponding anilines or aryl azides could be detected form different starting materials when we changed the standard conditions or reduced the loading of azides (Supplementary Section 4.3.1.3), which indicates that they are the common key intermediates of these reactions. Moreover, the ^{15}N-labelling experiment with ^{15}N-labelled naphthalen-1-amine demonstrates that NaN_3 provides only one nitrogen atom in the cleavage of anilines (Fig. 4a).

Quantum mechanical calculations using density functional theory (DFT) at the (U)M06-D3/6-311++G(d,p)-SDD(Cu)-SMD(DMF)//(U)B3LYP-D3-(BJ)/6-31G(d)-SDD(Cu)-SMD(DMF) (see Supplementary Information for details) level enriches the mechanistic details. Enlightened by the reactions of the copper complex with aryl azides[46,47] and the Cu(I)/Cu(II) redox cycle in related aerobic copper catalytic reactions[48,49], we explored the likelihood of a copper nitrene intermediate. A plausible mechanism is shown in Fig. 4b. It involves (1) capture of the azide radical by the triplet copper nitrene, (2) inner-sphere *ortho*-azidation, (3) hydrogen atom abstraction, (4) bis-nitrene formation and (e) copper-assisted dearomative C–C bond cleavage. The triplet copper nitrene (^{3}**Int1**) can capture the azide radical to give the copper azide (^{4}**Int2**) in the quartet state, which leads to the doublet one (^{2}**Int2**) through a minimum energy crossing point (**MECP1**). Following the inner-sphere azidyl group transfer from copper leads to an *ortho*-azidated species (^{2}**Int3**) regioselectively, whereas direct attack of the azide radical towards the phenyl ring is obstructed (Supplementary Fig. 11). Subsequent hydrogen atom abstraction by a second azide radical affords a copper *ortho*-azido nitrene (^{3}**Int4**). For comparison, the azide anion is not competent in both azidation of ^{3}**Int1** and deprotonation of ^{2}**Int3** (Supplementary Fig. 13). Extrusion of N_2 in ^{3}**Int4** furnishes a key intermediate, the triplet copper bis-nitrene (^{3}**Int5**), which features a substantially weakened C–C bond. Consequently, the ensuing ^{3}**TS4** of C–C bond cleavage, still in the triplet state, has an energy barrier as low as 3.4 kcal mol^{-1}, whereas the singlet analogue is energetically

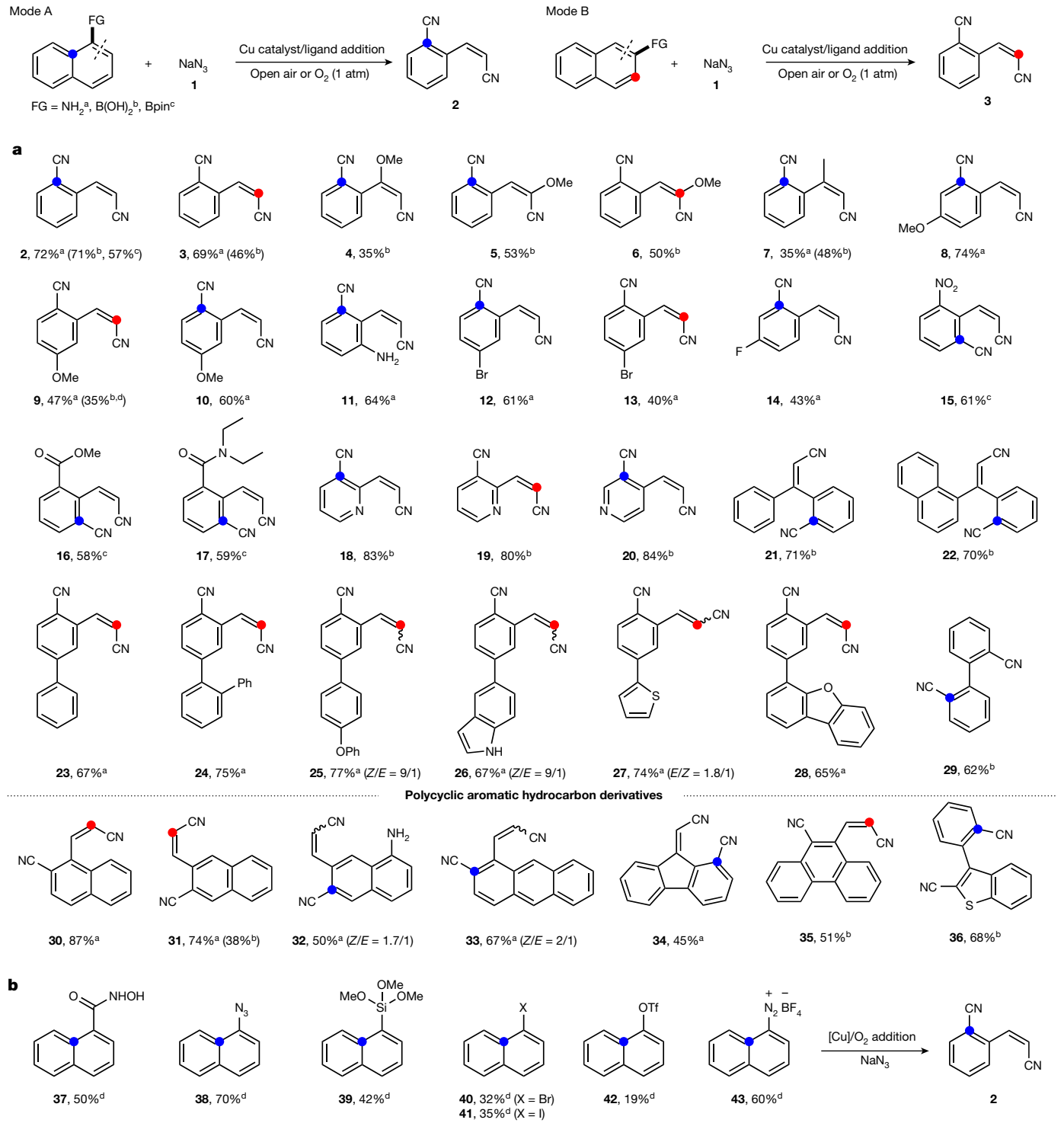

Fig. 2 | Scope of polycyclic aromatic compounds and transformations to *ortho*(*cis*-cyanovinyl) arylnitriles. a, The scope of naphthylamines and naphthylboronic acids. **b**, The scope of other substituted naphthalene compounds. Only isolated yields are shown. Only one *Z*- or *E*-isomer was detected, or the ratio is larger than 20:1 unless the ratio is given. [a]Prepared from naphthylamine (0.3 mmol), with $Cu(NO_3)_2{\cdot}3H_2O$, 2,2′-bipyridine and KH_2PO_4 in DMF at 40 °C under open air. [b]Prepared from naphthylboronic acid (0.3 mmol), with $Cu(hfacac)_2{\cdot}H_2O$ and 4-MeOPyridine in PhCl at 130 °C under O_2 (1 atm). [c]Using the boronic acid pinacol ester as the substrate under the same condition of naphthylboronic acid. [d]See the Supplementary Information for experimental details. hfacac, hexafluoroacetylacetonate.

prohibited (Supplementary Fig. 17). After ^{3}**TS4**, a complex of copper and product (^{3}**Int6**) forms, which facilely transforms into the singlet state (^{1}**Int6**) via **MECP2**, and a final ligand exchange with solvent releases the ring-opening product.

In addition, the kinetic isotope effect experiments and the study of reaction kinetics are consistent with the proposed pathways (Supplementary Section 4.3.1). A trace amount of the released HN_3 was detected by a gas chromatography–tandem mass spectrometry system via headspace sample injection, which is consistent with the hydrogen atom abstraction by the azide radical (Supplementary Section 4.3.3). More importantly, for the cleavage of aniline, electrospray ionization–high-resolution mass spectrometry (ESI–HRMS) analysis

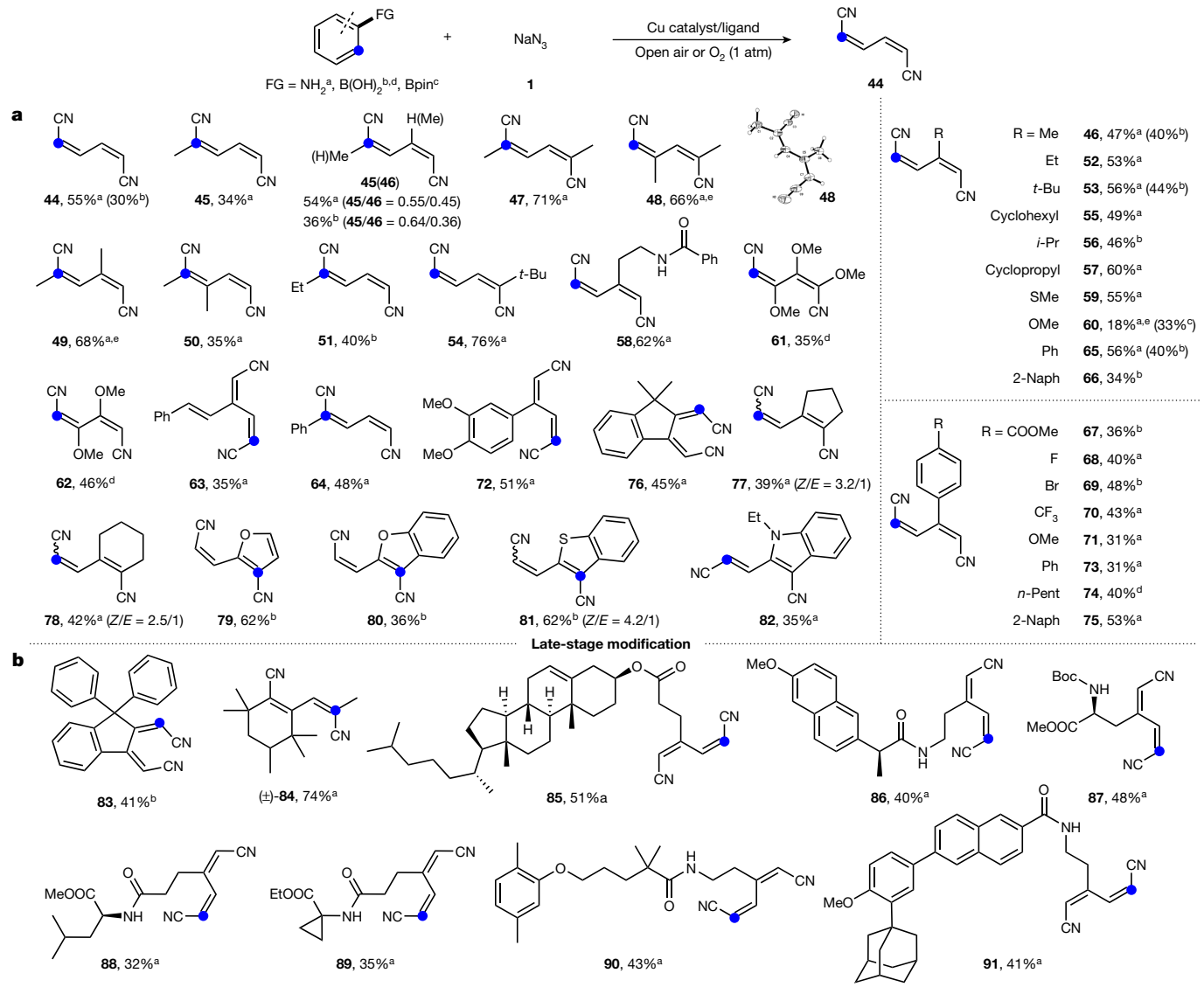

Fig. 3 | The cleavage of anilines and phenylboronic acids and downstream transformations. a, The scope of anilines and phenylboronic acids. **b**, Late-stage modification of complex molecules. Only isolated yields are shown. Only one *Z*- or *E*-isomer was detected, or the ratio is larger than 20:1 unless the ratio is given. [a]Reaction performed with aniline (0.3 mmol), with $Cu(NO_3)_2{\cdot}3H_2O$, 4-MeOPyridine in DMF at 40 °C under open air. [b]Reaction performed with phenylboronic acid (0.3 mmol), with $Cu(hfacac)_2{\cdot}H_2O$, Ph-BOX and 3-MeOPyridine in PhCl at 130 °C under O_2 (1 atm). [c]Using the phenylboronic acid pinacol ester (0.3 mmol), with $Cu(hfacac)_2{\cdot}H_2O$, 2,2′-bipyridine in PhCl at 130 °C under O_2 (1 atm). [d]Reaction performed with phenylboronic acid (0.3 mmol), with $Cu(hfacac)_2{\cdot}H_2O$, 2,2′-bipyridine in PhCl at 130 °C under O_2 (1 atm). [e]See the Supplementary Information for experimental details. Ph-BOX, (4*S*,4′*S*)-2,2′-(cyclopentane-1,1-diyl)bis(4-phenyl-4,5-dihydrooxazole).

of the reaction sample (diluted in acetonitrile) detected ion peaks and the isotope ion peaks of two copper nitrene species resembling ^{2}**Int3** and ^{3}**Int4** (Fig. 4b). Although the ESI–HRMS analysis could not provide information of the quantity of the detected species, the high-sensitivity detection of the generated intermediates indicates the possible involvement of copper nitrene intermediates in the process (Supplementary Section 4.3.4).

By inspecting the molecular orbitals (MO) of the triplet copper bis-nitrene intermediate, we noticed antibonding interaction between p_N and σ_{C-C}* in both singly occupied molecular orbitals HOMO(α) and HOMO-1(β). HOMO(α) represents the intrinsic orbital interaction in bis-nitrene, while HOMO-1(β) shows not only the intrinsic contributions but also the involvement of the d_{Cu} orbital (Extended Data Fig. 1c). These two MOs together unveil a unique bonding pattern leading to C–C bond cleavage: chelation of bis-nitrene with copper efficiently facilitates lone pairs of two adjacent nitrogen atoms to interact with the antibonding orbital of the intervening C–C bond, which facilitates the arene ring C–C bond cleavage.

Compared with the thermolysis pathway of 1,2-diazidobenzene, the current mechanism has a lower energy barrier for ring cleavage (^{3}**TS4**, 3.4 kcal mol^{-1} versus ^{1}**TS-II**, 6.1 kcal mol^{-1}; Supplementary Figs. 7 and 25). As antibonding interaction exists in ^{1}**Int-I** (the intermediate before ^{1}**TS-II**) as well, the decreased barrier for catalytic ring cleavage is ascribed to a better mixing of σ_{C-C}* and p_N in ^{3}**Int5**, probably owing to the presence of transition metal.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-021-03801-y.

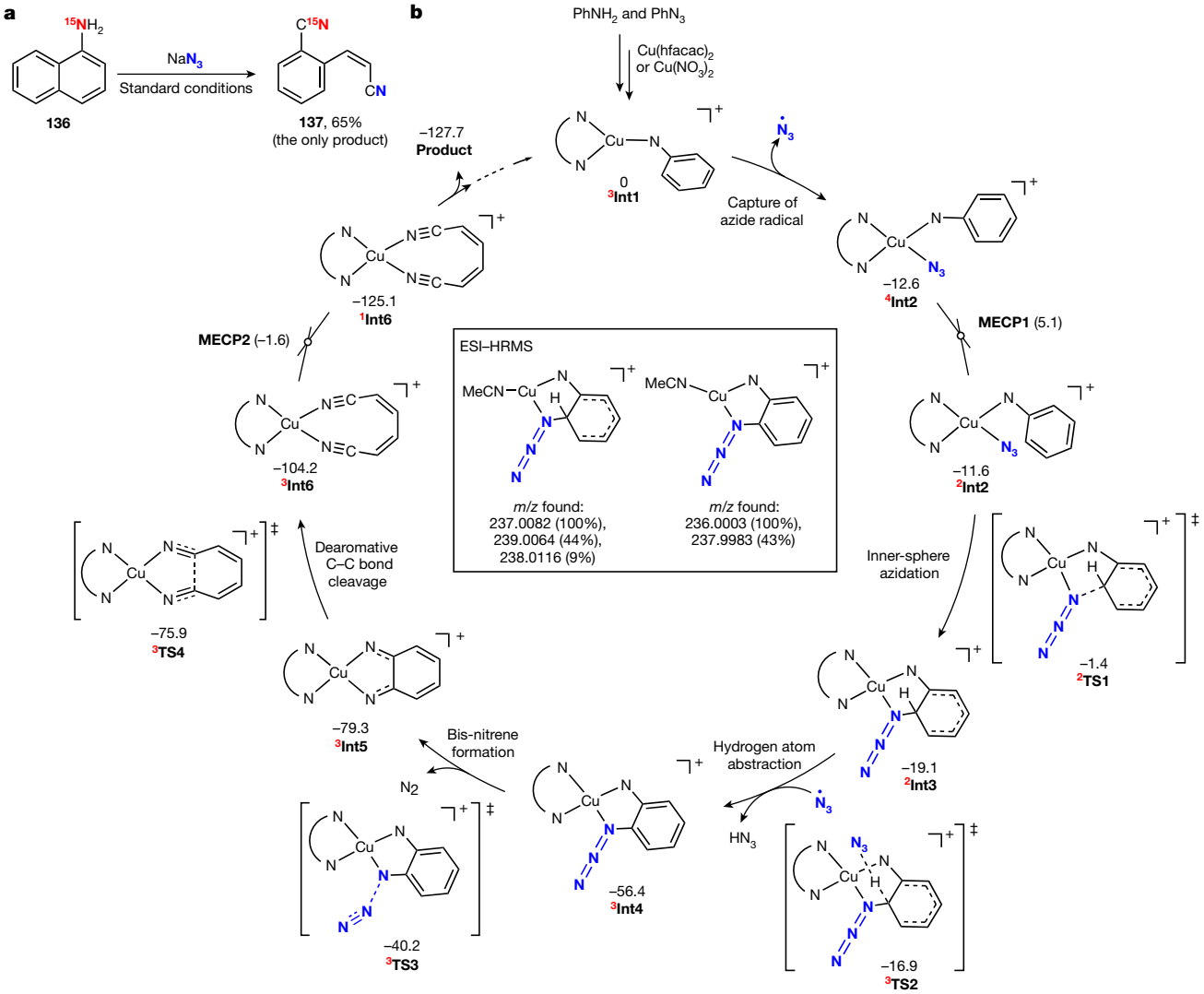

Fig. 4 | Mechanism studies. a, Isotopic labelling experiment with the ^{15}N-labelled naphthalen-1-amine as the substrate. **b**, Proposed mechanism. Detected copper nitrene species from the reaction sample of aniline diluted with acetonitrile via ESI–HRMS and energies from DFT calculations ((U)M06-D3/6-311++G(d,p)-SDD(Cu)-SMD(DMF)//(U)B3LYP-D3-(BJ)/6-31G(d)-SDD(Cu)-SMD(DMF)). The superscript numbers on the top left corners of Int and TS denote spin multiplicity. All energies are in kcal mol^{-1}. ^{15}N, nitrogen-15 isotope with seven protons and eight neutrons.

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Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Author contributions N.J. conceived the project and directed the research. K.N.H. and X.-S.X. supervised the mechanistic study. X.Q., Y.S., X.-S.X., K.N.H. and N.J. wrote the paper. X.Q., H.W., Z.Y., Y.W., Z.C. and X.W. performed the experiments. Y.S. performed the DFT calculations. H.T, S.S., G.Z. and X.Z. discussed the results.

Competing interests The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to K.N.H. and N.J.

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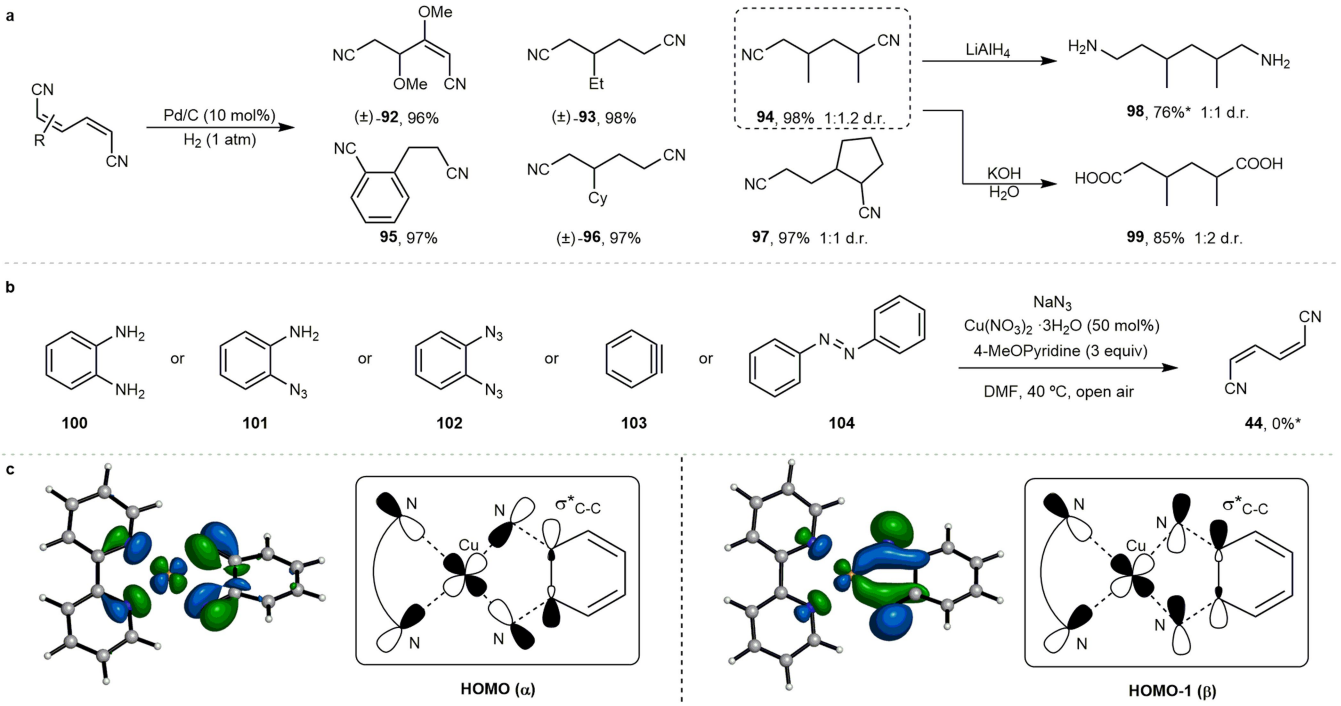

Extended Data Fig. 1 | Downstream transformations and mechanism studies. a, Downstream transformations of alkenyl nitriles. **b**, The excluded intermediates. **c**, HOMO(α) and HOMO-1(β) of the triplet copper bis-nitrene intermediate. *See Supplementary Information for experimental details.