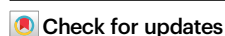


# Unveiling mechanistic patterns of copper-catalyzed radical bond formation through linear free energy relationship

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Guo-Xiong Xu<sup>1,5</sup>, Ji-Ren Liu<sup>1,5</sup>, Zeng Gao<sup>2,5</sup>, Miao-Jiong Tang<sup>1</sup>, Yi-Zhou Sun<sup>1</sup>, Zhong-Liang Li<sup>2</sup>, Xin-Yuan Liu<sup>3</sup>, Shuo-Qing Zhang<sup>1</sup>✉ & Xin Hong<sup>1,4</sup>✉

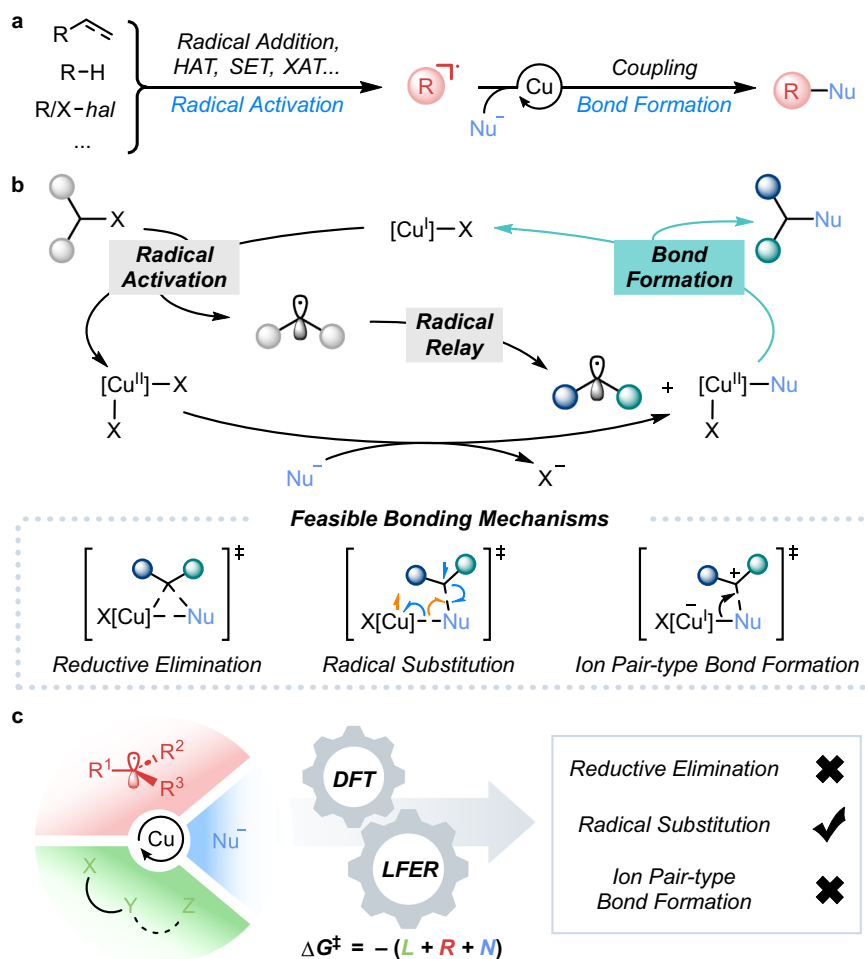
Copper-catalyzed radical transformations have seen extensive investigations over recent decades. Due to the complexity of controlling factors and the diversity of reaction components, accurately delineating the bond formation mechanisms—namely reductive elimination, outer-sphere radical substitution, and ion pair-type bond formation—poses a formidable challenge. This study reveals the linear free energy relationships (LFER) for the C–C bond formation of Cu-catalyzed radical transformations. Leveraging this discovery, we formulate an accurate LFER model for predicting radical bond formation mechanisms in this catalytic system. By establishing LFER scales for ligands, radicals, and nucleophiles, the bond formation mechanisms across 132,300 potential Cu-catalyzed radical transformations are revealed, offering a detailed mechanistic guide for future C–C bond designs. This research advances the mechanistic understanding of Cu-catalyzed radical transformations, providing systematic and quantitative insights into the mechanistic preference of radical bond formations.

As central intermediates in synthetic chemistry, radicals are prominently recognized for their high reactivity and diverse generation pathways<sup>1–3</sup>. However, this reactivity also presents significant challenges in selectivity control<sup>4</sup>, prompting chemists to employ open-shell transition metal catalysis in radical chemistry for taming these reactive species<sup>4–8</sup>. By leveraging the diverse d-electron configurations and the rich functionalities of ligands, radical transformations have achieved remarkable advancements in synthetic control and application scope<sup>4–6,9</sup>. Copper catalysis, in particular, is celebrated for its exceptional reactivity, efficient selectivity control, and versatility in radical bond formation modes<sup>5,10–13</sup>. These innovations have led to a variety of effective radical transformation strategies, especially radical transformation reactions that have opened additional avenues for stereoselective functionalization<sup>14</sup> and cross-coupling of C(sp<sup>3</sup>)–H

bonds<sup>6,15</sup>, establishing copper catalysis as a representative system for radical transformation (Fig. 1a).

The synthetic value of Cu-catalyzed radical transformations has sparked intense interest in unraveling their reaction mechanisms. Fruitful experimental and computational mechanistic studies have elucidated the molecular-level elementary processes of these catalytic systems (Fig. 1b), particularly highlighting the Cu(II)-mediated radical bond formation processes that play a decisive role in stereoselectivity determination<sup>5,13,16,17</sup>. These studies have culminated in the identification of three widely accepted bond formation modes: reductive elimination (RE) of Cu(III) intermediates, outer-sphere radical substitution (RS), and ion pair-type (IP, also known as radical-polar crossover) bond formation via carbocation<sup>5,10</sup>. Interestingly, as ligands, radicals, and nucleophiles vary, all three bond formation modes have proven to be

<sup>1</sup>Center of Chemistry for Frontier Technologies, Department of Chemistry, State Key Laboratory of Clean Energy Utilization, Zhejiang University, Hangzhou, China. <sup>2</sup>Dongguan Key Laboratory of Interdisciplinary Science for Advanced Materials and Large Scale Scientific Facilities, School of Physical Sciences, Great Bay University, Dongguan, China. <sup>3</sup>Department of Chemistry and Guangming Advanced Research Institute, Shenzhen Grubbs Institute, Southern University of Science and Technology, Shenzhen, China. <sup>4</sup>School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang, China. <sup>5</sup>These authors contributed equally: Guo-Xiong Xu, Ji-Ren Liu, Zeng Gao. ✉e-mail: [angellasty@zju.edu.cn](mailto:angellasty@zju.edu.cn); [hxchem@zju.edu.cn](mailto:hxchem@zju.edu.cn)



**Fig. 1 | Mechanistic insights into copper-catalyzed radical transformations.**

**a** Key elementary steps involved in copper-catalyzed radical transformations.

**b** Proposed catalytic cycle for copper-catalyzed radical transformations involving

three types of radical bond formation mechanism. **c** Linear free energy relationships (LFERs) in copper-mediated radical bond formation and mechanistic predictions (this study).

operative. The density functional theory (DFT) calculations from Liu, Stahl, and co-workers indicated that Cu/bisoxazoline(Cu/Box)-catalyzed C–H cyanation proceeds through a reductive elimination mechanism<sup>18</sup>, and Liu's subsequent research on C–H trifluoromethylation provided mass spectrometric evidence of the transient Cu(III) intermediates<sup>19</sup>. Stahl et al. were able to capture the carbocation intermediates in Cu/bisoxazoline(Cu/Biox)-catalyzed C–H alkoxylation, with DFT calculations also corroborating the ion pair-type bond formation mechanism<sup>20</sup>. Fu and Peters conducted a series of thorough mechanistic studies on Cu-catalyzed asymmetric alkylation of oxygen and nitrogen nucleophiles<sup>21–23</sup>, which led to collective evidence from EPR, stoichiometric experiments on organometallic intermediates, and DFT calculations supporting a radical-substitution-type C–N bond formation mode<sup>23</sup>. Our collaborations with Liu indicated that anionic copper catalyst with tertiary radicals tend to favor an outer-sphere radical substitution mechanism<sup>24</sup>. These studies have established the mechanistic foundation for the Cu-catalyzed radical transformation, affording chemists a detailed understanding of how copper catalysts facilitate radical bond formation processes.

Although the previous investigations have provided a solid basis for understanding the operative mechanisms, it is worth noting that there remains a lack of comprehensive insights into the controlling factors that determine the preference between the three bond

formation modes. Consequently, systematic rules that clarify how variations of bond formation mechanisms manifest in this catalysis are absent. To the best of our knowledge, among the myriad combinations of ligands, nucleophiles, and radicals within Cu-catalyzed radical transformations, there are no established protocols to predict the mechanistic pathway for each combination. Currently, knowledge about the operative bond formation mode under a given radical transformation predominantly stems from time-consuming post factum DFT calculations<sup>13</sup>, which cannot support the proactive design of new radical transformation reactions, posing challenges in further development and exploration within this catalytic system.

The elucidation of mechanistic principles in Cu-catalyzed radical transformations requires a precise and systematic understanding of the structure-activity relationships (SARs) for each radical bond formation pathway, thereby enabling the determination of mechanistic trends. In this context, linear free energy relationships (LFERs) emerge as a powerful strategy. As a milestone discovery in physical organic chemistry, LFER has unveiled fundamental correlations between reaction thermodynamics and kinetics, providing an effective means for quantifying substituent effects. Classical LFER models like the Hammett equation have played a pivotal role in mechanistic interpretation and rational reaction design, and contemporary LFER research has further expanded its scope and impact. A prominent

example of modern LFER discoveries is the Mayr equation<sup>25</sup>. It establishes quantitative scales for nucleophilicity and electrophilicity, offering a robust and practical framework for predicting rate constants across millions of polar reactions. Furthermore, Sigman's pioneering work has revolutionized the application of multivariate linear regression in organic synthesis, underscoring the importance and practicality of a multidimensional approach in SAR analysis<sup>26–28</sup>. These advancements have collectively contributed to the development of predictive linear models for reactivity and selectivity, profoundly shaping the rationalization and design of synthetic transformations in contemporary chemical research.

Inspired by the Mayr equation, we envisioned employing LFERs to build SARs for each bond formation mode in Cu-catalyzed radical transformations, aiming to systematically unravel the mechanistic trends for these transformations (Fig. 1c). Herein we report DFT calculations on hundreds of diverse catalytic combinations of ligands, radicals, and nucleophiles, which revealed that the influence of each component on the barriers of Cu(II)-mediated radical C–C bond formation is linearly additive. This enabled the development of quantitative scale for radicals, nucleophiles, and especially ligands, allowing the precise evaluation of all three bond formation modes with a high level of accuracy ( $R^2$  about 0.99, MAE within 1.8 kcal/mol). This methodology has rigorously quantified shifts in mechanistic pathways of Cu(II)-mediated radical C–C bond formation, predicting bond formation modes across tens of thousands of Cu-catalyzed radical transformation reactions. Selected predictions were further corroborated with transition state calculations, yielding compelling mechanistic revelations. This study not only offers a comprehensive and quantitative perspective on the radical bond formation mechanisms in Cu-catalyzed radical transformations but also broadens the scope of LFER application, providing valuable insights for developing quantitative SARs in transition metal catalysis.

## Results

### Workflow of mechanism space mapping

Figure 2 illustrates the workflow of mapping the mechanism space of radical bond formation in Cu-catalyzed radical transformations through predictive LFER modelling. Following the methodological principles of the Mayr equation and other classical LFER studies, our approach integrated three key steps: (1) DFT Calculation and LFER Evaluation: Starting with a statistically significant and chemically diverse array of catalytic combinations, transition states, and reaction barriers for all three bond formation modes were computed. Ternary linear equations were constructed to evaluate whether the LFER approach can quantitatively describe the reaction barriers of radical bond formation process and to assess the combined equations' accuracy in determining mechanistic preferences; (2) Building Quantitative Scale: Based on the ternary LFER equations, the most suitable reference reactions were identified. From these ternary LFER equations, the quantitative scales for commonly encountered radicals, nucleophiles,

and ligands in Cu-catalyzed radical transformations were established by comparing the barrier differences with the selected references; (3) Mapping the Mechanism Space: Utilizing these scales, the reaction mechanisms of conceivable Cu-catalyzed radical transformations are predicted. This not only provides a systematic guide map for an extensive chemical space of the titled reactions but also offers a quantitative analysis of the influence of each catalytic component on bond formation mechanism, especially the ligand effect.

### Definition of the target chemical space

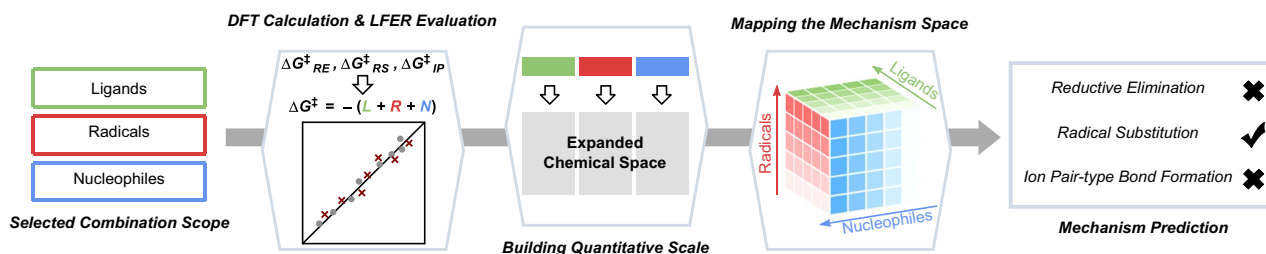
Driven by the objectives of this study, we first delineated a broad target chemical space with the aim of establishing a generalizable and predictive LFER framework to understand and characterize Cu-catalyzed radical bond formation. To this end, we systematically selected representative molecular sets from the three reaction components—radicals, nucleophiles, and ligands—based on their structural features and physicochemical properties. Specifically, the radical set includes 126 carbon radicals, spanning primary, secondary, and tertiary substitution patterns with variations in electronic effects and steric environments; the nucleophile set comprises 75 representative molecules, covering different hybridization states and diverse electronic and steric characteristics; and the ligand set contains 14 distinct cases, accounting for variations in denticity, charge state, and donor atoms. Together, these selections constitute approximately 132,300 possible radical bond formation reactions, reflecting the complexity and breadth of the system while providing sufficient theoretical scope and applicability for constructing the LFER model. Detailed component lists are provided in Supplementary Tables 4, 6 and 8.

In addition, assessing the reliability of the LFER also requires evaluating all linear relationships within a complete set, which necessitates focusing on a manageable subset. Therefore, we further selected a subset that is both representative and computationally feasible within the defined broader space. As shown in Fig. 3a, we ultimately chose 250 reactions comprising 5 ligands, 10 radicals, and 5 nucleophiles as the dataset to systematically evaluate whether LFER applies. This carefully curated subset captures the diversity of reaction components relevant to Cu-catalyzed radical transformations while ensuring statistical robustness and applicability of the model, thereby laying a solid foundation for the subsequent construction of the LFER.

### Evaluation of the LFERs in the radical bond formation process

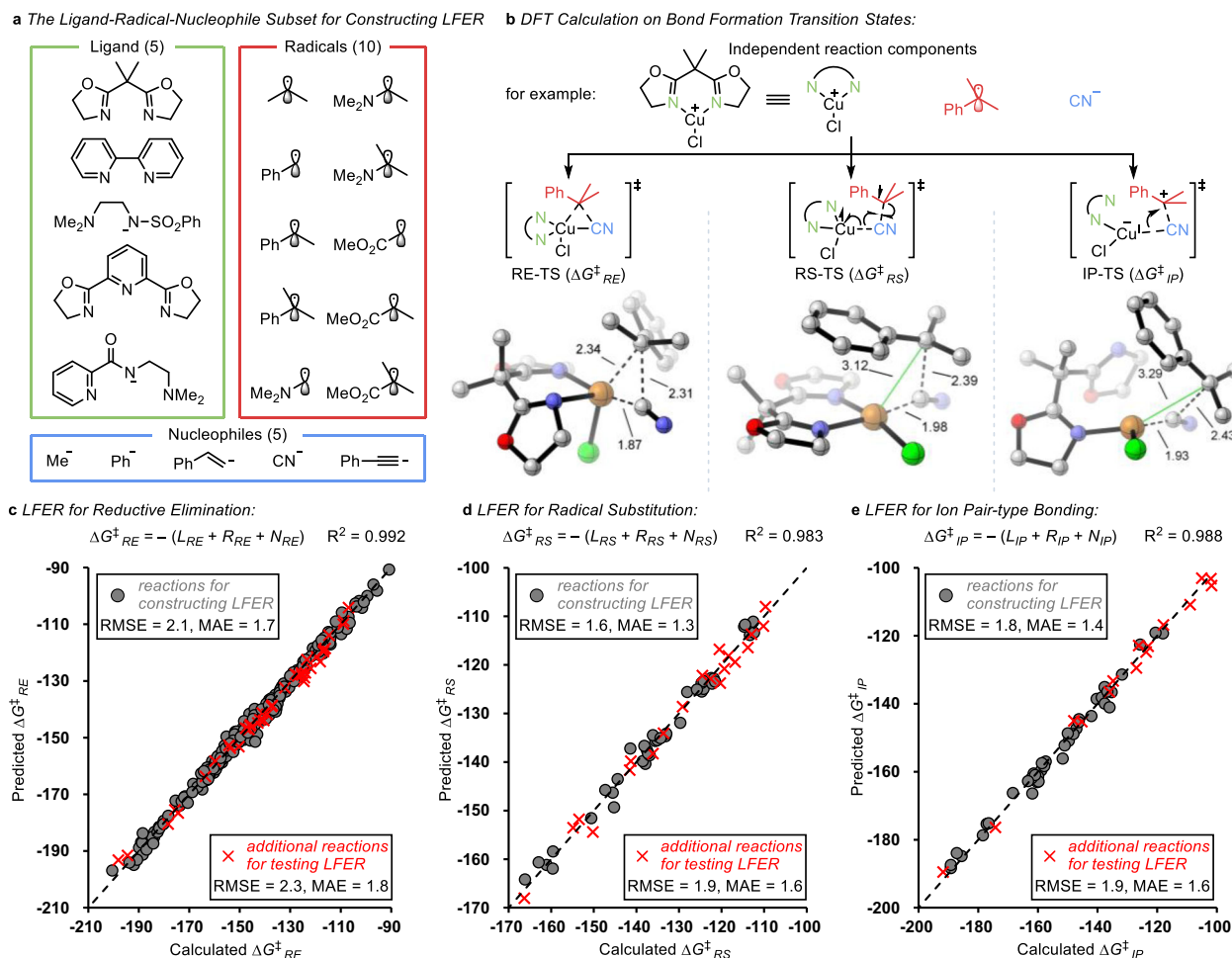
For the selected 250 reaction combinations, DFT calculations were performed on a total of 750 bond formation transition states. Following previous mechanistic studies by Bao<sup>29</sup>, Lin<sup>30</sup>, Liu<sup>18</sup> et al., our mechanistic model focuses on the radical bond formation process through a neutral transition state. Based on this, an additional chloride anion is introduced to coordinate with the LCu(II) complex when L is an electrically neutral ligand (Fig. 3b).

Due to inherent mechanistic preferences, optimizations intended for one bond formation mode may converge to another in certain



**Fig. 2 | Workflow for establishing linear free energy relationships and their application in mapping the mechanistic landscape of Cu-catalyzed radical bond formation.** The workflow comprises the following steps: selecting statistically significant and chemically diverse array of ligands, radicals, and nucleophiles;

performing DFT calculations of the bond formation transition states and constructing LFER equations; building quantitative LFER scales for other ligands, radicals, and nucleophiles; mapping the mechanism selectivity across the chemical space based on the LFER equations and scales.



**Fig. 3 | Linear free energy relationships in three Cu(II)-mediated radical bond formation processes.** **a** Combinations of ligands, radicals, and nucleophiles for constructing LFER. **b** Transition state calculations for radical bond formations and derived free energy changes. All distances are provided in Å. Hydrogen atoms are omitted for clarity. **c** LFER for the reductive elimination mechanism. **d** LFER for the radical substitution mechanism. **e** LFER for the ion pair-type bond formation

mechanism. The parameters  $L$ ,  $R$ , and  $N$  represent the contributions of the ligand, radical, and nucleophile, respectively, to the stabilization of the transition state. All energy values (in kcal/mol) are computed using DFT calculations. Gray circles represent reactions for constructing LFER. Red crosses represent additional reactions for testing LFER.

cases, particularly with RS and IP transitioning to RE. Nevertheless, we were eventually able to locate 199 RE, 62 RS, 52 IP transition states (see Supplementary Tables 14 to 16 for corresponding statistics). Quantitative scales of ligands, radicals, and nucleophiles were constructed by subjecting these computed free energy changes to a least-square minimization based on the equation of  $\Delta G^{\ddagger} = -(L + R + N)$ . To avoid the complexity associated with ternary combinations during the scale establishment, we did not choose the actual pre-intermediate copper complexes of the bond formation process as the energy reference for the transition state barriers. Instead, independent radicals, nucleophiles, and the ligand-coordinated Cu(II) catalysts served as references (Fig. 3b). Although this choice of reference did not allow for assessing the intrinsic bond formation efficiency of each pathway (due to the general instability of these reference species compared to the pre-intermediate copper complexes), the relative free energy differences between the isomeric transition states can still be accurately described, thereby reliably predicting mechanistic preferences and facilitating efficient mapping of mechanism space.

Subsequently, we formulated ternary linear equations under the LFER assumption to describe the energies of the bond formation transition states. To our delight, the LFER equations for the RE, RS, and IP bond formation modes demonstrated high precision on the subset used for constructing the LFER (Fig. 3c–e). The  $R^2$  values for these

equations were 0.992, 0.983, and 0.988, respectively, with mean absolute errors of less than 1.8 kcal/mol across an energetic range of up to over one hundred kcal/mol.

Building upon the results obtained for the selected subset, we further assessed the reliability of the LFER constructed from the DFT-computed free energy barriers from multiple perspectives to ensure that the derived statistical relationships are not only numerically accurate but also chemically meaningful. To this end, we first examined the 250 reaction combinations using additional density functionals. In addition to the original calculations with B3LYP-D3(BJ), single-point energy evaluations were carried out with three widely used functionals, M06, PBE0-D3(zer), and  $\omega$ B97X-D. The resulting LFER equations retained a high degree of robustness, with  $R^2$  values ranging from 0.972 to 0.994 and mean absolute errors of 1.3–1.7 kcal/mol (Supplementary Table 9). More importantly, when the LFER equations parameterized with different functionals were used to predict the operative mechanism of the same reaction, the predictions were largely consistent, with only 9 reactions showing discrepancies in the assigned mechanism.

In addition to this validation across different theoretical levels, we also evaluated the reliability of the LFER through dataset partitioning. Using a modified 5-fold cross-validation protocol, the mechanistic data were divided into five subsets, with each subset in turn serving as the

set for constructing LFER while the remaining reactions were used for testing. Under these data splittings, the accuracy of mechanistic predictions remained excellent, with  $R^2$  values consistently above 0.95 and MAEs within 2.0 kcal/mol (Supplementary Table 13). To further rigorously probe the extrapolative capacity and reliability of the model, we designed an additional test set consisting of 67 completely new reactions, incorporating 9 ligands, 51 radicals, and 32 nucleophiles not included in the reactions for constructing LFER. The parameters for these new components were derived from their barrier differences relative to predefined reference compounds, as detailed in Supplementary Fig. 14. Encouragingly, the LFER established on the 250 reactions also performed excellently on this extrapolative test set, with MAEs of 1.8, 1.6, and 1.7 kcal/mol for the RE, RS, and IP pathways, respectively (red crosses, Fig. 3c–e), thereby demonstrating the robustness and reliability of the proposed LFER model of Cu-catalyzed radical bond formation.

We want to emphasize that these linear equations should not be seen merely as interpolation within a limited dataset; rather, they elucidated the underlying LFER principles governing the bond formation SARs in this catalysis, indicating that the influences of radicals, nucleophiles, and catalysts on the stability of bond formation transition states are linearly additive. Due to the high accuracy of these equations, when used collectively, they can precisely describe the energy differences between bond formation transition states, enabling the accurate prediction of the favored reaction mechanisms. In Fig. 4, the  $\Delta\Delta G^\ddagger$  LFER equation showed an RMSE of 2.3 kcal/mol and an MAE of 1.8 kcal/mol, with a 93.9% accuracy in predicting the correct mechanism of the reactions for constructing LFERs, and an RMSE of 2.9 kcal/mol and an MAE of 2.3 kcal/mol, with a 92.3% accuracy in predicting the correct mechanism of additional reactions for testing LFERs, thus providing a robust framework for determining the favored bond formation mechanism in Cu-catalyzed radical transformations.

To assess the applicability of the model to real-world synthetic systems, solvation effects were also examined. Transition states were computed in solvents with varying polarities, and corresponding LFER models were constructed. Consistent LFER models were obtained for each solvent, all exhibiting  $R^2$  values above 0.98 (Supplementary Tables 10–12 of the supplementary information). However, variations

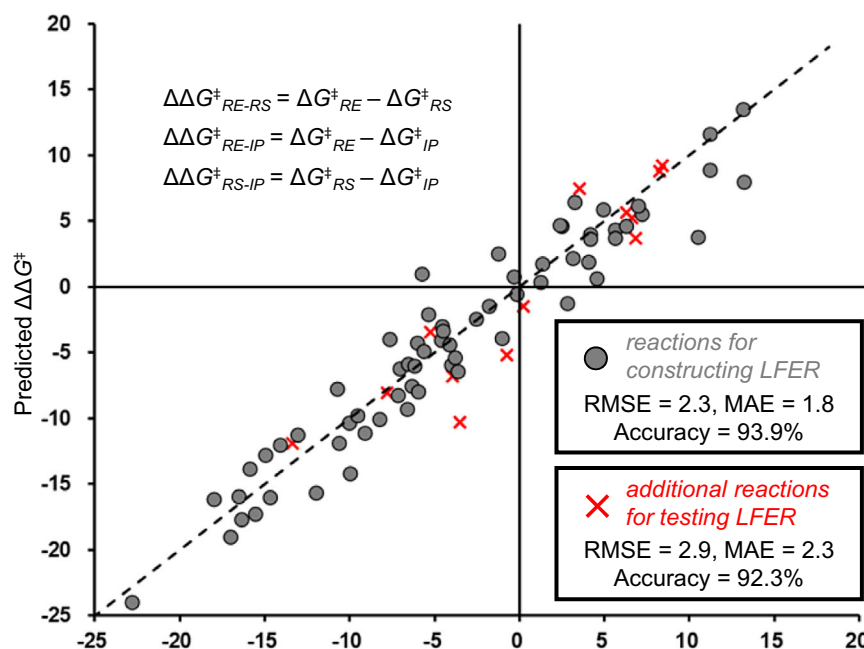
in LFER parameters were observed as solvent polarity changed, reflecting differential stabilization effects on radical bond formation transition states. These results suggest that the LFER model established in this study are directly applicable to nonpolar and low-polar solvents, while additional solvation corrections may be required for highly polar solvents to account for their specific stabilization effects, which is the subject of ongoing research in our laboratory.

For the chemical interpretability of our LFER parameters, our strategy essentially reflects the quantitative contribution of each reaction component in the three-component LFER equations describing Cu(II)-catalyzed radical bond formation, which is analogous to Mayr's LFER approach for defining nucleophilicity and electrophilicity scales. In this framework, the parameters  $L$ ,  $R$ , and  $N$  each carry explicit chemical meaning: they represent the contributions of the ligand, radical, and nucleophile, respectively, to the stabilization of the transition state. In other words, these parameters provide a quantitative measure of how each component modulates reactivity and influences the mechanistic preference within this catalytic system.

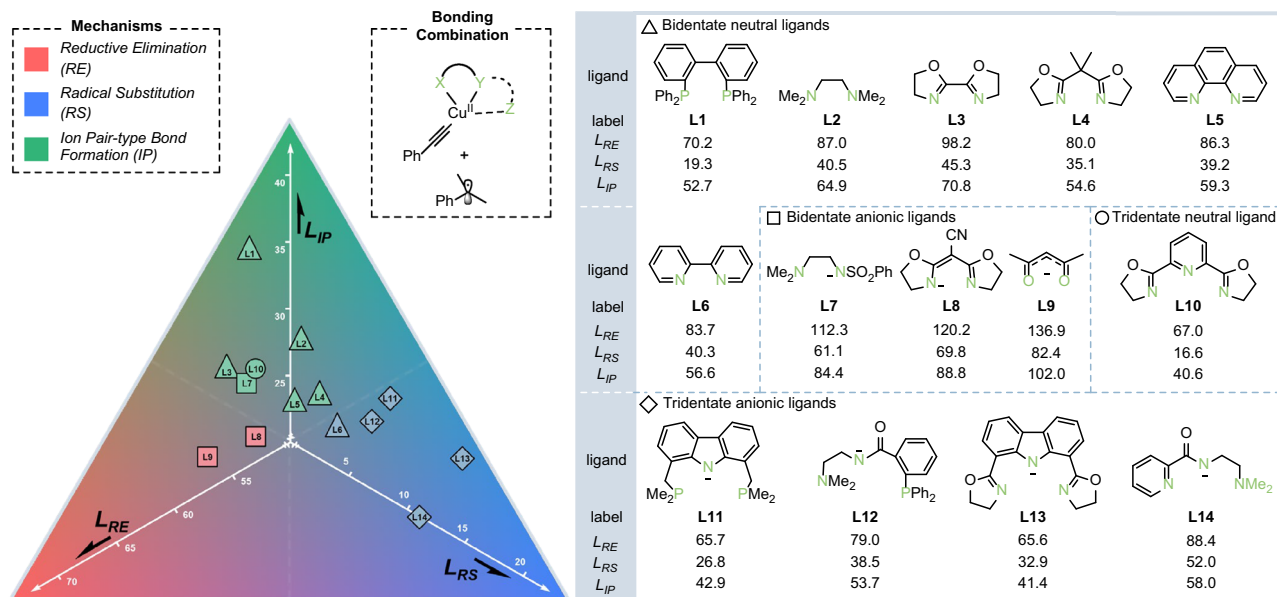
### Building quantitative LFER scales for the reaction components

Encouraged by the success of the LFERs established on the above 250-reaction subset, we further extended this framework to the entire target chemical space and constructed LFER parameters for all ligands, radicals, and nucleophiles (details provided in Supplementary Fig. 14). This extension enables us to quantitatively discuss how ligands, radicals, and nucleophiles influence mechanistic preferences in Cu(II)-mediated radical bond formation.

Figure 5 illustrates the LFER scales ( $L_{RE}$ ,  $L_{RS}$ , and  $L_{IP}$ ) for 14 widely applied ligand scaffolds in Cu-catalyzed radical transformations. The scales derived from these ligands are plotted on a mechanistic distribution diagram to represent their preferences, revealing intriguing ligand effects. Bidentate neutral nitrogen ligands (**L2** to **L6**) are located near the anchor point of the distribution diagram, exhibiting unremarkable mechanistic preferences. The bidentate phosphorus ligand **L1**, due to its significant  $\sigma$ -donor capability, is positioned far from the zone of bidentate neutral nitrogen ligands, prominently favoring the IP mechanism. Compared to bidentate neutral ligands, bidentate anionic ligands significantly shift towards the RE direction, particularly



**Fig. 4 | Accuracy of mechanism predictions based on the established linear free energy relationships for Cu(II)-mediated radical bond formation.** Gray circles represent reactions for constructing LFER. Red crosses represent reactions for testing LFER. All values are reported in kcal/mol.



**Fig. 5 | Distribution of linear free energy relationship parameters for representative ligands.**  $L_{RE}$ ,  $L_{RS}$ , and  $L_{IP}$  denote the LFER scales of ligands for reductive elimination (RE), radical substitution (RS), and ion pair-type (IP) bond formation processes, respectively. Values of  $L_{RE}$ ,  $L_{RS}$ , and  $L_{IP}$  are reported in kcal/mol. Different

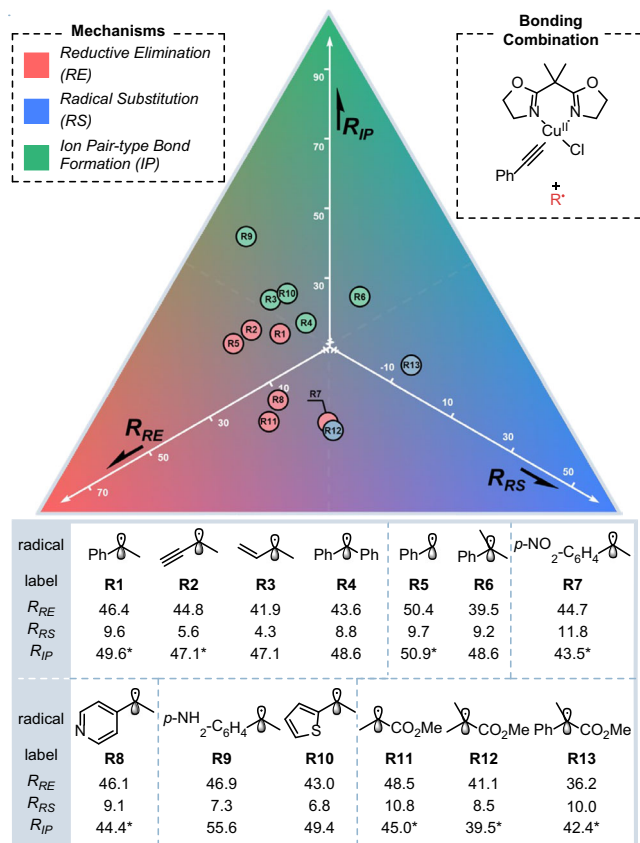
shapes of data points distinguish ligand types. Ligands located in the green region at the top preferentially undergo the IP bond formation process, while those in the red region at the bottom left favor the RE bond formation process, and those in the blue region at the bottom right favor the RS bond formation process.

acetylacetonate **L9**, which show a propensity for the RE mechanism. This is because the copper coordinated by anionic ligands does not have additional chloride coordination, freeing up coordination sites to support the RE pathway. As the ligand denticity increases, the tridentate neutral ligand PyBox **L10** aligns with the region of bidentate neutral nitrogen ligands, suggesting they possess similar mechanistic tendencies. However, when it comes to tridentate Pincer-type anionic ligands **L11** to **L14**, they consistently show a preference for the RS mechanism, likely because the increased coordination on Cu is unfavorable for RE processes and the oxidative capacity of anionic copper is insufficient to oxidize radicals for the IP mechanism. The pinpoint positioning of these ligands on the mechanistic distribution diagram allowed a quantitative comparison on mechanistic trends, providing a clear understanding of their role in directing reaction pathways.

We further investigated the influence of radicals on mechanism determination. Scales for 126 common carbon radicals were established, with 13 representative examples showcased in Fig. 6. The secondary benzyl radical **R1**, positioned near the anchor point, demonstrates negligible tendency towards the RE mechanism. Similarly, other conjugatively stabilized secondary radicals (**R2** to **R4**) are located in the zone where RE and IP mechanisms compete. The degree of substitution at the radical center markedly impacts the inclination towards the RE mechanism; compared to secondary radical **R1**, the primary benzyl radical **R5** distinctly favors RE, whereas the corresponding tertiary radical **R6** tends towards the opposite direction. Electronic effects also play a key role, mainly influencing the inclination towards IP, with notable shifts along the vertical axis of the mechanistic distribution diagram. Comparing to benzyl radical **R1**, electron-deficient  $\alpha$ -(hetero)aryl radicals (**R7** and **R8**), as well as the  $\alpha$ -acyl radical **R11**, are positioned away from IP, while electron-rich radicals (**R9** and **R10**) lean towards IP. Furthermore, these substituent effects are cumulative. The tertiary, conjugatively electron-withdrawing radicals **R12** and **R13**, distanced from both RE and IP mechanisms for the above-discussed reasons, thereby favor the RS mechanism. While these substituent effects are understandable through classical structural analogies in organic chemistry, it is

important to note that these LFER scales do not align with traditional physical organic parameters of radicals. Efforts to correlate  $R_{RE}$  and  $R_{RS}$  with common radical parameters such as global electrophilicity  $\omega$ <sup>31,32</sup> and SOMO energy revealed inapparent correlations, while  $R_{IP}$  can be approximately obtained by multivariate linear regression (MLR), as shown in Supplementary Table 22 and Supplementary Fig. 16. This observation indicated that known physical organic understandings on radical behavior may not fully apply to Cu(II)-mediated radical bond formation and highlights the new mechanistic insights embedded in these LFER scales.

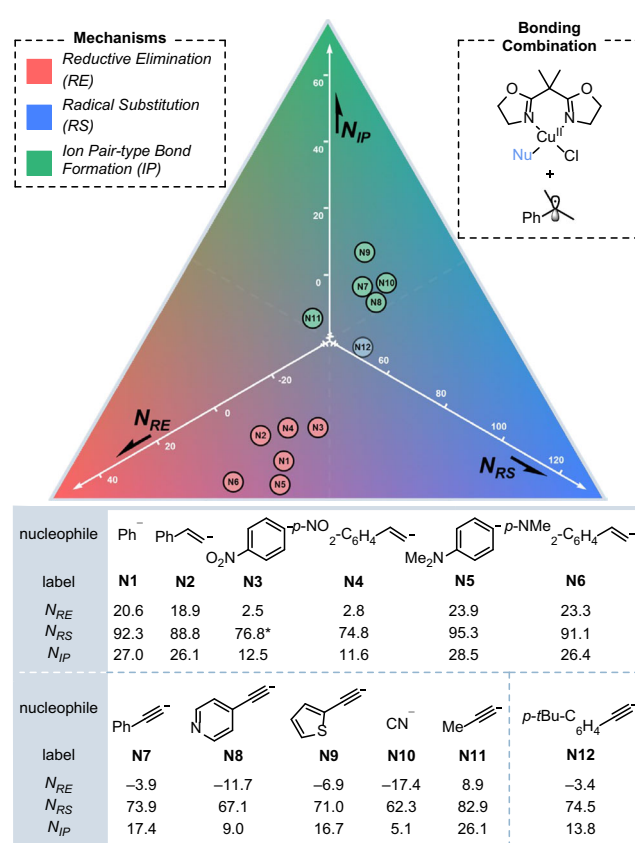
In addition, the LFER scales of nucleophiles also unveiled new mechanistic insights. We examined 75 common carbon nucleophiles relevant to the target catalysis, with 12 representative examples displayed in Fig. 7. As the LFER scale was constructed utilizing three different reaction components, the corresponding anionic species are adequate to quantitatively evaluate the impact of nucleophiles on the bond formation transition states. Aryl and vinyl anions **N1** and **N2** are closely positioned on the mechanistic distribution diagram, both showing a preference for the RE mechanism. The electronic effects on  $C(sp^2)$  nucleophiles manifest in their propensity towards the RE mechanism, with the electron-deficient aryl **N3** and vinyl **N4** more distinctly disfavoring RE, whereas the electron-rich aryl anion **N5** and vinyl anion **N6** demonstrate opposite trends. Intriguingly, for  $sp$ -hybridized nucleophiles, the electronic effects primarily affect the trend towards the IP mechanism. Compared to phenylethynyl **N7**, the electron-deficient pyridyl **N8** and the electron-rich thiophenyl **N9** shifts the corresponding nucleophiles along the IP axis on the trend diagram. Introducing a bulky *p*-*t*Bu group on the benzene ring results in **N12**, markedly disfavoring IP and positioned in the RS-favored region. Similar to the LFER scales of radical, the LFER scales of nucleophiles do not correlate with known nucleophilicity parameters. When compared with typical nucleophilicity indices such as electro-donating power<sup>33</sup> and HOMO energy, these scales show limited correlations (results are shown in Supplementary Tables 23 and 24), further emphasizing the distinctive structure-selectivity relationships of nucleophiles in Cu-catalyzed radical transformations as revealed by our LFER scales.



**Fig. 6 | Distribution of linear free energy relationship parameters for representative radicals.**  $R_{RE}$ ,  $R_{RS}$ , and  $R_{IP}$  denote the LFER scales of radicals for reductive elimination (RE), radical substitution (RS), and ion pair-type (IP) bond formation processes, respectively. Values of  $R_{RE}$ ,  $R_{RS}$ , and  $R_{IP}$  are reported in kcal/mol. Radicals located in the green region at the top preferentially undergo the IP bond formation process, while those in the red region at the bottom left favor the RE bond formation process, and those in the blue region at the bottom right favor the RS bond formation process.

### Mapping of the bond formation mechanism space

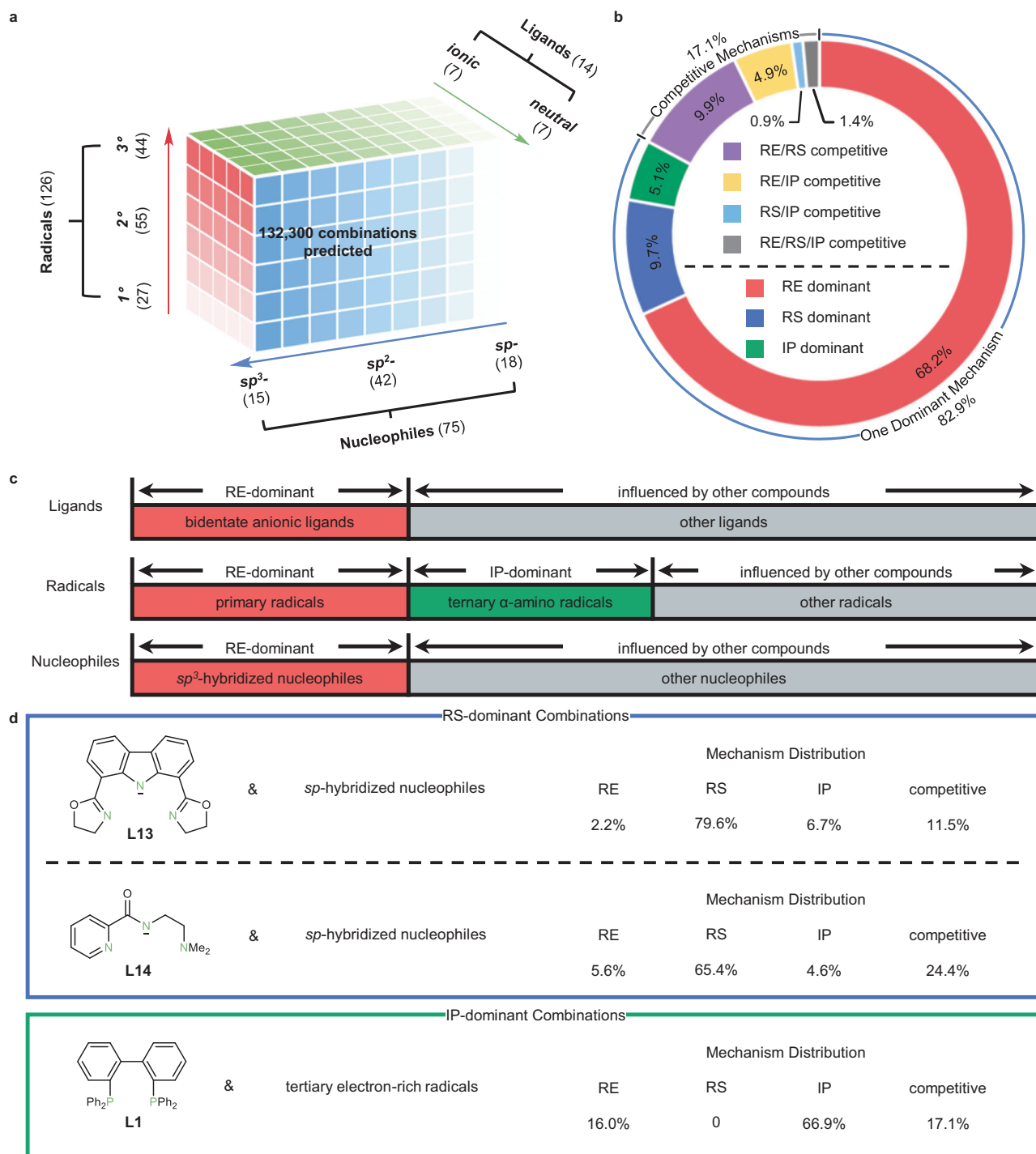
By applying the LFER scales and equations in combination, we can predict the bond formation mechanisms for all conceivable combinations of the studied ligands, radicals, and nucleophiles. This predictive scope encompassed a vast space involving 132,300 potential Cu-catalyzed radical transformations (Fig. 8a), with key statistical results presented in Fig. 8b. Among all the reaction combinations evaluated, 82.9% exhibited a single dominant mechanism, indicating that the favored pathway was energetically more favorable by at least 3 kcal/mol, while the remaining 17.1% showed competition between two or even three bond formation modes. Among the reactions with a single dominant mechanism, 68.2% were predominantly governed by the RE mechanism, affirming its role as the principal operative C–C bond formation mechanism in Cu(II)-catalyzed radical transformations. Additionally, 9.7% and 5.1% of reactions demonstrated a propensity towards the RS and IP mechanisms, respectively, with certain guiding principles detailed below. In the 17.1% where mechanism competition occurred, competitions involving the RE mechanism predominated, consistent with the overall tendency for RE across the chemical space; only 0.9% of reactions exhibited competition between RS and IP mechanisms. Furthermore, based on the parameter ranges for ligands, radicals, and nucleophiles (Supplementary Fig. 18), the influence of ligands on the bond formation mechanism is the most substantial, followed by nucleophiles, while the effect of radicals is markedly smaller than the other two components. All prediction



**Fig. 7 | Distribution of linear free energy relationship parameters for representative nucleophiles.**  $N_{RE}$ ,  $N_{RS}$ , and  $N_{IP}$  denote the LFER scales of nucleophiles for reductive elimination (RE), radical substitution (RS), and ion pair-type (IP) bond formation processes, respectively. Values of  $N_{RE}$ ,  $N_{RS}$ , and  $N_{IP}$  are reported in kcal/mol. Nucleophiles located in the green region at the top preferentially undergo the IP bond formation process, while those in the red region at the bottom left favor the RE bond formation process, and those in the blue region at the bottom right favor the RS bond formation process.

results are available in a SMILES-queryable spreadsheet on GitHub (<https://github.com/XuGuoXiong/LFER-on-Mechanism-Prediction.git>).

The multitude of mechanism predictions reveals insightful statistical patterns. Perhaps the most practically valuable of these insights is the identification of characteristic structural features that, studied C–C bond formations, we indeed identified a series of mechanistic principles, with key findings displayed in Fig. 8c. Among all ligands, the presence of bidentate anionic ligands consistently leads to nearly 90% of mechanisms being RE-dominant. The presence of primary carbon radicals or C(*sp*<sup>3</sup>) nucleophiles also implies that the RE mechanism is operative. However, for tertiary α-amino radicals, nearly 80% of C–C bond formations proceed through the IP mechanism. When structural features promoting RE or IP are both present (i.e., tertiary α-amino radicals with C(*sp*<sup>3</sup>) nucleophiles), conflicting rules lead to competitive mechanisms, displaying a competition between IP and RE without clear dominance. However, binary combinations still demonstrate clear mechanistic preferences, as detailed in Fig. 8d. When tridentate anionic ligands **L13** and **L14** are paired with C(*sp*) nucleophiles, the majority of reactions undergo the RS mechanism, with a minor portion of RE and IP mechanisms arising from the radical effects. Moreover, when the strong σ-donating bidentate phosphorus ligand **L1** is combined with tertiary electron-rich radicals, 66.9% of the corresponding transformations favor the IP pathway.



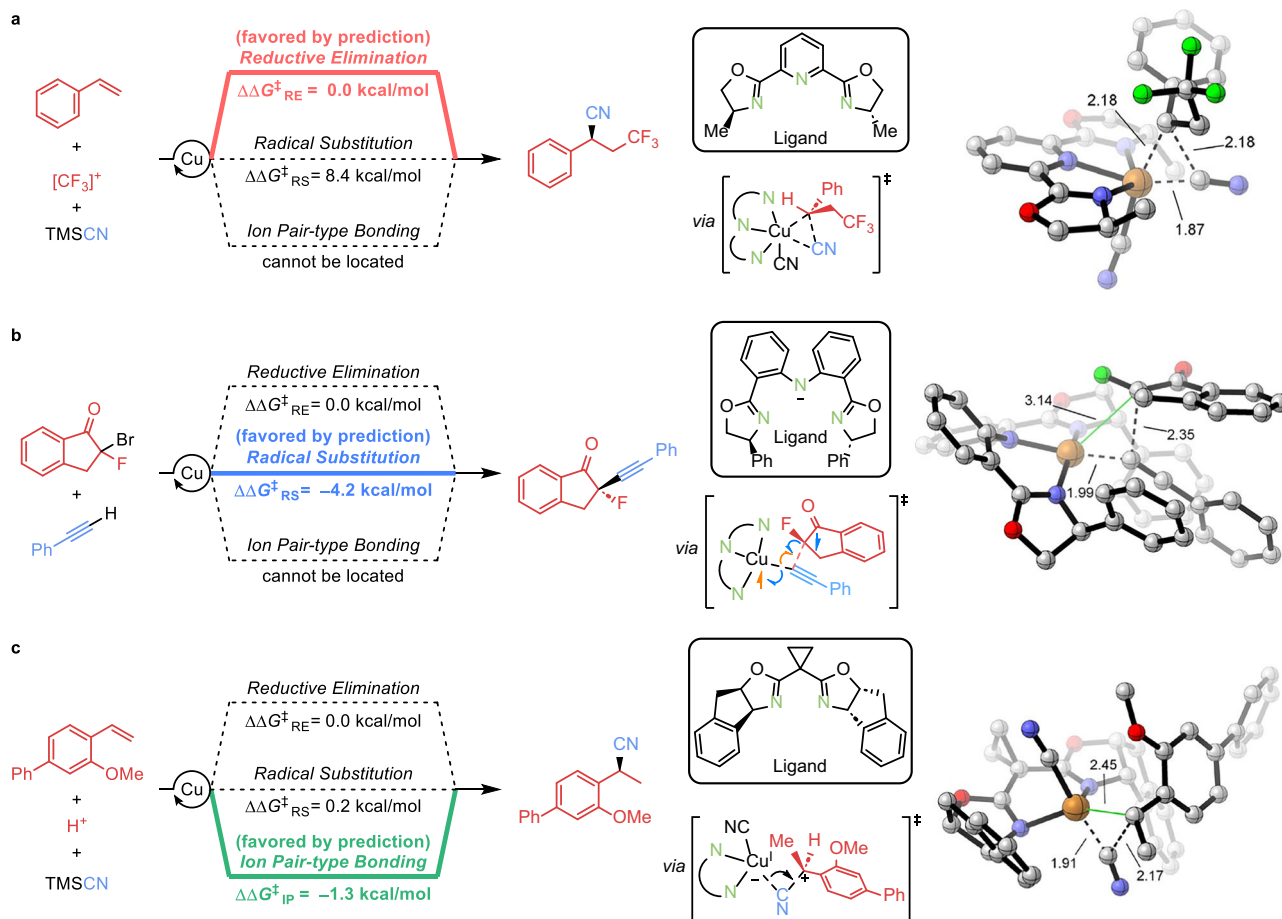
**Fig. 8 | Mapping the mechanistic landscape of Cu(II)-mediated radical C–C bond formations.** **a** Explored chemical space encompassing 132,300 combinations for mechanistic predictions. **b** Distribution of predicted mechanisms for the

combinations derived from the explored chemical space. **c** Mechanistic patterns based on single reaction components. **d** Mechanistic patterns based on two-component combinations.

It should be emphasized that our LFER model is not intended to replace DFT transition state calculations for individual reactions. For the mechanistic elucidation of a specific transformation, direct DFT calculations are often more accurate and straightforward. The value of the LFER approach lies in its ability to efficiently uncover overarching patterns and trends across large chemical spaces. Compared with the  $O(n^3)$  complexity of calculating every transition state one by one, the LFER framework requires only limited DFT data and reduces the problem to  $O(n)$ , thereby enabling systematic prediction and comparison

over a vast number of reaction combinations. This approach not only captures mechanistic changes induced by substituent effects but also provides a more comprehensive and reliable assessment of mechanistic trends than traditional strategies that rely on a few model systems, thus serving as a powerful complement to individual DFT calculations aimed at clarifying specific mechanisms.

After completing the prediction and distribution analysis of 132,300 reaction combinations in the chemical space, we further selected a series of catalytic systems that are either closely related to



**Fig. 9 | Applications and DFT validations of mechanistic predictions in practical catalytic systems.** **a** A representative example favoring the reductive elimination mechanism. **b** A representative example favoring the radical substitution mechanism. **c** A representative example favoring the ion pair-type bond formation mechanism. Bold solid lines indicate the predicted favored bond formation

mechanisms, while dashed lines denote the predicted unfavored mechanisms.  $\Delta\Delta G^{\ddagger}$  represents the energy barrier differences for various bond formation mechanisms computed by DFT in real reaction systems, with reductive elimination as the reference ( $\Delta\Delta G^{\ddagger}_{RE} = 0.0$  kcal/mol). All distances are provided in Å.

the frontiers of synthetic chemistry or mechanistically representative, in order to validate and challenge the established LFER model. A total of 20 representative cases were examined, including 10 reactions reported in the literature whose competing radical bond formation mechanisms had been thoroughly investigated by other groups using DFT calculations, as well as an additional 10 reactions predicted by our model to favor RS or IP pathways, thereby ensuring a balanced representation of all three mechanistic classes in the evaluation. Among these 20 cases, the LFER model correctly identified the operative bond formation mechanism in 17 reactions, with only 3 cases showing discrepancies compared to the reference DFT results. These findings further demonstrate that the LFER model not only uncovers general trends across large chemical spaces but also provides reliable and applicable mechanistic predictions for specific catalytic reactions. Detailed results and the full list of reactions are provided in Supplementary Figs. 19 and 20.

One representative example for each bond formation mechanism is presented in Fig. 9, with more detailed results available in Supplementary Fig. 19. Liu et al. previously reported a copper-catalyzed radical-mediated cyanotrifluoromethylation of alkenes (Fig. 9a), where the LFER model predicted a dominant RE mechanism<sup>34</sup>; our DFT calculations indeed confirmed that the corresponding RE transition state was more favorable by 7.8 kcal/mol. In the Sonogashira coupling of cyclic gem-dihaloketones developed by the Zhang group<sup>35</sup> (Fig. 9b), characterized by a tridentate anionic ligand and an alkynyl

nucleophile, our model anticipated a dominant RS mechanism, the prediction was supported by a significantly favorable RS transition state. Interestingly, in the hydrocyanation of olefins developed by Xiao, Chen, and colleagues, although the previous DFT mechanistic study on model reaction suggested a preference for RE mechanism<sup>36</sup>, our analysis indicated potential reversals in the mechanism for certain substrates within the reported substrate scope. Following this prediction, we specifically studied the bond formation process between the electron-rich para-methoxybenzyl radical and the cyanide nucleophile, confirming that this combination indeed proceeds through an IP mechanism, as suggested by our LFER model (Fig. 9c).

Moreover, our review of previous mechanism studies on Cu-catalyzed radical transformations revealed that the RS mechanism is often overlooked in transition state calculations, yet our LFER model and DFT calculations have identified that many cases favor the RS mechanism as the predominant bond formation pathway (see also Supplementary Fig. 19 and Supplementary Tables 25 and 26). Therefore, evaluating the RS mechanism is a noteworthy issue for Cu-catalyzed radical transformations, and we recommend referencing our LFER scales and predictions in future mechanism studies to provide a more comprehensive understanding.

## Discussion

In summary, this study employed predictive LFER modeling to elucidate the intricate mechanistic landscape of C–C bond formation in Cu-

catalyzed radical transformations, providing a comprehensive and quantitative understanding of the distribution and the rules that govern these three bond formation modes: Cu(III)-mediated reductive elimination, outer-sphere radical substitution, and ion-pair bond formation via carbocation. It was found that the influences of ligands, radicals, and nucleophiles on the bond formation transition states are linearly additive. This foundational relationship allowed for the construction of simple ternary LFER equations to accurately depict the quantitative impact of each reaction component on bond formation transition states. These LFER equations achieved an accuracy with an  $R^2$  approaching 0.99 and precisely modeled free energy perturbations within 2 kcal/mol across an energy range spanning hundreds of kcal/mol. This provides a quantitative, systematic framework for predicting the preferred mechanism in Cu-mediated C–C bond formation, enabling the discussion of mechanistic trends in Cu-mediated C–C bond formation mechanisms on a quantitative, rational perspective.

Based on the revealed LFER relationships, quantitative scales were constructed for hundreds of radicals, nucleophiles, and ligands to depict each component's impact on the bond formation transition states. The establishment of these scales uncovered intriguing mechanistic insights, revealing previously unreported controlling factors on bond formation mechanisms. Comparisons of these LFER scales with classic physical organic parameters describing the reactivity and stability of radicals or nucleophiles indicated that they are not equivalent, illustrating that the behavior of radicals and nucleophiles in Cu(II)-mediated radical bond formation cannot be simplistically translated from traditional concepts. Using these LFER scales and equations combined, we predicted the C–C bond formation mechanisms for 132,300 Cu-catalyzed radical transformations, providing a reliable mechanism handbook for conceivable C–C bond designs within this field. From these extensive predictions, mechanistic guidelines have emerged, identifying specific structural features that dominantly influence the bond formation mechanisms. For example, combinations of tridentate anionic ligands with C(sp) nucleophiles predominantly favor radical substitution processes. Furthermore, we validated the LFER model's prediction with transition state calculations in previously reported synthetic examples, and an oversight of the radical substitution pathway in previous mechanistic studies was identified. Overall, this work establishes the applicability of LFER principles in Cu(II)-mediated radical C–C bond formation. The provided LFER parameters enable the rapid and accurate determination of the preferred radical bond formation mechanism, offering a quantitative and reliable guide map for mechanistic understanding in related catalytic transformations.

## Methods

### Computational Protocol

All DFT calculations were performed using Gaussian 16 program at B3LYP-D3(BJ)/6-311+G(d, p)-SDD// B3LYP-D3(BJ)/6-31 G(d)-LANL2DZ level of theory.

A computational workflow was developed to reliably identify the transition states of each bond formation process (see Supplementary Fig. 1 for more details).

Conformers of each bond formation transition state were thoroughly considered, and the lowest-energy conformer was selected as the optimal result for DFT calculations (see Supplementary Fig. 2 for more details).

### Generation of LFER parameters

For components of the reactions for constructing LFERs, quantitative scales were constructed by subjecting these computed free energy changes to a least-square minimization based on the equation of  $\Delta G^\ddagger = -(L + R + N)$ .

For components of the reactions for testing LFERs, quantitative scales were derived from their barrier differences relative to

predefined reference compounds. Detailed scaling method is shown in Supplementary Fig. 14.

## Data availability

All data are available from the corresponding author upon request. Cartesian coordinate and corresponding energies of all transition states located in this study are provided in ZIP S1 at <https://doi.org/10.6084/m9.figshare.28607624>. Source Data are also provided in ZIP S2 at <https://doi.org/10.6084/m9.figshare.28607624>. The free energy changes of all transformations used in this study and the details of mechanism prediction for 132,300 ligand-radical-nucleophile combinations are available in the GitHub database<sup>37</sup> under accession <https://github.com/XuGuoXiong/LFER-on-Mechanism-Prediction>.

## Code availability

The code of the least-square regression and multivariate linear regression are available at GitHub<sup>37</sup>: <https://github.com/XuGuoXiong/LFER-on-Mechanism-Prediction>.

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## Author contributions

G.-X.X. conducted the DFT calculations. G.-X.X. and J.-R.L. design the computational procedure. G.-X.X., M.-J.T., Y.-Z.S., Z.G., Z.-L.L., and X.-Y.L. analyzed the data. X.H. and S.-Q.Z. designed the research. G.-X.X. and X.H. wrote the paper.

## Competing interests

The authors declare no competing interests.

## Additional information

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**Correspondence** and requests for materials should be addressed to Shuo-Qing Zhang or Xin Hong.

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