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Multiligand-enabled, copper-catalyzed Hiyama coupling of arylsilanes with unactivated secondary alkyl halides: reaction development and mechanistic insights†

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Construction of carbon–carbon bonds is the cornerstone in organic synthesis, and Hiyama coupling is the representative synthetic approach for realizing linkages between silyl compounds and organohalides. In previous literature, such couplings are mainly utilized for the bond formations of arylsilanes with sp^2 -aryl halides, yet Hiyama couplings with sp^3 -hybridized alkyl halides still remain scarce. Copper catalysis has recently been scrutinized in several important transformations of unactivated secondary alkyl halides, whereas their conversions with organosilanes are far less developed. Herein, we leverage a multiligand catalysis to offer a solution for efficient copper-catalyzed Hiyama couplings with such unactivated alkyl halides. Detailed mechanistic studies disclosed that the incorporation of an NHC ligand with a phenanthroline–copper system would dramatically enhance the reaction efficiency, where the copper species with NHC and phenanthroline-type ligands were most likely to account for the $C(sp^2)$ –Si bond activation and $C(sp^2)$ – $C(sp^3)$ bond formation process, respectively.

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Introduction

Cross-coupling reactions allow the construction of various compounds from small to highly complex molecules by the utilization of simple and commercially available chemicals, and the exploration of efficient catalytic systems has witnessed a tremendous advancement in organic synthesis along with the lines of methodology development in past decades.¹ In this context, Hiyama coupling is one important transformation for providing reliable synthetic approaches to the linkages between silyl compounds with organic (pseudo)halides.² Considering the low toxicity, ready availability and high abundance of silicon chemicals, the exploration of such coupling systems would be highly valuable in synthesis.³

The majority of the reported Hiyama couplings are focused on the reactions between aryl or vinyl silane nucleophiles with sp^2 -electrophiles.^{2,3} Recently, with the increasing demand for $C(sp^3)$ -rich scaffolds in numerous research fields, a surge of interest has been initiated in the conversions of alkyl halides.⁴ However, late transition-metal-catalyzed conversions of alkyl halides often encounter several problematic issues including

sluggish oxidation of alkyl electrophiles and facile β -hydride elimination of alkyl-metal species.⁵ Thus, approaches for efficient couplings with alkyl halides are in high demand.

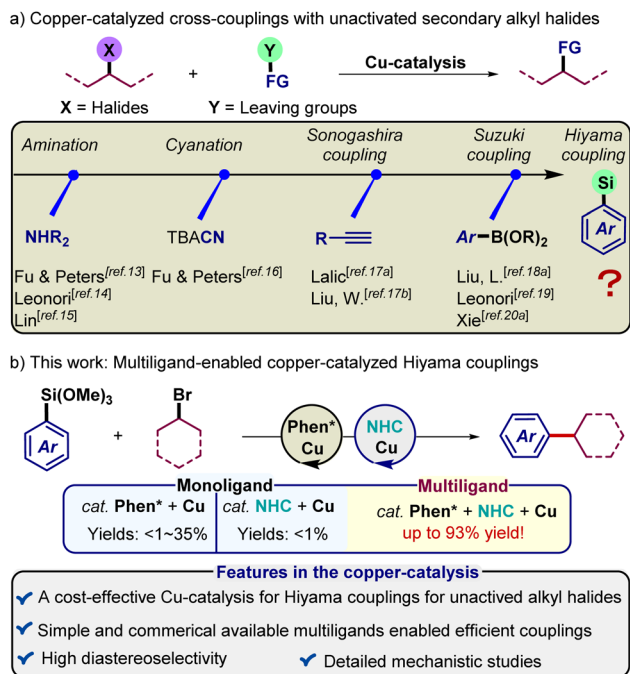
In this line, first-row transition metals were proven to be promising catalysts in coupling with sp^3 -alkyl halides *via* single-electron mechanisms, where nickel, cobalt and iron have recently been scrutinized in this realm.⁶ In comparison, copper catalysis utilized in this field is still lagging far behind,⁷ although copper-mediated Ullmann reactions are regarded as the earliest transformations in organic synthesis.⁸ Thus, further methodology development of copper systems would be valuable from the aspects of both important theoretical significance and practical advantages, including earth abundance, cost efficiency and environmental benignity of such catalytic systems.⁹

The last two decades have witnessed the significant achievement of copper-catalyzed sp^2 -aryl halide transformations,^{10–12} and a burgeoning interest has recently been aroused in the development of unactivated secondary sp^3 -alkyl halides (Scheme 1a).^{4–7} Fu *et al.*, in a seminal report, disclosed a photo-enabled copper catalyzed amination of secondary alkyl halides with carbazoles.¹³ Later, Leonori *et al.* illustrated a halogen-atom-transfer (XAT) approach assisting copper-catalyzed amination of alkyl iodides.¹⁴ Recently, Lin and colleagues reported an NHC–copper system catalyzing the coupling of alkyl halides with amines under photo-catalysis.¹⁵ Cyanation¹⁶ and Sonogashira couplings¹⁷ of alkyl halides were also recently achieved by several research groups. Meanwhile, Suzuki couplings of alkyl halides with arylborons were also

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Scheme 1 Copper-catalyzed cross-couplings of unactivated secondary alkyl halides.

achieved. For instance, primary alkyl halides coupling with arylborons was previously disclosed by Liu *et al.*¹⁸ and unactivated secondary alkyl iodides were recently reported by Leonori and co-workers using preactivated boronates with the assistance of XAT approaches.¹⁹ Our group recently established a practical copper system catalyzing Suzuki couplings of various alkyl halides with arylborons.^{20a} Motivated by the aforementioned reports, and also in continuation of our research interest in copper catalysis,²⁰ we endeavor to develop Hiyama couplings of unactivated alkyl halides with copper systems.

In fact, Hiyama reactions with sp^3 -alkyl electrophiles still remain scarce.²¹ Fu *et al.* reported palladium-catalyzed reactions of aryltrialkoxysilanes with primary alkyl halides.^{21a} Later, the same group developed nickel-catalyzed cross-couplings of secondary alkyl halides with highly polarized trifluorosilylarennes.^{21b,c} The problematic issues impeding the development might lie in the relatively lower propensity for bond activation of the inherent lower Lewis acidity $C(sp^2)$ -Si bonds, compared with arylborons in Suzuki coupling.

In the scenario for the enhancement of the catalytic performance of traditional catalytic systems, considerable efforts have been devoted to developing a variety of synthetic strategies recently. For instance, modification of the ligand shell of catalysts would provide efficient systems.²² However, tedious synthetic processes and capricious reactivity of catalysts often require massive efforts. Bimetallic catalysis with two distinct systems have also been proven to be successful by capitalizing on the advantages of different transition metal systems.²³ On the other hand, the sole metal-based multiligand relay catalysis has also emerged as an attractive approach for efficient C-C bond formation.²⁴ This strategy could trigger different reaction

patterns by using two types of simple ligands rather than a complicated ligand design, thus providing a more efficient approach. Buchwald *et al.* demonstrated that palladium-mediated C-N cross-couplings could be accelerated by binary phosphine ligand mixtures.^{25a} Recently, the Wang group successfully developed a two-ligand system involving assisted palladium catalysis for the polyfluoroarylation-allylation of diazocompounds.^{25b} Sevov and co-workers established a nickel-catalyzed reductive coupling system to construct $C(sp^3)$ - $C(sp^2)$ bonds enabled by pyrazolylpyridine and phosphine binary ligands.^{25c} Mauleón and colleagues reported that copper-catalyzed carboboration or hydroboration of alkynes could also be enhanced by mixed ligands.^{25d,e} Herein, we first develop a multiligand-enabled copper catalysis for the efficient Hiyama couplings of unactivated secondary alkyl halides and arylsilanes with the assistance of phenanthroline and N-heterocyclic carbene (NHC) ligands (Scheme 1b). Detailed mechanistic studies revealed that the phenanthroline ligand was crucial for C-C bond formations, and the strong σ -electron-donating NHC ligands accounted for C-Si bond activation. Notably, the current protocol operated in conjunction with the different advantages of two-ligand/copper systems, thus eliminating complicated ligand design and providing a facile and straightforward synthetic route.

Results and discussion

Reaction optimization

We commenced the study by investigating the coupling of phenyltrimethoxysilane (**1a**) with bromocyclohexane (**2**) with the copper catalyst ($CuBr \cdot SMe_2$), nitrogen bidentate ligands and base at 80 °C (Fig. 1a, and also see Table S1–S6 in the ESI† for details). The desired coupling product **3** could be obtained in a moderate yield with the employment of phenanthroline ligand **L1** (32%). Sterically congested ligand **L2** having methyl groups adjacent to the nitrogen atoms could barely form the desired product (<1%). These sterically accessible ligands with electronically distinct groups including phenyl, methoxide, nitro and methyl groups did not enhance the coupling efficiency (**L3–L6**, <1–35%). Bipyridines were also found to be sluggish for the current $C(sp^2)$ - $C(sp^3)$ bond formation (**L7–L9**, 11–18%). Further efforts with other ligands including NHCs, phosphines and terpyridines were observed to be inefficient for the current alkylation reactions.

We reasoned that the mediocre performance of the current coupling probably resulted from a certain rate-determining step of the reaction pathways. Thus, a proposed reaction mechanism is depicted in Fig. 1b to illustrate the possible key steps of the catalytic cycle for the phenanthroline ligand-enabled copper-catalyzed Hiyama coupling system. Based on prior literature,^{18,20a} the catalytic cycle would consist of the following steps: the ligand exchange of the phenanthroline-copper bromide with alkoxide base, the transmetalation step of the arylsilane forming the copper-aryl species, the radical activation of alkyl halides, the radical rebounding process of the alkyl radicals to form high-valent copper species, and the final reductive elimination step to generate the cross-coupling



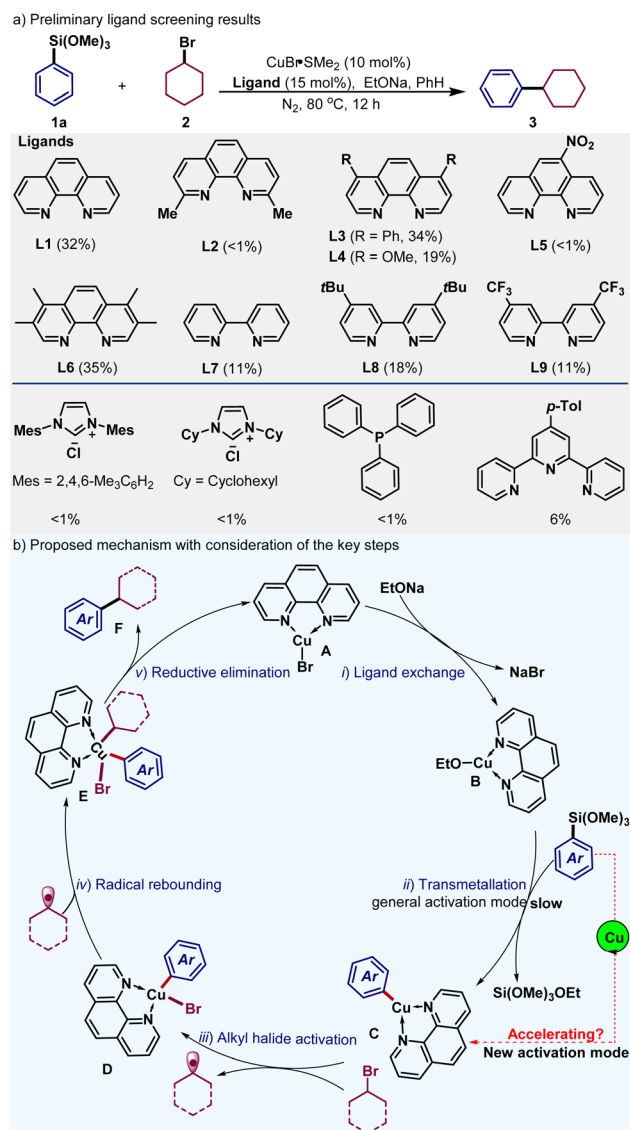


Fig. 1 (a) Preliminary results for the ligand effect of copper-catalyzed sp^2 - sp^3 Hiyama couplings. (b) Simplified mechanistic considerations of the key steps.

product. Copper-aryl species have been reported to be capable of activation of alkyl halides,^{18,20a} and the reductive elimination step from high-valent copper is well documented to be facile.^{9c} Thus, we reasoned that the current Hiyama coupling was probably inhibited by the transmetalation process. In fact, the polarity of the C(sp^2)-Si bond is much weaker than that of the C(sp^2)-B bond in arylborons, which might lead to the sluggish bond activation of arylsilanes. In this circumstance, polar trifluorosilylarenes have been previously utilized in nickel-catalyzed Hiyama coupling.^{21b,c} Thus, the exploration of an alternative activation pathway for the arylsilane reagents might address the problematic issues in the current system (dashed red arrow in Fig. 1b).

We envisioned that the leverage of an efficient copper catalyst for C(sp^2)-Si bond activation might facilitate the current reactions effectively. In fact, strong σ -electron-donating NHC

ligands have been utilized for the transmetalation of arylsilanes or arylborons in copper systems to form the corresponding copper-aryl species, reported by the Ball, Hou and other groups.^{26,27} Thus, we assumed that the incorporation of NHCs with the above phenanthroline-copper system might offer a solution for the development of efficient Hiyama couplings.

Toward this end, the model reaction was further investigated with copper, a phenanthroline-type ligand (L6) and a variety of NHC ligands (Table 1). Gratifyingly, the product yield was dramatically increased from 35% to 72% with the combination of NHC-1 (5.0 mol%), L6 (5.0 mol%) and the same loading of copper (CuBr·SMe₂, 10 mol%). Encouraged by this observation, a series of NHC ligands with distinct steric environment substituents were subsequently examined. Sterically hindered NHC ligands were found to give high yields (NHC-1-NHC-3: 72–78%). An NHC ligand with a saturated backbone did not affect the efficiency (NHC-4, 73%). Notably, the cyclohexyl group-

Table 1 Optimization of the multiligand-enabled Cu-catalyzed Hiyama coupling conditions^a

NHC Ligands

NHC-1 (72%), NHC-2 (77%), NHC-3 (78%), NHC-4 (73%), NHC-5 (93%), NHC-6 (74%), NHC-7 (6%, R¹ = Et, R² = Me), NHC-8 (2%, R¹ = R² = Me), NHC-11 (11%)

Mes = 2,4,6-Me₃C₆H₂, Dipp = 2,6-*i*-Pr₂C₆H₃, Ad = 1-adamantyl, Cy = cyclohexyl

Entry	[Cu] (X)	Solvent	Base	Yield ^c (%)
1	CuBr·SMe ₂ (10)	PhH	EtONa	93
2	CuBr·SMe ₂ (5)	PhH	EtONa	90
3	CuBr (5)	PhH	EtONa	78
4	CuI (5)	PhH	EtONa	57
5	CuCl (5)	PhH	EtONa	38
6	CuTc (5)	PhH	EtONa	75
7	Cu(acac) ₂ (5)	PhH	EtONa	85
8	—	PhH	EtONa	<1
9	CuBr·SMe ₂ (5)	Toluene	EtONa	83
10	CuBr·SMe ₂ (5)	CyH	EtONa	80
11	CuBr·SMe ₂ (5)	1,4-Dioxane	EtONa	64
12	CuBr·SMe ₂ (5)	THF	EtONa	23
13	CuBr·SMe ₂ (5)	PhH	<i>t</i> BuONa	72
14	CuBr·SMe ₂ (5)	PhH	MeONa	89
15	CuBr·SMe ₂ (5)	PhH	MeOK	36
16	CuBr·SMe ₂ (5)	PhH	MeOLi	<1

^a Reaction conditions: PhSi(OMe)₃ (0.80 mmol), CyBr (0.40 mmol), copper catalyst (X mol%), L6 [(1/2)X mol%], NHC [(1/2)X mol%], EtONa (0.60 mmol) in the indicated solvent (0.50 mL) at 80 °C for 12 h under nitrogen. ^b X = 10. ^c Yields were determined by GC analyses against a calibrated internal standard of *n*-hexadecane.

substituted carbene precursor **NHC-5** gave an excellent yield of 93%. However, decreased yields were observed with sterically accessible ligands (**NHC-6**–**NHC-8**, 2–74% yields). Collectively, the steric environment of NHC ligands has a profound effect on the efficiency, and the bulkier ligands were comparably more effective than the small-size NHCs. This observation could be rationalized in that the unhindered NHCs were likely to form heteroleptic copper species, thus leading to a lower activity (*vide infra*). Redox-active ligand **NHC-11** was found to be sluggish. Additionally, the use of NHC alone was inefficient (<1%; see Table S1 in the ESI† for details), indicating that the cooperation effect between the NHC and phenanthroline ligands probably accelerated the current multiple ligand-enabling coupling system.

Further investigation of other reaction parameters was performed. The reaction efficiency was slightly diminished with a decreased catalyst loading (entry 2, 90% yield with 5.0 mol% of copper). The evaluation of the copper catalysts disclosed that the efficiency was related to the counter anions. Copper bromide promoted the coupling in a yield of 78% (entry 3), and other copper salts with iodide and chloride anions enabled the reactions with decreased yields (entries 4 and 5, 57% and 38%, respectively). Copper catalysts with thiophene-2-carboxylate and acetylacetonate anions were also effective (entries 6 and 7, 75–85%). The coupling product could not be detected in the absence of copper, indicating the necessity of copper in the current reaction (entry 8, <1%). Solvent screening disclosed that the polarity has a pronounced effect on the efficiency, and nonpolar solvents were observed to be superior to polar solvents (entries 9–12). Further investigation of the base revealed that sodium bases were optimal (entries 13–16). The reaction could not proceed below 40 °C (see the ESI† for details).

Reaction scope

After the optimization of the current multiligand-enabled copper catalysis, we proceeded to evaluate the feasibility of substrate scope. An array of arylsilanes was firstly tested in the current system (Table 2). Phenyltrimethoxysilane was reacted with bromocyclohexane and afforded the desired product **3** in a high yield of 89%. Arylsilanes with carbon substituents including methyl, ethyl, *tert*-butyl and phenyl groups all generated the corresponding products smoothly (**4**–**8**, 64–90%). Reagents containing an electron-rich methoxide group gave the corresponding products **9** and **10** in good yields with increasing catalyst loading (10 mol% of copper; 78% and 72% yields, respectively). However, a highly electron-rich substrate with two methoxide groups failed to generate the alkylation product **11**, which was probably due to the low polarity of the C(sp²)–Si bond induced by the electronic effect, thus leading to an ineffective transmetallation. Substrates with electron-deficient groups, such as chloro, fluoro, and trifluoromethyl moieties, were all able to afford the products in moderate to good yields (**12**–**15**, 50–77%). Low isolated yields of the fluorine-containing products could probably be ascribed to their volatility property.

A substrate containing the reactivity distinct trialkylsilyl and trialkoxysilyl moieties was tested, and the coupling proceeded

Table 2 Reaction scope with regard to arylsilanes^a

3, 89%	4, 90%
5, 89%	6, 81%
7, 64%	8, 86%
9, 78% ^b	10, 72% ^b
11, <1%	12, 77%
13, (71%) ^c 35%	14, (50%) ^c 22%
15, 64%	16, 74%
17, 82%	18, 45% (R = H) ^b
	19, <1% (R = Me) ^b

^a **1** (0.80 mmol), **2** (0.40 mmol), CuBr·SMe₂ (5.0 mol%), **L6** (2.5 mol%), **NHC-5** (2.5 mol%), EtONa (0.60 mmol), PhH (0.50 mL), 80 °C, 12 h under nitrogen atmosphere, isolated yields. ^b CuBr·SMe₂ (10.0 mol%), **L6** (5.0 mol%), **NHC-5** (5.0 mol%). ^c NMR yields of the crude mixtures.

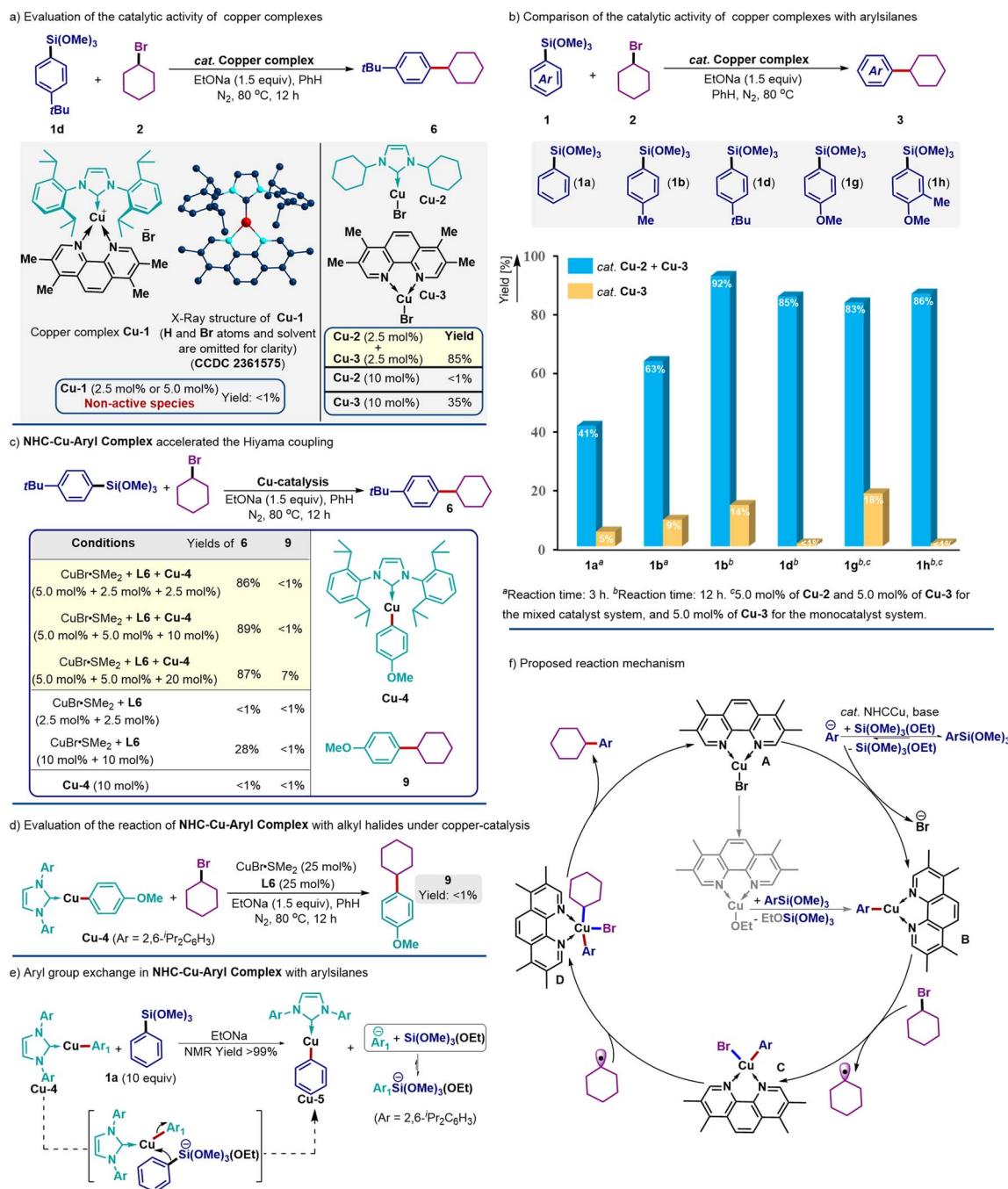
selectively at the polarized carbon site of the trialkoxysilyl group, leading to the formation of product **16** in 74% yield. A π -extended arylsilane coupled with cyclohexyl bromide generated the alkylation product in a high yield (**17**, 82%). Furthermore, the steric influence on the coupling system was also tested. 2-Methylarylsilane formed the alkylation product in a moderate yield with increased catalyst loading (**18**, 45%; 10 mol% of copper). Unfortunately, sterically congested 2,6-disubstituted coupling reagents failed to generate the desired product (**19**, <1%).

The catalytic ability with various alkyl halides was further investigated (Table 3). The compound *tert*-butylphenyltrimethoxysilane was employed as the coupling partner due to the volatility of certain products. Cyclic alkyl bromides including seven-, six- and five-membered rings were all arylated without difficulty (**6**, **20** and **21**, 78–82%). Interestingly, a substrate of the strained four-membered cyclobutyl bromide was subjected to the coupling system, and the target product **22** could be obtained in a high yield of 83%. However, a highly strained bromocyclopropane failed to generate the product.

Linear alkyl halides including 2-bromobutane and 2-bromopropane both gave the C(sp²)–C(sp³) coupling products in good isolated yields (**23** and **24**, 61% and 55%, respectively), and the lower isolated yields were probably due to the volatility of the products. Tetrahydropyranyl-4-bromide was coupled to afford the desired product **25** in 50% isolated yield. Subsequently, alkyl electrophiles containing aryl moieties were reacted, and both of the target products were obtained without the isomerization of the reactive sites to their benzylic positions (**26** and **27**, 70% and 66%, respectively). Next, the tolerance of other



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Scheme 3 Evaluation of the activity of copper complexes and proposed reaction mechanism.

conditions. The use of the sole NHC ligand could not promote the current coupling (see the ESI† for details), disclosing the crucial role of phenanthroline ligand for C(sp²)-C(sp³) bond formation, and the additional NHC ligand could promote the Hiyama couplings effectively.

Furthermore, we questioned the possibility of the heteroleptic copper complexes incorporating the phenanthroline-type ligand and NHC ligand catalyzing the current cross-coupling reactions. Thus, copper complex **Cu-1** supported by **NHC-2** and **L6** was independently prepared and its structure was

confirmed by NMR spectroscopic and X-ray crystallographic analyses (CCDC 2361575). The utilization of **Cu-1** as the catalyst in the current cross-coupling system was observed to be ineffective for C(sp²)-C(sp³) bond formation (Scheme 3a), thus precluding the involvement of the heteroleptic copper species as catalytically active in the cross-coupling process.

Importantly, a combination of the NHC-copper complex **Cu-2** and a phenanthroline-type ligand-supported complex **Cu-3** was observed to afford the alkylation product **6** in 85% NMR yield. The efficiency was almost identical to that for conditions

using premixed $\text{CuBr}\cdot\text{SMe}_2$, **L6** and **NHC-5** (Table 2, 81%). Especially noteworthy was that the Hiyama coupling product **6** was not detected with either **Cu-3** or **Cu-2** copper complex at 2.5 mol% catalyst loading, and the productive yield could be increased to 35% with 10 mol% loading of **Cu-3** as the catalyst. As anticipated, the employment of 10 mol% of **Cu-2** could not afford the coupling product (see the ESI† for details). The above observation strongly supported that the two individual copper complexes accounted for the highly efficient $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ coupling reactions.

Subsequently, a comparison of the catalytic performance for copper catalyst **Cu-3** and the binary catalyst system of **Cu-3** and **Cu-2** was conducted with a variety of arylsilanes (Scheme 3b). Evidently, the experimental data disclosed that the additional NHC–copper complex **Cu-2** showed a prominent effect on the efficiency enhancement. For instance, the mixed catalyst systems gave good to high yields in 3 h or 12 h, and using complex **Cu-3** alone afforded the products in low yields. Moreover, arylsilanes with the electron-rich methoxide group required an increased catalyst loading to achieve high product yields (**1g** and **1h**, 5.0 mol%), indicating that $\text{C}(\text{sp}^2)\text{--Si}$ bond activation probably has a crucial effect on the coupling system.

With the observation of catalytically active copper complexes, further mechanistic scrutiny was performed in due course. NHC–copper alkoxides have previously been reported to react with arylsilanes, forming the relevant copper–aryl species *via* the transmetallation process.²⁷ Thus, a copper–aryl complex, **Cu-4**, was separately prepared, and employed as a cocatalyst with 2.5 mol% catalyst loading (Scheme 3c). The alkylation product **6** was obtained in 86% yield with the assistance of the copper–aryl catalyst **Cu-4**. From GC–MS and NMR spectral analyses of the reaction mixtures, the 4-methoxyphenyl group was not transferred from the NHC–copper complex to couple with alkyl halides even with a 10 mol% loading of **Cu-4**. However, increasing its loading to 20 mol% would allow the detection of the coupling product **9** in 7% NMR yield. This observation indicated that the current system was unlikely to be triggered either by the transfer of the aryl moieties from the NHC–copper catalyst to the phenanthroline–copper catalyst or by the dynamic ligand exchange process between the binary ligands.²⁵ Furthermore, the Hiyama reaction was not workable with ligand **L6** as the sole ligand in parallel controlled experiments. Increasing its loading to 10 mol% only afforded the product **6** in a low yield of 28%. In addition, the inability of **Cu-4** to catalyze the cross-coupling reactions was confirmed experimentally, and this result indicated that the phenanthroline ligand was integral to $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bond formation.

Next, a chemically stoichiometric reaction of complex **Cu-4**, bromocyclohexane and base even with a high loading of copper catalyst ($\text{CuBr}\cdot\text{SMe}_2$) and phenanthroline-type ligand **L6** (25 mol%) did not generate the coupling product **9** (Scheme 3d). These experimental data further precluded the ligand exchange process in the current multiligand-enabled copper catalysis. Interestingly, a reaction of complex **Cu-4** with an excess amount of phenyltrimethoxysilane (**1a**, 10 equiv) would generate an aryl group exchanged copper complex, **Cu-5**, which was probably formed by the reaction of copper–aryl species with the base-

activated pentacoordinate silicate species. The concomitantly generated aryl anion would be in equilibrium with silyl ethers to form arylsilanes, and such transient naked and reactive aryl anions could probably account for the high efficiency of the current multiligand-enabled couplings. However, revealing the detailed pathways for the aryl group transfer might require further effort.

Based on the above experimental data and prior literature,^{10–12,18–20,27} a plausible mechanism is proposed in Scheme 3f. An *in situ* generated phenanthroline–copper complex **A** would react with a transient aryl anion, generating *via* the NHC–copper catalyst the aryl group release from arylsilanes, to form a copper–aryl species **B**. Subsequently, the copper–aryl species **B** would activate the sp^3 -alkyl halides *via* a single-electron process to afford the copper species **C** with concomitant formation of alkyl radical species, and a following rebounding step of the radical species would afford the high-valent copper species **D**. Finally, the ensuing reductive elimination of **D** would afford the Hiyama coupling product with the regeneration of copper species **A**. It should be mentioned that the coupling reactions also could be enabled by phenanthroline ligand alone in a slower fashion *via* the traditional transmetallation process (gray arrows).²⁸

Conclusions

In conclusion, the current study first demonstrates multiligand-enabled copper-catalyzed Hiyama couplings of arylsilanes with unactivated secondary alkyl halides to forge $\text{C}(\text{sp}^2)\text{--C}(\text{sp}^3)$ bonds, thus offering an efficient method for Hiyama couplings with a cost-effective copper system. A simple combination of phenanthroline and NHC ligands remarkably increased the reaction efficiency, and mechanistic studies disclosed that the two types of ligands supported copper catalysis shown by their respective abilities in the coupling system, where the NHC–copper catalyst accounted for the transmetallation process of arylsilanes and the phenanthroline–copper catalyst was responsible for carbon–carbon bond formation. This protocol offered a new solution for the development of Hiyama couplings. Further effort would be required to understand the mechanistic aspects and broaden the application range of the current multiligand-enabled copper system.

Data availability

ESI† is available and includes the experimental procedures, characterization data and crystallographic data for **Cu-1**. Deposition number 2361575 (for **Cu-1**) contains the supplementary crystallographic data for this paper.²⁹ The data are provided free of charge by the Cambridge Crystallographic Data Centre.

Author contributions

W. X. conceived the project. J. Z., Z. Z. and Y. C. conducted the experiments. W. X., J. Z., Z. Z. and Y. C. analysed the data and W. X. wrote the manuscript with the assistance of all authors.



Conflicts of interest

The authors declare that they have no conflict of interest.

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