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A General Copper-Catalyzed Radical Cross-Coupling of Unactivated Alkyl Halides

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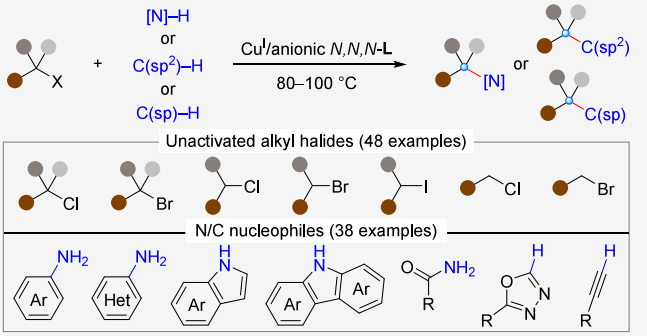
ABSTRACT: The first-row transition metal-catalyzed C(sp^3)−carbon/heteroatom cross-coupling of unactivated alkyl halides is a powerful strategy for constructing diverse molecular frameworks. Copper-based systems dominate C(sp^3)−N cross-coupling, likely owing to their strong propensity for reductive elimination, whereas other first-row transition metal catalysts have been reported only in rare cases. However, the intrinsically lower reducing capability of copper catalysts greatly limits their application to unactivated alkyl halides—particularly alkyl chlorides—in C(sp^3)−N cross-coupling reactions. Here, we demonstrate a general copper-catalyzed C(sp^3)−C/N cross-coupling of unactivated alkyl halides with diverse nucleophiles under mild thermal conditions. The success of this reaction relies on the use of anionic *N,N,N*-ligands to enhance the reducing capability of Cu(I) catalysts for the reduction of alkyl halides. This protocol accommodates a wide range of coupling partners, including primary to tertiary alkyl bromides and bench-stable chlorides, as well as primary and secondary alkyl iodides, and an array of nucleophiles (such as (hetero)aromatic amines, indoles, carbazoles, amides, azoles, and alkynes) with good functional-group compatibility. Furthermore, the present system provides a highly versatile platform for the late-stage functionalization of complex molecules.



INTRODUCTION

The cross-coupling of alkyl halides with nucleophiles to construct C(sp^3)-based carbon centers represents a powerful strategy in the synthesis of three-dimensional molecular frameworks.[1] Among them, an appealing approach involves the single-electron reduction of alkyl halides mediated by first-row transition metal catalysis, which affords active transient radical intermediates and has attracted much attention.[2] This radical-based approach provides a versatile platform for diverse coupling transformations. In this context, early investigations mainly focused on activated alkyl halides with α-functional groups, owing to their relatively high reduction potentials (E_{red} > −1.5 V vs SCE (saturated calomel electrode)). In stark contrast, unactivated alkyl halides without a proximal functional group remain largely underexplored due to their lower reduction potentials (E_{red} < −2.0 V vs SCE), which pose a big hurdle for radical initiation. In the past decades, Ni-,[3] Fe-,[4] and Co-based[5] catalytic systems have demonstrated remarkable progress in enabling the radical cross-coupling of unactivated alkyl halides, owing to their relatively high reducing capabilities (Scheme 1A; $E_{red}(Ni^{2+/+})$ = −0.26 V vs SCE; $E_{red}(Co^{2+/+})$ = −0.28 V vs SCE; $E_{red}(Fe^{2+/+})$ = −0.44 V vs SCE).[6] Despite these advances, most of these studies have focused on C(sp^3)−C bond formation using prefunctionalized carbon-based nucleophiles (e.g., organoboron, organozinc, organomagnesium). As such, it is of great significance to develop a general metal-catalyzed system that enables the reaction of such unactivated electrophiles with C−H-based nucleophiles (e.g., terminal alkynes or azoles) or even heteroatom-based nucleophiles (e.g., amines or amides).

Copper catalysts have emerged as an eminent option for coupling chemistry, owing to their stability, cost-effectiveness, and ready accessibility.[7] Moreover, a notable advantage of copper catalysts lies in the propensity of high-valent copper to undergo facile reductive elimination with not only carbon but also heteroatom coupling partners.[8] These properties render copper catalysts particularly suitable for the construction of carbon−heteroatom bonds. Nevertheless, copper exhibits a relatively weaker reducing ability ($E_{red}(Cu^{2+/+})$ = 0.15 V vs SCE) than other first-row transition metals, which might impede the initiation of the radical process. To address this

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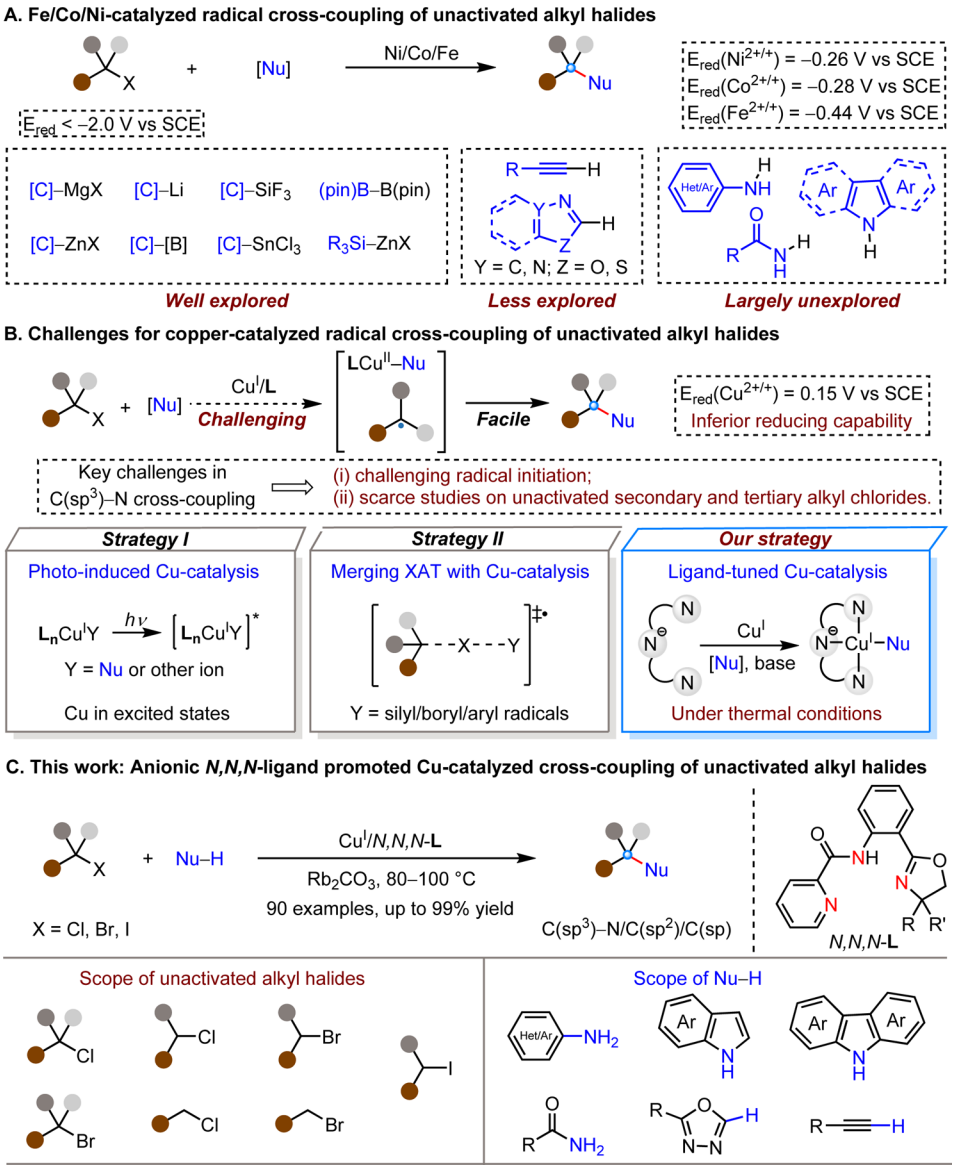
Scheme 1. Copper-Catalyzed Radical C(sp^3)−C/N Cross-Coupling of Unactivated Alkyl Halides



limitation, pioneering studies by Peters, Fu, and others have introduced photoactive copper catalysts,[9,10] which enhance copper's reducing capability to facilitate the initiation of radical reactions under light irradiation (Scheme 1B, Strategy I). Another approach is the halogen atom transfer (XAT) strategy. By incorporating an external oxidizing agent or other additives, highly reactive radicals can be generated to abstract halogen atoms from unactivated alkyl halides, thereby leading to the formation of alkyl radicals. In this regard, MacMillan,[10] Leonori,[11] Martin,[12] Liu[13] and others have demonstrated the amination, arylation, and alkynylation of unactivated alkyl halides, respectively (Scheme 1B, Strategy II). Given operational simplicity, it is important to develop a copper-catalyzed cross-coupling strategy under mild thermal conditions. In this respect, Hu[14] and Xie[15] have elegantly verified the feasibility of C(sp^3)−C bond formation under copper catalysis through ligand modulation.[2d,16,17] Nevertheless, these precedent protocols are only applicable to carbon-based nucleophiles, whereas heteroatom-based—particularly nitrogen-based—nucleophiles have so far remained largely unreported.[18] This is most likely due to the higher electronegativity of nitrogen-based nucleophiles than their carbon-based counterparts, resulting in less reducing copper catalysts after coordination to the metal center. Accordingly, enhancing the reducing capability of copper catalysts via ligand tuning becomes more challenging. In terms of electrophiles, while considerable progress has been achieved in copper-catalyzed cross-couplings of unactivated alkyl halides using the aforementioned three strategies, advancements involving unactivated secondary alkyl chlorides remain rather limited. To the best of our knowledge, there are no prior reports on cross-couplings between unactivated tertiary alkyl chlorides and nitrogen nucleophiles. Given the significance of amines and *N*-heterocycles in organic synthesis and drug discovery, the development of a general copper-based catalytic system that can facilitate the C(sp^3)−N cross-coupling of unactivated alkyl halides—particularly alkyl chlorides—under relatively mild thermal conditions is highly desirable.

We have recently discovered that a series of chiral, electron-rich, multidentate anionic ligands can remarkably enhance the single-electron reduction of Cu(I) species, thereby enabling alkyl halides to participate in enantioselective C(sp^3)−

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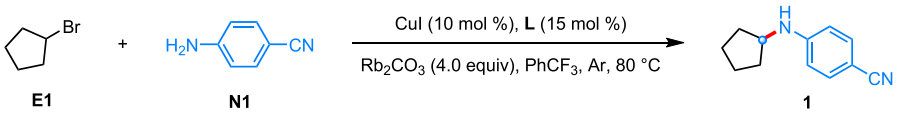
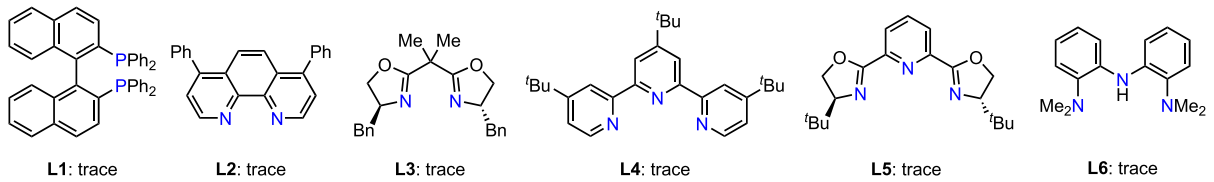
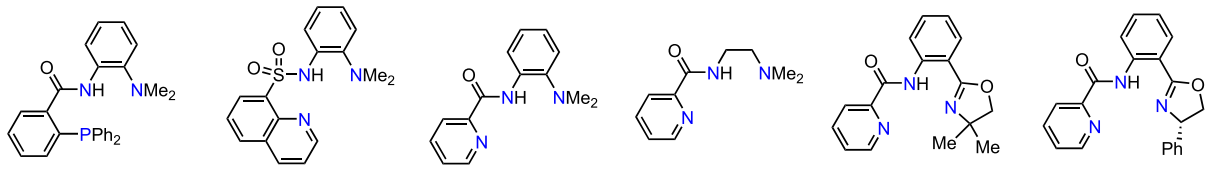
Table 1. Ligand Effect in the Model Reaction[a]



E1 N1 1



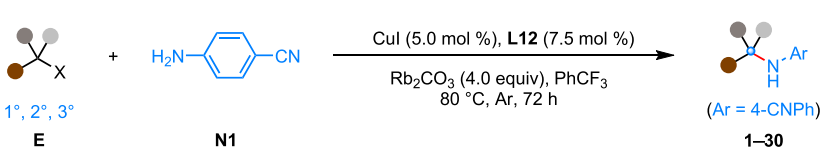
L1: trace L2: trace L3: trace L4: trace L5: trace L6: trace



L7: trace L8: trace L9: 18% L10: 10% L11: 64% L12: 97% (95%[b])

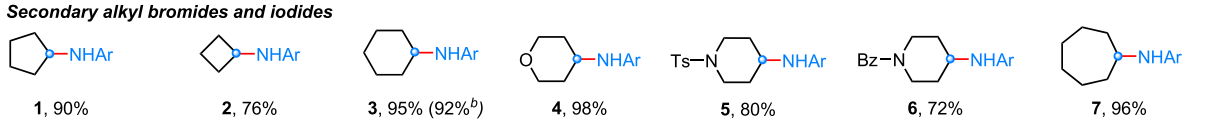
[a]Reaction conditions: alkyl bromide **E1** (0.060 mmol, 1.2 equiv), aromatic amine **N1** (0.050 mmol), CuI (10 mol %), **L** (15 mol %), and Rb_2CO_3 (4.0 equiv) in $PhCF_3$ (0.50 mL) at 80 °C for 48 h under argon; yield of **1** was based on ^1H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard. [b]CuI (5.0 mol %) and **L** (7.5 mol %) for 72 h.

Table 2. Substrate Scope of Unactivated Alkyl Halides[a]

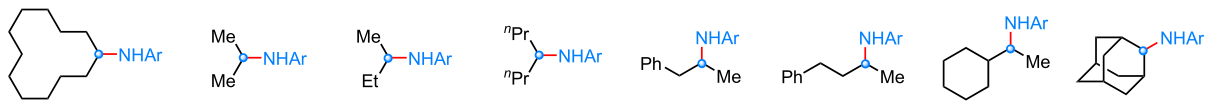


E N1 1–30 L12

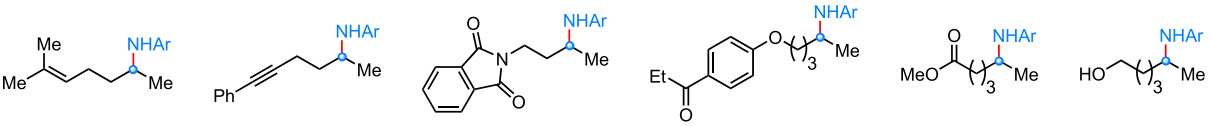
Secondary alkyl bromides and iodides



1, 90% **2**, 76% **3**, 95% (92%[b]) **4**, 98% **5**, 80% **6**, 72% **7**, 96%

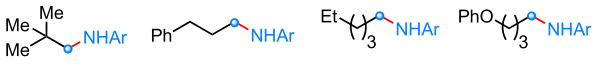


8, 58% **9**, 91% **10**, 95% **11**, 96% **12**, 97% **13**, 99% (95%[b]) **14**, 85% **15**, 59%



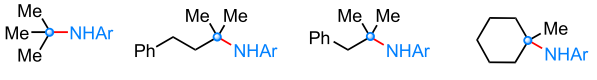
16, 95% **17**, 80% **18**, 80% **19**, 58% **20**, 87% **21**, 81%

Primary alkyl bromides



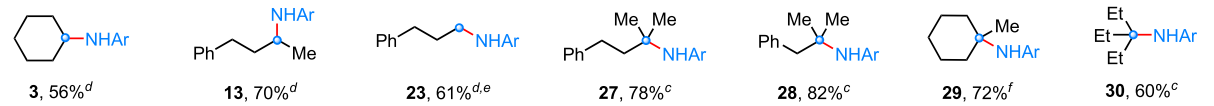
22, 92% **23**, 95% **24**, 96% **25**, 75%

Tertiary alkyl bromides



26, 75%[c] **27**, 65%[c] **28**, 77%[c] **29**, 63%[c]

Alkyl chlorides



3, 56%[d] **13**, 70%[d] **23**, 61%[d,e] **27**, 78%[c] **28**, 82%[c] **29**, 72%[f] **30**, 60%[c]

[a]Reaction conditions: alkyl bromide **E** (0.24 mmol, 1.2 equiv), aromatic amine **N1** (0.20 mmol), CuI (5.0 mol %), **L12** (7.5 mol %), and Rb_2CO_3 (4.0 equiv) in $PhCF_3$ (2.0 mL) at 80 °C for 72 h under argon; isolated yield is shown. [b]With alkyl iodide (0.24 mmol, 1.2 equiv) for 48 h. [c]CuI (10 mol %) and **L11** (15 mol %) for 4 days. [d]At 100 °C. [e]With $^nBu_4NI$ (0.24 mmol, 1.2 equiv). [f]With alkyl chloride (0.40 mmol, 2.0 equiv), CuI (10 mol %) and **L11** (15 mol %) for 5 days. Ts, *p*-toluenesulfonyl; Bz, benzoyl.

heteroatom bond formations.[19] Inspired by this success in ligand modulation, we envisioned the development of a robust, ligand-tuned, copper-based catalytic system to strongly enhance the reducing capability of Cu (Scheme 1B, Our

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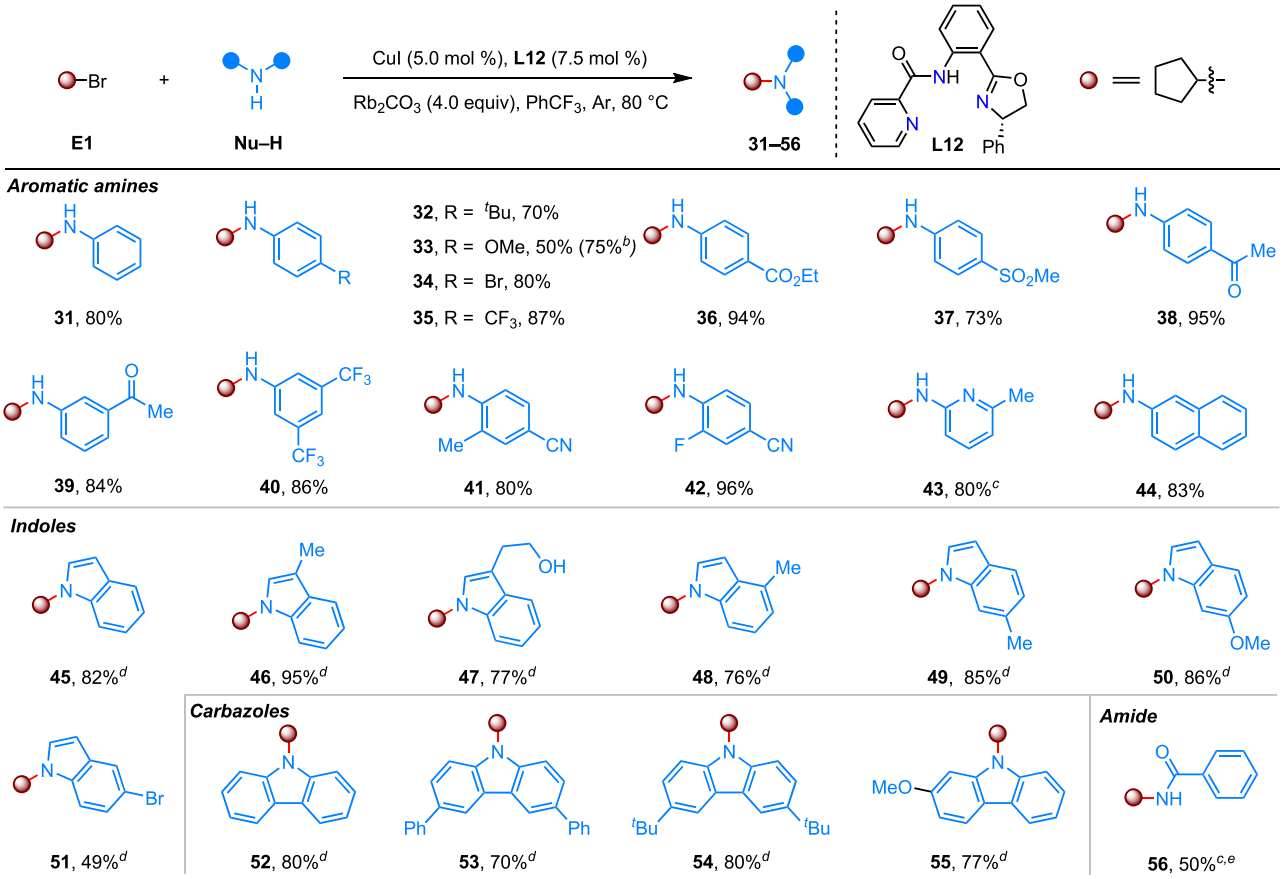
Table 3. Substrate Scope of N-Nucleophiles[a]



[a]Reaction conditions: **E1** (0.24 mmol, 1.2 equiv), **Nu-H** (0.20 mmol), CuI (5.0 mol %), **L12** (7.5 mol %), and Rb_2CO_3 (4.0 equiv) in $PhCF_3$ (2.0 mL) at 80 °C for 72 h under argon; isolated yield is shown. [b]With K_3PO_4 (4.0 equiv). [c]CuI (10 mol %), **L12** (15 mol %). [d]**L11** was used. [e]**E1** (0.30 mmol, 1.5 equiv), benzamide (0.20 mmol), K_3PO_4 (3.0 equiv).

strategy), which, if achieved, would effectively promote the coupling of unactivated alkyl halides with both nitrogen- and carbon-based nucleophiles under mild thermal conditions.

Herein, we disclose the development of amide-derived anionic *N,N,N*-ligands that enable general copper-catalyzed radical cross-coupling of unactivated alkyl halides with nitrogen- and carbon-based nucleophiles under relatively mild thermal conditions[17] (Scheme 1C). This reaction features a broad substrate scope for both coupling partners, encompassing primary to tertiary alkyl bromides, bench-stable chlorides, and primary and secondary alkyl iodides, as well as an array of nucleophiles—including (hetero)aromatic amines, indoles, carbazoles, amides, azoles, and alkynes—with good functional-group compatibility. As such, it provides a versatile means to construct diverse C(sp^3)−C/N bonds. Furthermore, the method is highly compatible with complex bioactive molecules, making it a flexible platform for C(sp^3)−C/N bond construction in organic synthesis and related disciplines.

RESULTS AND DISCUSSION

Reaction Development. Considering that copper-catalyzed cross-coupling of unactivated alkyl halides with aromatic amines via the ligand-tuning strategy has not yet been reported, we initially explored the reaction conditions using cyclopentyl bromide **E1** and 4-aminobenzonitrile **N1** as model substrates. To investigate the influence of ligands on the proposed radical process, an extensive screening of various ligands was conducted using CuI/Rb_2CO_3 in $PhCF_3$ (Table 1). Initial attempts with neutral ligands, including bisphosphine **L1** for Fu's N-alkylation,[9e] bathophenanthroline **L2** for Xie's C-alkylation,[15b] and multinitrogen ligands **L3**−**L5**, failed to promote the reaction. Drawing inspiration from previous studies, including our own, which demonstrated that electron-rich anionic ligands can enhance the reducing capacity of copper under thermal conditions, we turned our attention to multidentate anionic ligands. However, when we initially employed the anionic bis(amino)amide ligand **L6** in Hu's C-alkylation protocol,[14] the reaction failed to proceed, presumably because the weak base was insufficient to deprotonate the ligand effectively. We hypothesized that further modifications to the ligands would be necessary to enhance the acidity of the N−H group. To our delight, when screening amide- and sulfonamide-derived **L7**−**L9**, the tridentate amide *N,N,N*-ligand **L9** successfully initiated the reaction, delivering the desired product **1** in 18% yield. Structural modification of ligand **L9** through replacement of the phenylenediamine moiety with ethylenediamine afforded the flexible tridentate *N,N,N*-ligand **L10**. Surprisingly, this modification led to a significant decrease in reaction yield. This observation led us to question whether a more rigid ligand scaffold might stabilize the copper complex, thereby improving the yield. We further evaluated additional oxazoline-derived amide *N,N,N*-ligands **L11** and **L12**.[20] Notably, the tridentate ligand **L12**—first reported by Lu's group in the cobalt-catalyzed asymmetric

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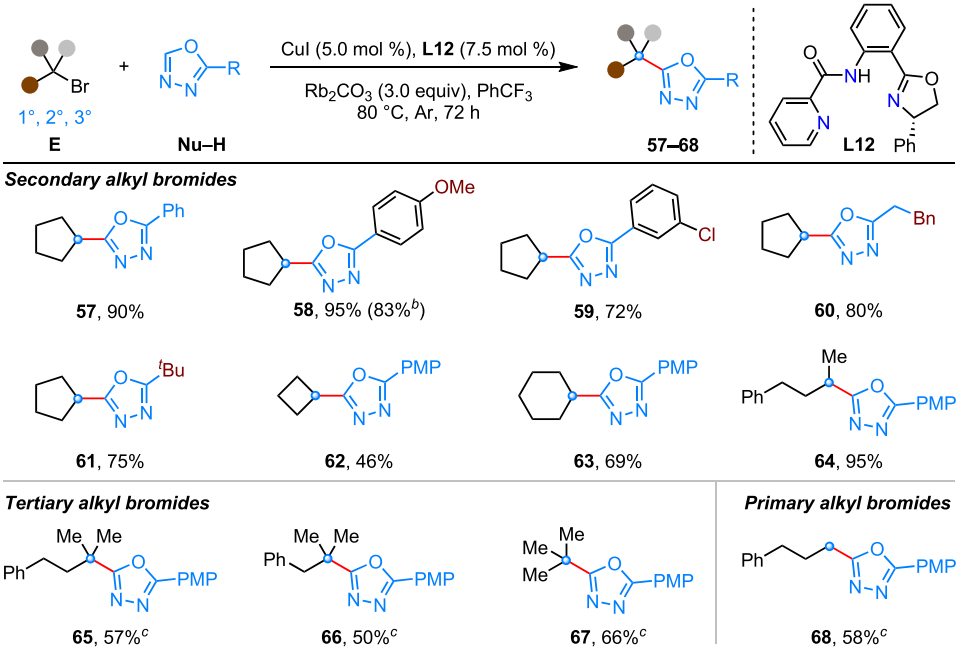
Table 4. Substrate Scope of Azoles and Unactivated Alkyl Halides[a]



[a]Reaction conditions: alkyl bromide **E** (0.24 mmol, 1.2 equiv), azole **Nu-H** (0.20 mmol), CuI (5.0 mol %), **L12** (7.5 mol %), and Rb_2CO_3 (3.0 equiv) in $PhCF_3$ (2.0 mL) at 80 °C for 72 h under argon; isolated yield is shown. [b]Cyclopentyl chloride was used. [c]With CuI (10 mol %), **L12** (15 mol %). PMP, *p*-methoxyphenyl.

hydroboration of styrenes[20c]—afforded product **1** in an almost quantitative yield, substantially higher than that of **L11** likely due to steric congestion around the oxazoline nitrogen binding site (Table S2). After further optimization, examining the impact of other parameters, including inorganic bases, solvents, copper salts, the molar ratio of catalysts, reaction temperature, and reaction time (Table S1), we identified the optimal conditions as follows: 1.2 equiv **E1**, 1.0 equiv **N1**, 5 mol % CuI, 7.5 mol % **L12**, and 4.0 equiv Rb_2CO_3 in benzotrifluoride at 80 °C for 72 h. Under the optimal conditions, the desired product **1** was obtained in 95% yield (Table 1).

Scope of Unactivated Alkyl Halides. With the optimized conditions in hand, we evaluated the scope of unactivated alkyl halides (Table 2). Cyclic secondary alkyl bromides bearing nonstrained rings (five- to 12-membered) or a strained four-membered ring were effectively converted to the corresponding coupling products in moderate to good yields (**1**–**8**, 58–98%). Unsurprisingly, highly reactive cyclohexyl iodide was also compatible, affording **3** in good yield. Acyclic secondary alkyl bromides were likewise suitable, delivering the target products in moderate to excellent yields (**9**–**14** and **16**–**21**, 58–99%). Acyclic and cyclic alkyl bromides with *β*-branching (**14** and **15**) underwent N-alkylation under the standard coupling conditions. Various functional groups—including cyclic ether (**4**), protected amine (**5** and **6**), olefin (**16**), alkyne (**17**), amide (**18**), ketone (**19**), ester (**20**), and even free alcohol (**21**)—were well tolerated. Primary alkyl bromides also participated smoothly, giving the desired products in good yield (**22**–**25**). The radical cross-coupling of unactivated tertiary alkyl halides is an underexplored and challenging field.[9−15] We were pleased to find that ligand **L11** enabled the conversion of unactivated tertiary alkyl bromides to the desired products in good yields (**26**–**29**, 65–77%). Notably, typically unreactive alkyl chlorides, particularly tertiary ones, were readily converted to the coupled products (**27**–**30**) under finely tuned conditions, demonstrating the robustness of this N-alkylation protocol. Competition experiments between secondary and primary alkyl halides indicated that the more substituted secondary alkyl halides are more reactive, consistent with the generation of a radical intermediate in the C–X cleavage step (Scheme S1).

Scope of Nucleophiles. Next, we investigated the substrate scope of N-nucleophiles (Table 3). For aromatic amines, the reaction showed excellent compatibility with both electron-donating and electron-withdrawing groups at either the *para* or *meta* positions, affording products **31**–**40** in 50–95% yield. Compared with electron-withdrawing anilines, electron-donating anilines are less acidic at N–H, making deprotonation more difficult under our conditions and resulting in lower yield. To address this, we screened inorganic bases and found that the stronger base K_3PO_4 increased the yield of product **33** to 75%. Notably, the reaction displayed remarkable steric tolerance, efficiently coupling *ortho*-substituted aromatic amines to give **41** and **42** in good yield. Furthermore, 2-aminopyridine and 2-naphthylamine were viable substrates, delivering **43** and **44** in satisfactory yields. The scope was then expanded to medicinally relevant azaheterocycles. Indole derivatives with various substitution patterns underwent smooth transformation to give products **45**–**51** in 49–95% yield. The methodology was also applicable to carbazole alkylation without additional optimization, providing products **52**–**55** in 70–80% yield. In preliminary studies, benzamide proved to be a viable substrate, affording **56** in moderate yield; further optimization is ongoing in our laboratory. Unfortunately, alkyl amines are not applicable to this $C(sp^3)$–N cross-coupling.

Given the pharmaceutical importance of azole motifs, we next applied the Cu^I/*N,N,N*-ligand catalytic system to the cross-coupling between unactivated alkyl halides and azole $C(sp^2)$–H bonds under thermal conditions (Table 4). The

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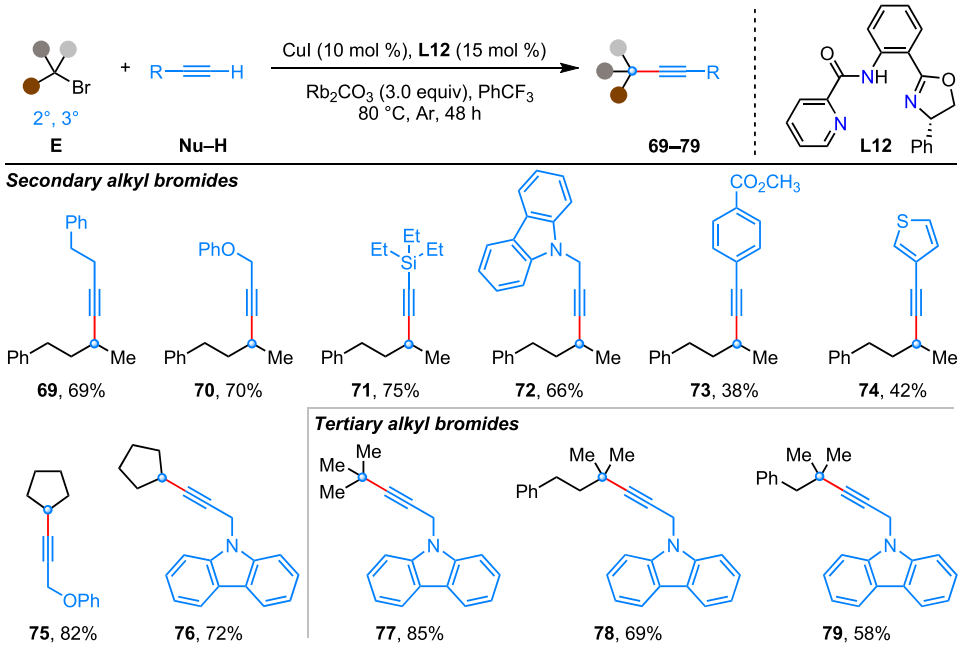
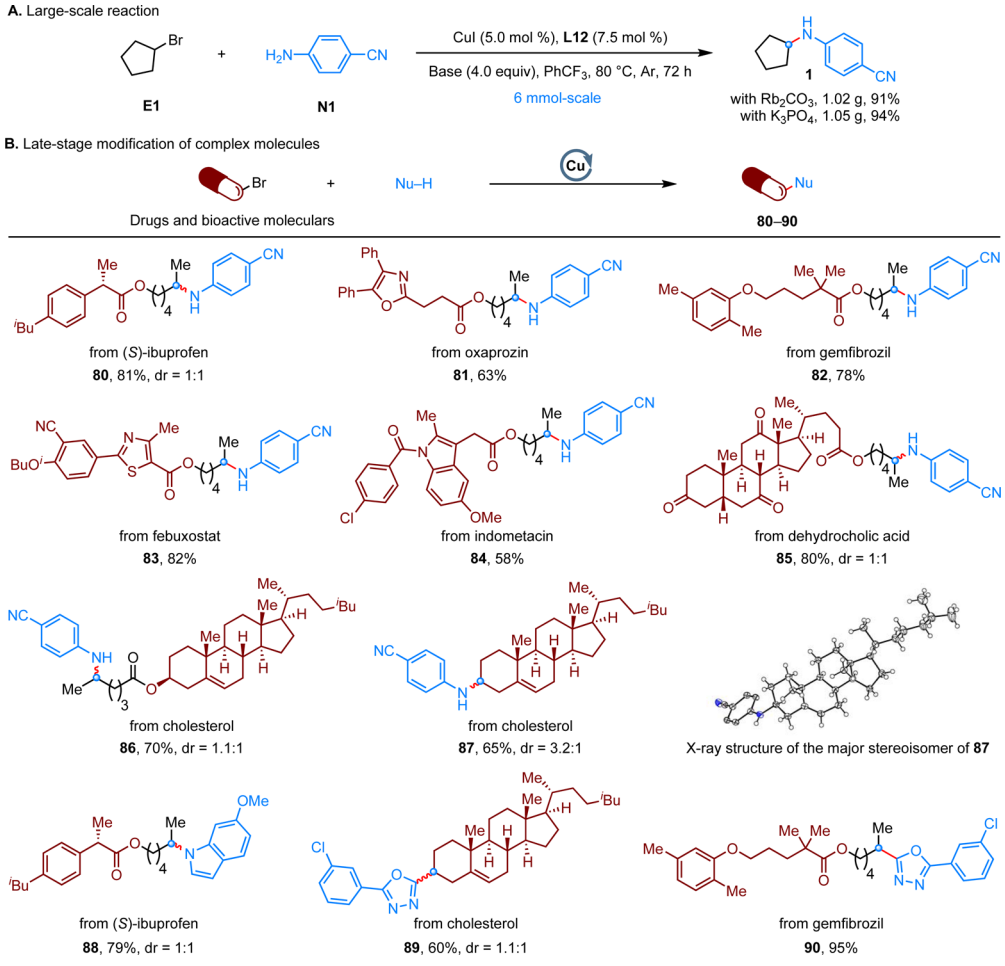
Table 5. Substrate Scope of Alkynes and Unactivated Alkyl Halides[a]



[a]Reaction conditions: alkyl bromide **E** (0.24 mmol, 1.2 equiv), alkyne **Nu-H** (0.20 mmol), CuI (10 mol %), **L12** (15 mol %), and Rb_2CO_3 (3.0 equiv) in $PhCF_3$ (2.0 mL) at 80 °C for 48 h under argon; isolated yield is shown.

Scheme 2. Synthetic Utility



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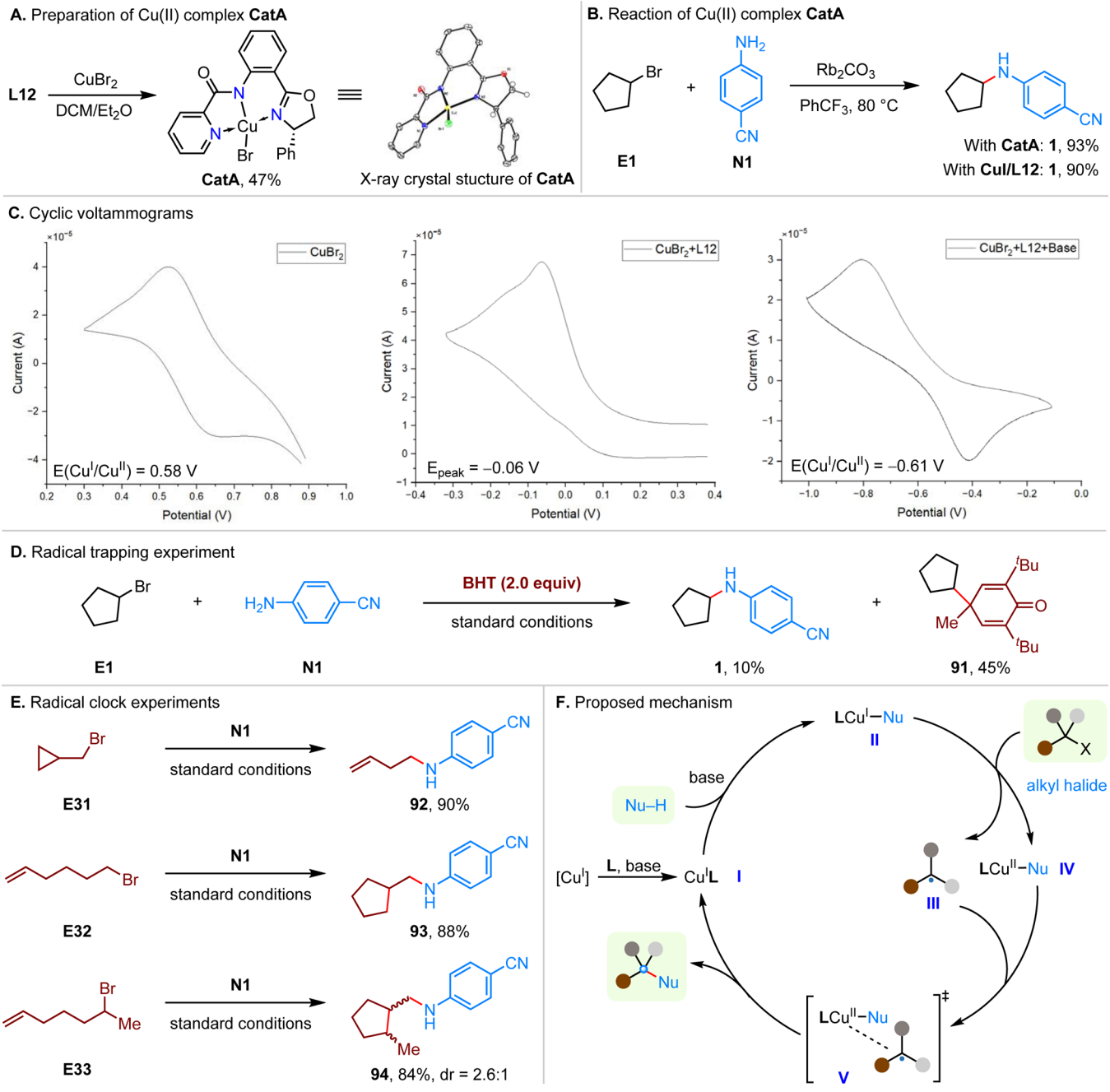
Scheme 3. Mechanistic Investigations and Mechanistic Proposal



reaction proceeded smoothly with a wide range of 1,3,4-oxadiazole derivatives, delivering **57**–**64** in 46–95% yield. Aryl-substituted azoles bearing electron-neutral (**57**), electron-donating (**58**), or electron-withdrawing (**59**) groups were all tolerated. Alkyl-substituted azoles also coupled efficiently, giving **60** and **61** in high yield. Regarding electrophile scope, unactivated alkyl chlorides such as cyclopentyl chloride coupled successfully, providing **58** with comparable efficiency (83% yield). Importantly, both tertiary and primary unactivated alkyl bromides were viable, generating **65**–**68** in moderate yield, which highlights the synthetic potential of this radical alkylation protocol.

To further showcase the generality of this methodology and exploit the versatile transformability of alkynyl groups, we examined the cross-coupling of unactivated alkyl halides with terminal alkynes (Table 5). Aliphatic alkynes bearing phenyl (**69**), ether (**70**), silyl (**71**), or carbazole (**72**) substituents all underwent efficient coupling, affording products in 66–75% yield. (Hetero)aryl alkynes were also tolerated, delivering **73** and **74** in lower yield, likely due to their higher acidity and competing side reactions. Both cyclic and acyclic electrophiles participated successfully, as shown by the formation of **69**–**76**. Notably, even tertiary alkyl bromides reacted smoothly under the same conditions, providing **77**–**79** in 58–85% yield.

Synthetic Utility. To demonstrate the scalability and synthetic utility of this methodology, the reaction was performed on a 6 mmol scale using either Rb_2CO_3 or K_3PO_4 as the base. In both cases, coupling product **1** (>1.0 g) was obtained in >90% yield (Scheme 2A), underscoring its potential for application in organic synthesis. The method-

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ology was also applied to the late-stage functionalization of complex bioactive molecules and natural products (Scheme 2B). Ibuprofen (**80**), oxaprozin (**81**), gemfibrozil (**82**), febuxostat (**83**), indomethacin (**84**), dehydrocholic acid (**85**), and cholesterol (**86**) proved to be excellent substrates, affording the corresponding C(sp^3)−N coupled products in moderate to good yields. In the case of cholesterol, the coupled product **87** was obtained in 65% isolated yield via an Appel reaction followed by cross-coupling; the major diastereomer of **87** was characterized by X-ray crystallographic analysis (CCDC 2464325). In addition, the method was successfully applied to the alkylation of indole and azole C(sp^2)−H bonds, delivering **88**−**90** in 60−95% yield, further highlighting its versatility for drug optimization studies.

Mechanistic Studies. To gain insight into the reaction mechanism, we performed a series of experiments. First, complex **CatA** was readily obtained by mixing **L12** with $CuBr_2$, and X-ray structural analysis confirmed an anionic tridentate coordination mode for the ligand (Scheme 3A and Figure S2). We found that **CatA** and the CuI/**L12** catalyst system delivered product **1** in comparable yield under the otherwise identical conditions (Scheme 3B). We next examined the redox properties of the Cu(I) catalyst using $CuBr_2$ as a precursor. Cyclic voltammetry (CV) studies revealed that the Cu(I)/Cu(II) redox potential decreased from approximately +0.58 V to −0.61 V upon addition of **L12** and base (Scheme 3C). In contrast, a control experiment without base gave an E_{peak} of −0.06 V, likely due to incomplete deprotonation of the amide. These results demonstrate that the coordination of the anionic ligand markedly enhances the reductive power of the copper catalyst.[21] Additional CV measurements with a nucleophile (3,5-bis(trifluoromethyl)aniline **N11**) in the $CuBr_2$/**L12**/base system showed an E_{peak} at − 0.98 V (Figure S6), which we attribute to an **L**Cu−Nu intermediate. The nucleophile thus further increases the reducing ability of the complex. Although this potential is still insufficient for outer-sphere SET with unactivated alkyl halides, we hypothesize that halogen-atom transfer processes may operate under the standard thermal conditions.[22] Radical trapping experiments supported a radical pathway: addition of BHT (2,6-di-*tert*-butyl-4-methylphenol) significantly inhibited C−N bond formation, and the BHT-trapped product **91** was isolated in 45% yield (Scheme 3D). A radical clock experiment with **E31** gave exclusively the ring-opened product **92** under standard conditions. Primary and secondary alkyl bromides bearing an alkene moiety underwent tandem 5-*exo*-*trig* cyclization and C−N coupling to furnish the radical-cyclization products **93** and **94**, respectively in high yield (Scheme 3E). Moreover, the use of enantioenriched chiral ligand **L12** resulted in essentially no enantioselectivity. Collectively, these results strongly support the involvement of alkyl radicals in the reaction. Based on these findings and previous reports,[9−17] we propose a possible mechanism shown in Scheme 3F. In the presence of base, the Cu^I**L** complex **I** forms and reacts with a nucleophile (Nu−H) to generate Cu^I intermediate **II**. This intermediate next reduces the alkyl halide to alkyl radical **III**, forming Cu^{II} complex **IV**. C(sp^3)−C/N coupling then proceeds, possibly via either a Cu(III) intermediate or radical substitution to the Cu−Nu bond, to furnish the product and regenerate Cu^I**L** complex **I**. An alternative pathway, in which transmetalation of the nucleophile occurs after direct reduction of the alkyl halide by Cu^I species **I**, cannot be excluded at this stage (Scheme S2).

CONCLUSIONS

In summary, we have developed an anionic *N,N,N*-ligand-based copper catalytic system that enables the thermal cross-coupling of unactivated alkyl halides with a broad spectrum of nucleophiles. The method accommodates primary, secondary, and tertiary alkyl bromides, even alkyl chlorides, as well as primary and secondary alkyl iodides, along with diverse nucleophiles including (hetero)aromatic amines, indoles, carbazoles, azoles, and alkynes. This robust protocol offers a versatile platform for constructing a wide range of C(sp^3)−C and C(sp^3)−N bonds. Ongoing studies are directed toward extending this radical carbon−heteroatom cross-coupling to unactivated halides with more heteroatomic nucleophiles under mild conditions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c10285.

Experimental procedures, characterization of compounds, Tables S1 and S2, Figures S1−S6, Schemes S1 and S2, and crystallographic data of **87-major** and **CatA** (PDF)

Accession Codes

Deposition Numbers 2464325 and 2464327 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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