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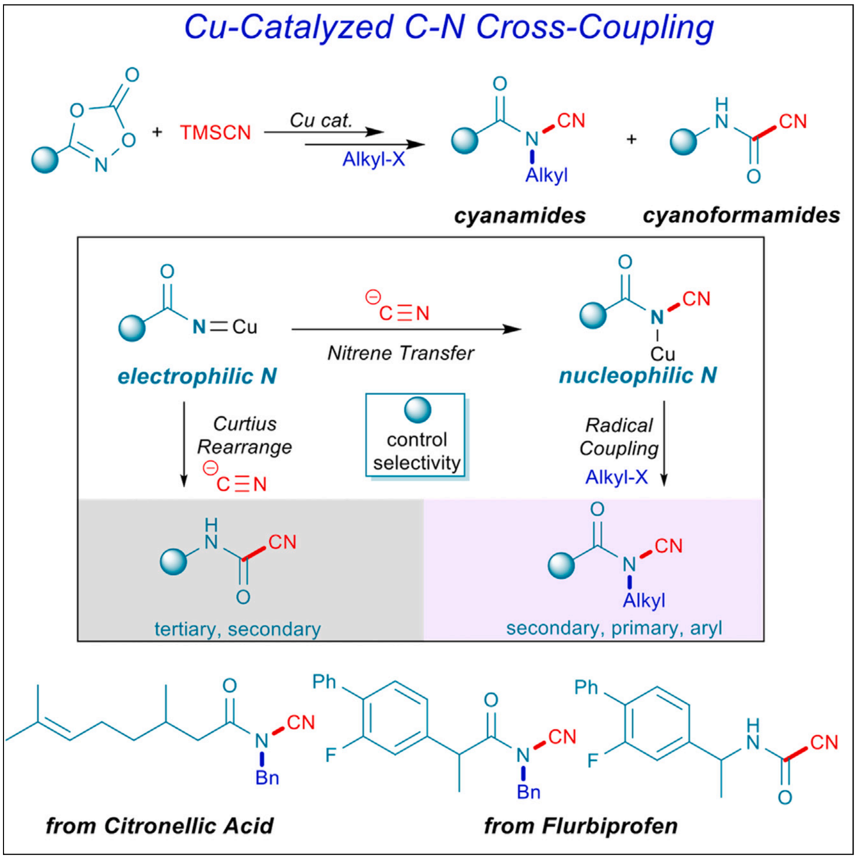
Copper-catalyzed C–N cross-coupling for construction of alkylated *N*-cyanamide derivatives via nitrogen umpolung



Unlocking new pathways in chemical synthesis is crucial for advancing drug discovery and materials science. Here, we have developed a straightforward and efficient approach for synthesizing alkylated *N*-cyanamides through a nitrogen-umpolung strategy. The one-pot two-step process merges a Cu-nitrene transfer (electrophilic nitrogen) with a Cu-catalyzed *N*-alkylation (nucleophilic nitrogen). This synthesis strategy not only promises accessibility to the late stage of complex natural products and drugs but also establishes an innovative methodology.

Yanjun Wan, Harriet K. Zhang, Jin Qian, Muinat A. Aliyu, Jack R. Norton

jrn11@columbia.edu

Highlights

Cu-catalyzed one-pot two-step synthesis of *N*-cyanamides via nitrogen umpolung

Cu-nitrene transfer and Cu-catalyzed radical alkylation

Late-stage functionalization of natural products and pharmaceuticals

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Article

Copper-catalyzed C–N cross-coupling for construction of alkylated *N*-cyanamide derivatives via nitrogen umpolung

Yanjun Wan,[1] Harriet K. Zhang,[1] Jin Qian,[1] Muinat A. Aliyu,[1] and Jack R. Norton[1,2,*]

SUMMARY

The cyano group is found in numerous bioactive compounds. Although cyano groups are easily introduced into target molecules by the formation of C–CN, the coupling of CN to nitrogen is more challenging because of the high electronegativity of that element. We have developed an efficient one-pot two-step method of preparing alkylated *N*-acyl cyanamides and cyanoformamides through a nitrogen-umpolung strategy. The strategy involves a Cu-nitrene transfer and a Cu-catalyzed *N*-alkylation, with various dioxazolones, trimethylsilyl cyanide (TMSCN), and halides. This transformation exhibits broad substrate scope and excellent functional-group tolerance by a straightforward procedure under mild conditions. Our reaction can also carry out the late-stage functionalization of complex natural products and pharmaceuticals.

INTRODUCTION

Nitriles are found in many bioactive chemicals[1] and generally exhibit remarkable biocompatibility.[2] They often function as hydrogen-bond acceptors, particularly with amino acids, in protein-small molecule interactions. They are easily converted into amines, carbonyl groups, and heterocycles.[3] Nitriles have been traditionally prepared by the dehydration of amides,[4] the nucleophilic attack of cyanide ion on carbon,[5] or radical cyanation.[3] However, an alternative way of introducing nitriles into target molecules is the addition of cyanide ion to electrophilic nitrogen. The resulting cyanamides, particularly *N*-acyl cyanamides, are versatile building blocks in organic synthesis.[6] The two-nitrogen and one-carbon skeleton of *N*-acyl cyanamides enables their transformation into a variety of heterocycles (Figure 1A).[7–14] Furthermore, they can be incorporated into bioactive molecules as carboxylic acid bioisosteres, enhancing the membrane permeability of drug candidates, such as the ones in Figure 1B.[15–19]

The classical approach to constructing *N*-aroyl cyanamides involves the reaction of aryl acid chlorides with sodium cyanamide.[20–22] The direct addition of a CN^- to nitrogen may be more convenient but will require that the electronegative nitrogen be made electrophilic—a nitrogen umpolung that may be practical in organic synthesis.[23] One possibility is a metal nitrenoid complex because such compounds are known to have electrophilic reactivity.[24–29]

Metal nitrenoid complexes have been used for the construction of amide derivatives,[30] by processes such as aziridination,[31,32] $C(sp^3)$–H bond functionalization,[33–35] sulfimidation,[36–39] hydrazidation,[40] and amidation.[41–43] Traditional precursors for

THE BIGGER PICTURE

N-Acyl cyanamides are versatile building blocks, easily integrating into bioactive molecules, which augment the membrane permeability of potential drug candidates. Traditionally, the approach to constructing *N*-acyl cyanamides involved the reaction of aryl acid chlorides with sodium cyanamide. However, the use of an electrophilic nitrogen allows for the rapid construction of alkylated *N*-acyl cyanamides. This innovative approach entails the combination of a Cu-catalyzed nitrene transfer and a Cu-catalyzed *N*-alkylation, with various dioxazolones, trimethylsilyl cyanide (TMSCN), and halides. This procedure enables the late-stage functionalization of natural products and pharmaceuticals. In a broader scientific context, this one-pot two-step method should attract significant interest within the research community.

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A Synthetic applications of *N*-acyl cyanamides

B Bioactive molecules with *N*-acyl cyanamide and cyanoformamide

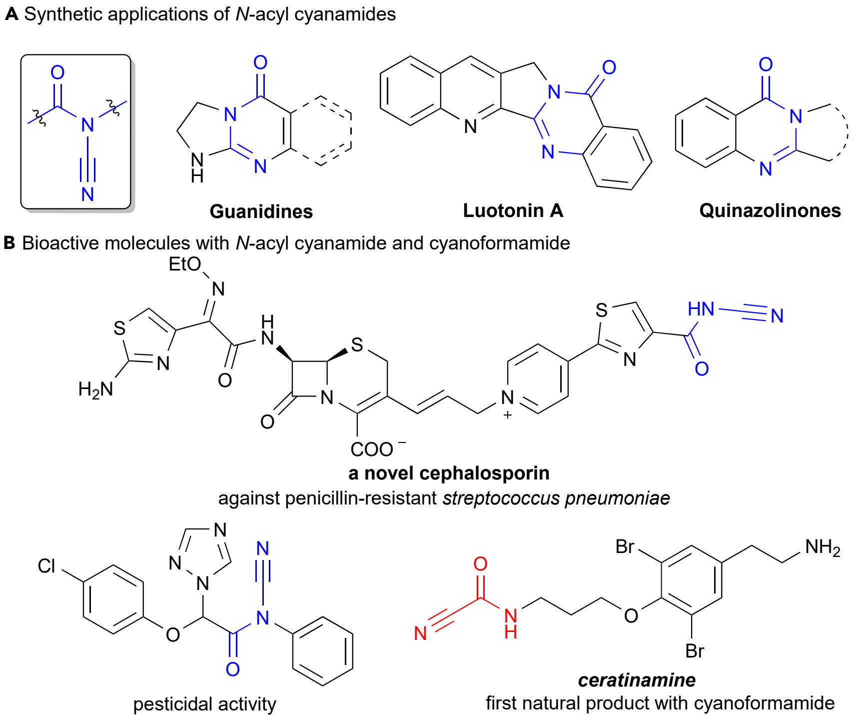

Figure 1. Synthetic applications of *N*-acyl cyanamides and their bioactive molecules

nitrene complexes have been azides,[44–47] iminoiodinanes,[26,48] and hydroxylamines,[24] but dioxazolones have recently attracted attention because of their ease of handling, ready availability, and bench-top stability (Figure 2).[49,50] The synthesis of ruthenium nitrene complexes from dioxazolones has been reported by Bolm (Figure 2A)[37,51] and used for the construction of *N*-acyl sulfoximines and sulfimides. Dioxazolones have also been used for the construction of new C–N bonds, as in the C–H amidation reactions of Chang and others; either a C–N reductive elimination or a radical rebound mechanism (Figure 2A) appears to be involved.[52–63] Nucleophilic attack on electron-deficient nitrenoid complexes formed from dioxazolones has been used for intermolecular coupling reactions, as in Chen's iridium- or iron-catalyzed intermolecular N–N coupling with arylamines.[40] Mechanistic studies have established the strong electrophilicity of acyl nitrene complexes, leading to Rh, Ru, Cu, and Fe-catalyzed *S*-imidations, *P*-imidations, and the formation of *N*-acyl amidines (Figure 2B).[38,64–66] Motivated by these precedents and the availability of copper, we felt that *N*-acyl cyanamides might be available by the Cu-catalyzed addition of cyanide to the electrophilic nitrene complexes from various 1,4,2-dioxazol-5-ones (Figure 2C).

Cu-catalyzed C–N coupling, involving amines and alkyl halides, is another method for C–N bond formation and has been successfully demonstrated by the Fu, Peters, Leonori, and Liu groups[67–71]; these reactions may occur by an S_N2 mechanism or by a radical coupling. With copper catalysis, we have achieved the one-pot two-step synthesis of alkylated *N*-acyl cyanamide derivatives (Figure 2C). The attack of CN^- on the electrophilic nitrene ligand results in the formation of a nucleophilic cyanamide nitrogen, and the reaction of that nitrogen with alkyl halides yields the desired alkylated *N*-acyl cyanamides, although the low nucleophilicity of such cyanamides does make the reaction difficult.

[1]Department of Chemistry, Columbia University, 3000 Broadway, New York, NY 10027, USA

[2]Lead contact

*Correspondence: jrn11@columbia.edu

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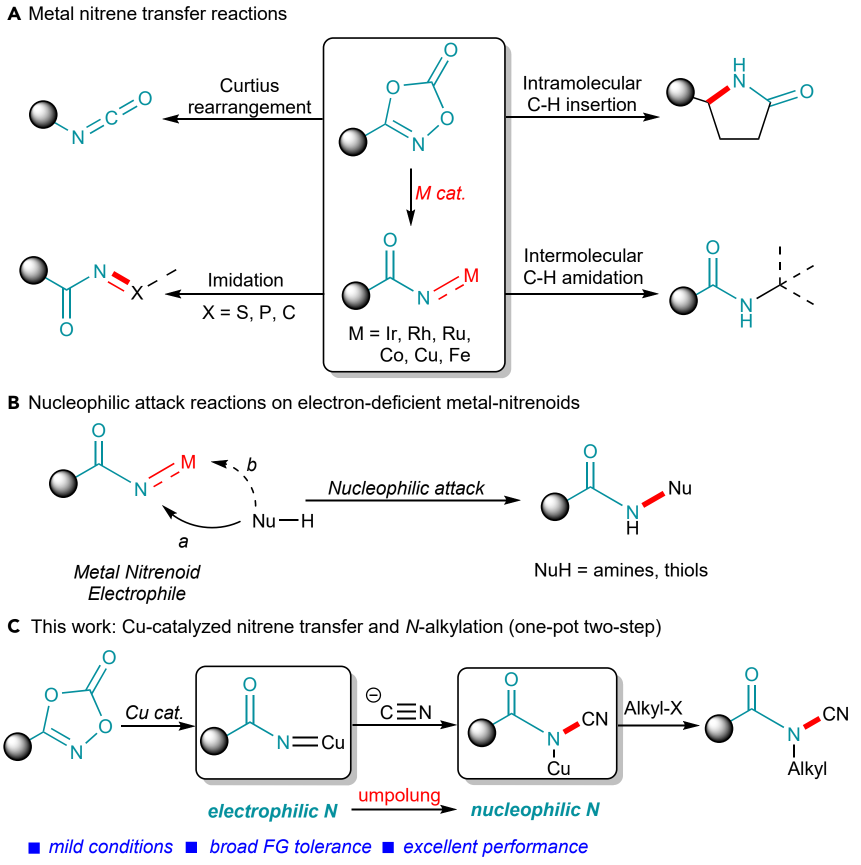

Figure 2. Metal nitrene transfer reactions

(A) Metal nitrene transfer reactions.

(B) Nucleophilic attack on an electrophilic nitrogen of metal nitrenoid.

(C) This work: Cu-catalyzed one-pot two-step *N*-difunctionalization for the synthesis of alkylated *N*-acyl cyanamides mediated by a nitrogen umpolung.

RESULTS AND DISCUSSION

Optimization of reaction

We began by treating 3-phenyl-1,4,2-dioxazol-5-one $\mathbf{S_1}$ with 1.5 equiv of trimethylsilyl cyanide (TMSCN) in the presence of 5 mol % $Cu(MeCN)_4PF_6$ in *N*,*N*-dimethylacetamide (DMA) under air (60°C, 6 h), and then added 1.2 equiv of MeI along with 1.2 equiv of *t*BuOLi for desilylation of the intermediate **A** (another 2 h, entry 1 in Figure 3). The result was a one-pot, two-step synthesis of *N*-cyano-*N*-methylbenzamide **1** with an isolated yield of 95%. Other copper catalysts (entries 2–4), including CuI, CuCN, and $CuBr_2$, proved less effective at the Cu-nitrenoid transfer. The use of $Cu(OTf)_2$ gave a slight decrease in yield (to 91%) (entry 5). We then replaced TMSCN with NaCN and $n$$Bu_4NCN$; however, both proved to be worse CN ion sources (entries 6 and 7). The reaction worked well in *N*,*N*-dimethylformamide (DMF) (94% yield, entry 8), the yields were lower in 1,4-dioxane and 1,2-dichloroethane (DCE) (entries 9 and 10), whereas acetonitrile and methanol gave none of the desired product, presumably as a result of their coordination to the copper (entries 11 and 12).[66] No improvement in the yield was obtained with other bases, such as K_2CO_3 and *t*BuOK (entries 13 and 14), and no change in yield was observed when the reaction was conducted under argon (entry 15). Increasing or decreasing the reaction temperature led to lower yields (entries 16 and 17). Carrying out the reaction in a single step (entry 18) led to a dramatically lower yield of 1 (15%) because of the decomposition of $\mathbf{S_1}$ in the presence of a strong base.

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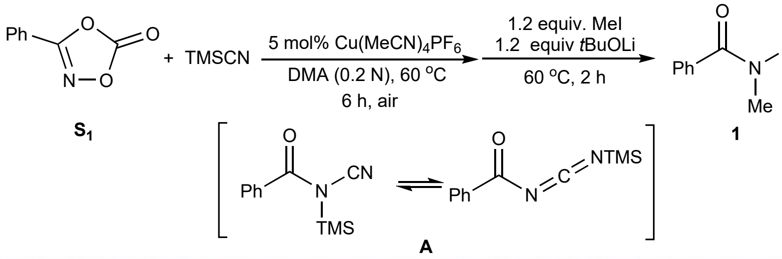

Entry	Deviation from standard conditions^a	Yield^b of **1** (%)
1	None	95
2	CuI instead of $Cu(MeCN)_4PF_6$	53
3	CuCN instead of $Cu(MeCN)_4PF_6$	45
4	$CuBr_2$ instead of $Cu(MeCN)_4PF_6$	36
5	$Cu(OTf)_2$ instead of $Cu(MeCN)_4PF_6$	91
6	NaCN instead of TMSCN	16
7	*n*Bu_4NCN instead of TMSCN	63
8	DMF instead of DMA	94
9	1,4-dioxane instead of DMA	68
10	DCE instead of DMA	31
11	MeCN instead of DMA	trace
12	MeOH instead of DMA	trace
13	K_2CO_3 instead of tBuOLi	73
14	*t*BuOK instead of *t*BuOLi	55
15	Under Ar protection	95
16^c	At 40 °C, 24 h	81
17^d	At 80 °C, 3 h	88
18	One-pot one-step	17

Figure 3. Optimization of the synthesis of alkylated *N*-acyl cyanamides

^{a}Standard conditions: substrate $\mathbf{S_1}$ (0.2 mmol), TMSCN (0.3 mmol), and $Cu(MeCN)_4PF_6$ (5 mol %) in 1 mL DMA were conducted for 6 h at 60°C, then 1.2 equiv of MeI and *t*BuOLi were added into reaction solution for another 2 h, unless otherwise noted.

^{b}Isolated yields were calculated.

^{c}Full conversion of $\mathbf{S_1}$ at 40°C in 24 h.

^{d}Full conversion of $\mathbf{S_1}$ at 80°C in 3 h.

Substrate scope

The reaction of 3-aryl-1,4,2-dioxazol-5-ones with TMSCN in the presence of MeI has consistently produced *N*-methyl-*N*-cyanamides (**1–12**) in excellent yields, as high as 96%. As shown in Figure 4A, aryl dioxazolones with many functional groups, including H, Me, *t*Bu, MeO, halides, NO_2, and CF_3, are compatible with our mild reaction conditions. Aliphatic dioxazolones also work, as exemplified by the successful isolation of unprotected *N*-acyl cyanamides (**13–17**) in nearly quantitative yields.

The MeI can be replaced by benzyl bromide, giving **18–45** from our one-pot two-step process. Various alkyls on C3 of the dioxazolones have worked well, giving compounds **19–23**, with the yield of **19** slightly lower (65%). Heteroatom-containing (Br, N, and O) dioxazolones have proven quite compatible, giving compounds **24–29**. A range of dioxazolone substituents are tolerated well, including linear alkyl (**30–32**), chloroalkyl **33**, cycloalkyl (**34–38**), alkenyl (**39** and **40**), and alkynyl (**41** and **42**). Products **39** and **41**, featuring terminal C=C and C≡C bonds, have been obtained in excellent yields. A similar reactivity has been observed with internal C=C, which gives **40**, **42**, and the citronellic-acid-derived **44**. The dioxazolone from an *N*-Phth-protected γ-amino-acid precursor has provided the phthalimido product **43** in nearly quantitative yield, whereas the lithocholic acid derivative **45** was obtained in 95% yield.

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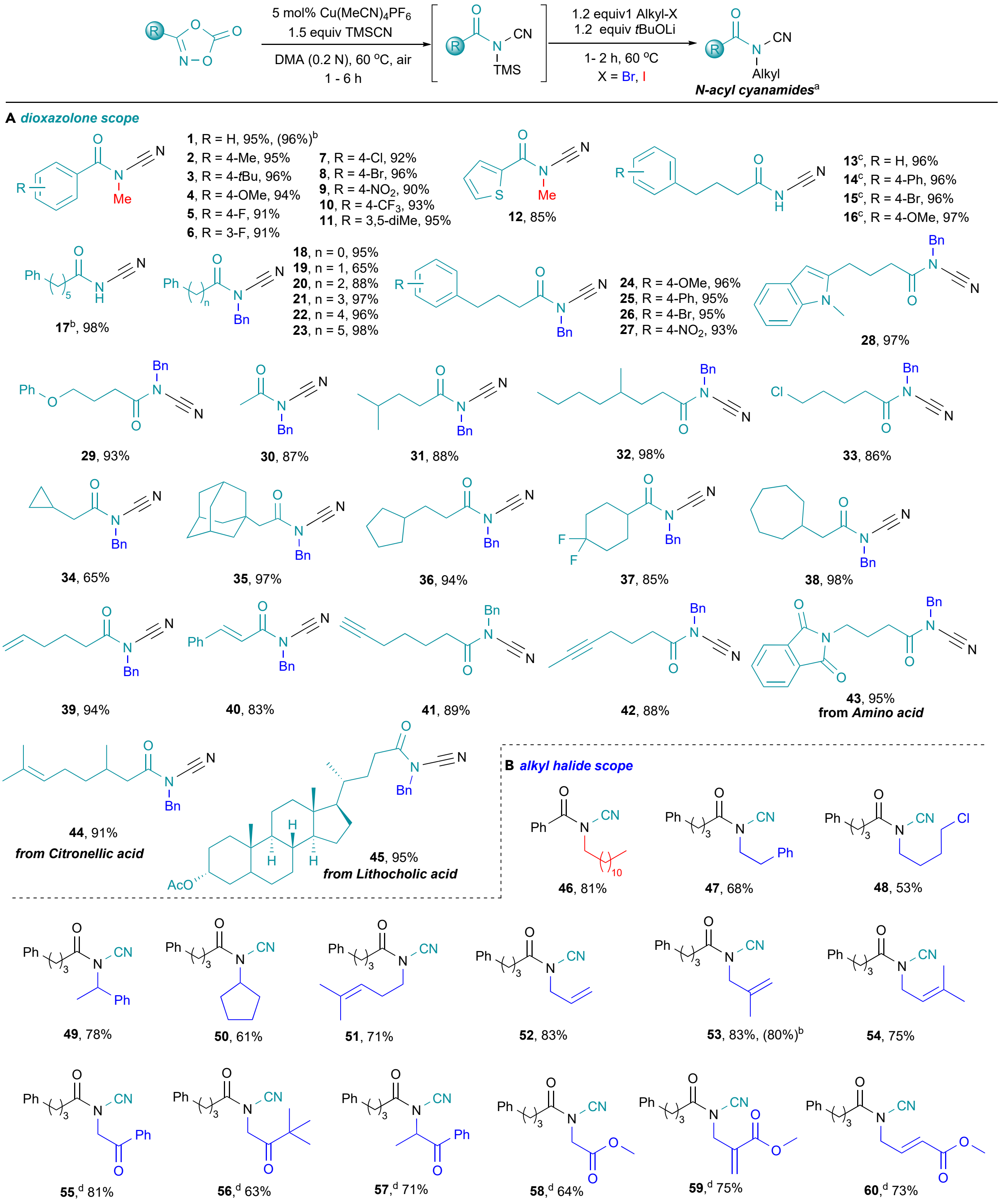

Figure 4. Substrate scope of dioxazolones and alkyl halides

[a]Reaction conditions: substrates (0.2 mmol), TMSCN (0.3 mmol), and 5 mol % $Cu(MeCN)_4PF_6$ in 1 mL DMA at 60°C for 1–6 h under air, then R^2X (1.2 equiv) and *t*BuOLi (1.2 equiv) were added for another 2 h at 60°C; isolated yields.

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Figure 4. *Continued*

[b]Large scale: substrates (10 mmol), TMSCN (11 mmol), and 5 mol % $Cu(MeCN)_4PF_6$ in 20 mL DMA at 60°C for 5 h under air, then R^2X (11 mmol) and *t*BuOLi (11 mmol) were added for another 1–2 h at 60°C; isolated yields.

[c]Substrates (0.2 mmol), TMSCN (0.3 mmol), and 5 mol % $Cu(MeCN)_4PF_6$ in 1 mL DMA at 60°C for 2 h under air, then NH_4Cl (5 mL, aqueous) was added to quench the reaction; isolated yields.

[d]Substrates (0.2 mmol), TMSCN (0.3 mmol), and 5 mol % $Cu(MeCN)_4PF_6$ in 1 mL DMA at 60°C for 2 h under air, then R^2X (1.2 equiv) and *t*BuOLi (1.2 equiv) were added for another 1–2 h at room temperature; isolated yields.

We then considered the possibility that other alkyl halides could be employed with *N*-acyl cyanamides (Figure 4B). Commercially available 1-iodododecane proved effective, providing **46** in 81% yield. Primary alkyl bromides (2-bromoethyl benzene, 1-bromo-4-chlorobutane) gave the corresponding products **47** and **48** in moderate yields. Secondary and cyclic bromides worked well, as demonstrated by the formation of **49** and **50**. Halide substrates bearing C=C bonds (5-bromo-2-methylpent-2-ene, and bromo allyls) gave **51–54** in good yields, whereas carbonyl alkyl bromides were converted into alkylated *N*-acyl cyanamides **55–60** in 64%–81% yields. Ester and acrylate substituents were tolerated (**58–60**) as well.

A similar approach gives cyanoformamide derivatives (carbamoyl cyanides) via the Curtius rearrangement. These compounds have been used in the synthesis of useful intermediates[72–76] and exist in natural products,[77,78] for example, ceratinamine. If we employ our Cu-catalyzed nitrenoid transfer reaction on the substrate **S61**, with a secondary alkyl substituent, we obtain 28% of the cyanoformamide **61′** along with the benzylated *N*-acyl cyanamide **61** (Figure 5). The **61′** has surely come from an isocyanate intermediate, the result of a Curtius rearrangement of the Cu-nitrenoid. When the R is replaced with a *t*-butyl, a 1-adamantyl, or a 1-methylcyclohexyl, only the cyanoformamides **62′–64′** are observed, as we would expect from the migratory aptitude of these tertiary substituents.[79] This strategy has been successfully applied to the preparation of pharmaceutically relevant molecules, including gemfibrozil, ibuprofen, and flurbiprofen derivatives **65′–67′**. The cyanoformamide **67′** is formed along with **67**.

Mechanism experiments

After the successful development of these transformations, we shifted our attention to learning their mechanism. First, we began by investigating the mechanism of Cu-catalyzed nitrene transfer reaction (step 1). *In situ* nuclear magnetic resonance (NMR), with DMF-d_7 as the solvent at 60°C (Figure 6A, details in supplemental information), revealed the smooth generation of two isomers, **68** and **69**, in a ratio of 2.2:1. The fact that $Cu(MeCN)_4PF_6$ catalyzes the generation of Cu-nitrenoid intermediates from dioxazolones is confirmed by the reaction (Figure 6B) of the dioxazolone **S13** with $Cu(MeCN)_4PF_6$ in the presence of 1.5 equiv of triphenylphosphine (PPh_3); plainly the $Cu(MeCN)_4PF_6$ is an active catalyst without the need for TMSCN activation. The formation of *N*-iminophosphorane **70** (Figure 6B) has been confirmed by high-resolution mass spectrometry and NMR.

We have investigated the kinetics of the reaction of $\mathbf{S_1}$ with TMSCN in the presence of the Cu catalyst (see Figures 6C and S1–S3; Tables S1–S3). The initial rate $\Delta[P]/\Delta t$ is linear in $[\mathbf{S_1}]$ (Figure 6C, left), showing the reaction is first-order in $[\mathbf{S_1}]$ with $k_1 = 1.24 \times 10^{-2}\ \text{min}^{-1}$ from $\Delta[P]/\Delta t = k_1[\mathbf{S_1}]$. A plot of k_{obs} via fitting the first-order equation vs. variable [Cu] shows the reaction to be first-order in [Cu] (Figure 6C, middle), implying a second-order rate constant k_2 of $2.95 \times 10^{-2}\ M^{-1}\ s^{-1}$ in $d[P]/dt = k_2[\mathbf{S_1}][Cu]$. To our surprise, the reaction rate $\Delta[P]/\Delta t$ decreases (Figure 6C, right) with increasing [TMSCN]. We think that the slow step involves the formation of the acyl nitrene complex from Cu(I) and substrate, that TMSCN reacts rapidly with that nitrene complex, and that TMSCN also coordinates reversibly to the $Cu(MeCN)_4PF_6$.

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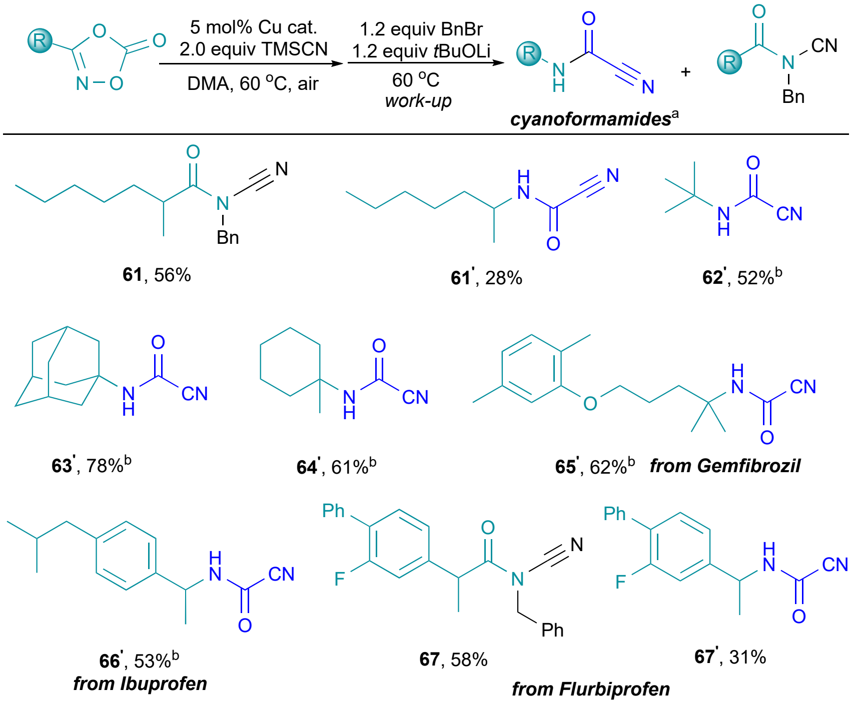

Figure 5. Synthesis of cyanoformamides

[a] Reaction conditions: substrate (0.2 mmol), TMSCN (0.3 mmol), and 5 mol % $Cu(MeCN)_4PF_6$ in 1 mL DMA at 60°C for 1–3 h under air, then RX (1.2 equiv) and *t*BuOLi (1.2 equiv) were added for another 1–2 h at 60°C. The reaction was worked up by the saturated NH_4Cl (aq); isolated yields.

[b] Reaction conditions: substrate (0.2 mmol), TMSCN (0.3 mmol), and 5 mol % $Cu(MeCN)_4PF_6$ in 1 mL DMA at 60°C for 2 h under air, then *t*BuOLi (1.2 equiv) was added for another 0.5 h at 60°C. The reaction was worked up by the saturated NH_4Cl (aq); isolated yields.

We have also examined the mechanism of the Cu-catalyzed *N*-alkylation of *N*-acyl cyanamides with alkyl halides (step 2). Control experiments have revealed that $Cu(MeCN)_4PF_6$ plays an important role in the *N*-alkylation of *N*-acyl cyanamide (Figure 7A); only an 8% yield of **21** is obtained from **13**, BnBr and *t*BuOLi after 12 h in the absence of the Cu catalyst. The addition of 5 mol % $Cu(MeCN)_4PF_6$ leads to a high yield of **21** (85%) in 1 h. The cyclopropyl-opening product **72** was observed in 11% yield from the reaction of **13-TMS** with (bromomethyl)cyclopropane (Figure 7B), suggesting a radical mechanism for the Cu-catalyzed *N*-alkylation, although (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) failed to trap any radical species (Figure 7C). The use of enantioenriched **73** gave the racemic product **21** (2% *ee*) along with recovered racemic 73 (27%) (Figure 7D), in agreement with a radical mechanism. There are also precedents[67,70] for Cu-catalyzed radical coupling.

Left circle (Cu-nitrene transfer): the first step in our reaction is presumably the decarboxylation of the dioxazolone by the copper(I) catalyst, which leads to the formation of the electrophilic Cu-nitrene I. The intermediate I can then rearrange to the isocyanate, which will add the cyanide of TMSCN and make the cyanoformamide (Figure 8). The rearrangement outcome is dependent on the α substituents of Cu-nitrene I. Alternatively, the complex I can coordinate the cyano group of TMSCN to its electrophilic nitrogen, thus generating II, which can give the *N*-acyl cyanamide via reductive elimination[40,65] (the cyanide anion may coordinate to the copper (*path b*) before it attacks the nitrogen).

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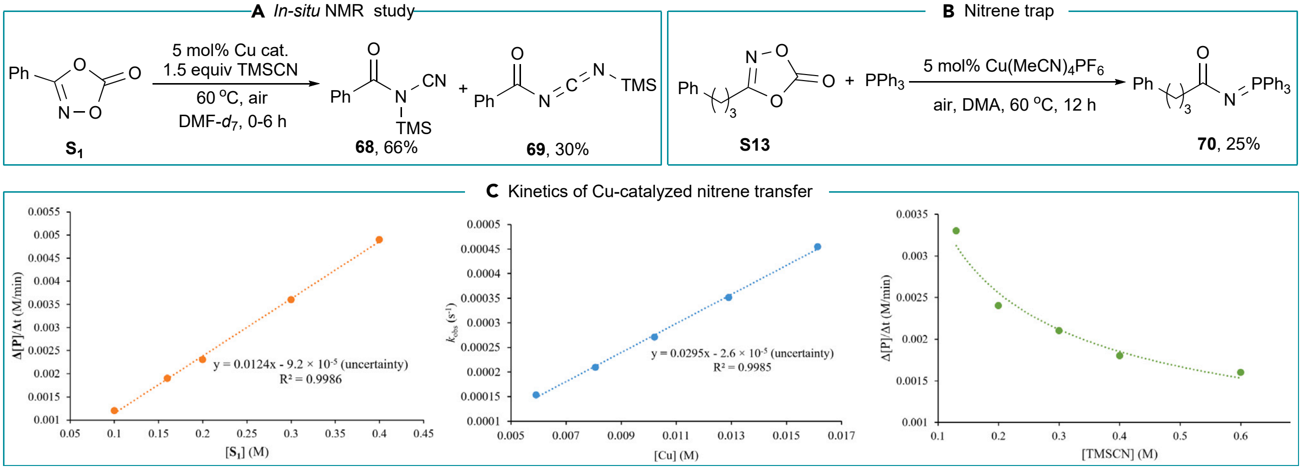

Figure 6. Mechanism experiments of Cu-catalyzed nitrene transfer (step 1)

(A) Study of *N*-acyl cyanamide isomers via *in situ* NMR.

(B) Nitrene trapping experiments.

(C) Kinetics of Cu-nitrene transfer. (Left) initial-rate fit; (middle) first-order equation fit; and (right) initial-rate fit.

Right circle (Cu-catalyzed alkylation of the cyanamide): removal of the trimethylsilyl from the *N*-acyl cyanamide by the LiO*t*Bu will permit the amide ligand to coordinate to the copper, giving **III**. Electron transfer from the copper(I) of **III** to the alkyl halide will give the Cu(II) cation **IV**, X^- and alkyl radical. The alkyl• will then add to the Cu(II) or the N of **IV**, making the alkylated *N*-acyl cyanamide and regenerating the Cu(I) catalyst.

Conclusions

We have developed a straightforward and efficient method for synthesizing alkylated *N*-acyl cyanamides through a nitrogen-umpolung strategy. The one-pot

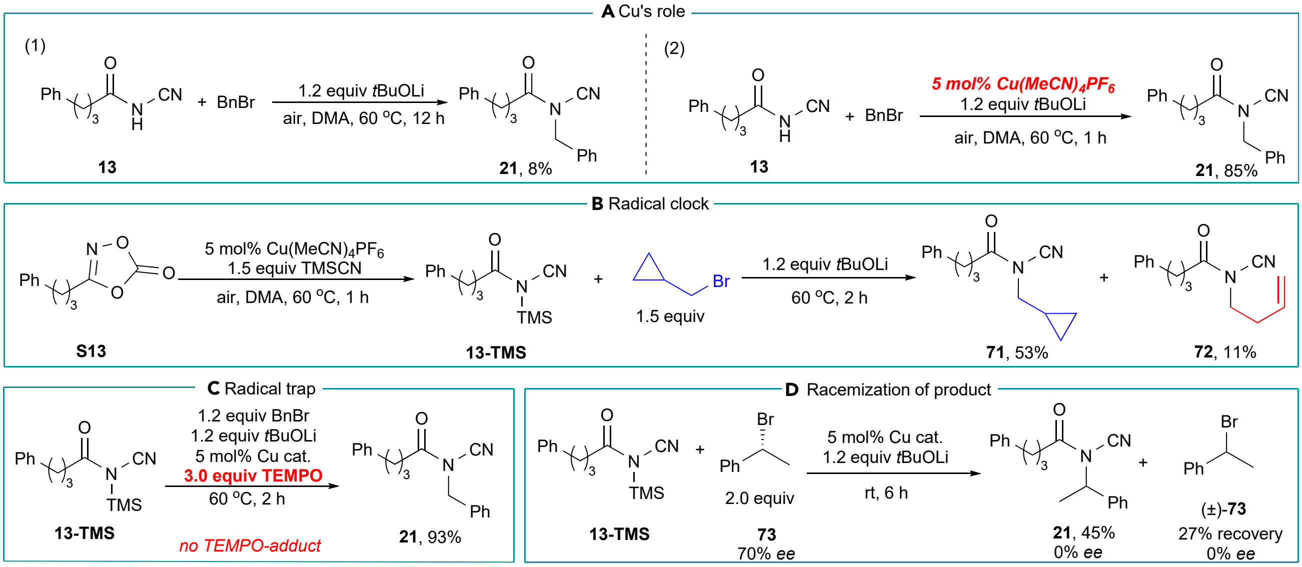

Figure 7. Mechanism experiments of Cu-catalyzed *N*-alkylation (step 2)

(A) Control experiments for the study of Cu's role.

(B) Radical clock experiment.

(C) Radical species trapping experiment.

(D) Racemization of the product **21** and (*R*)-(1-bromoethyl)benzene **73**.

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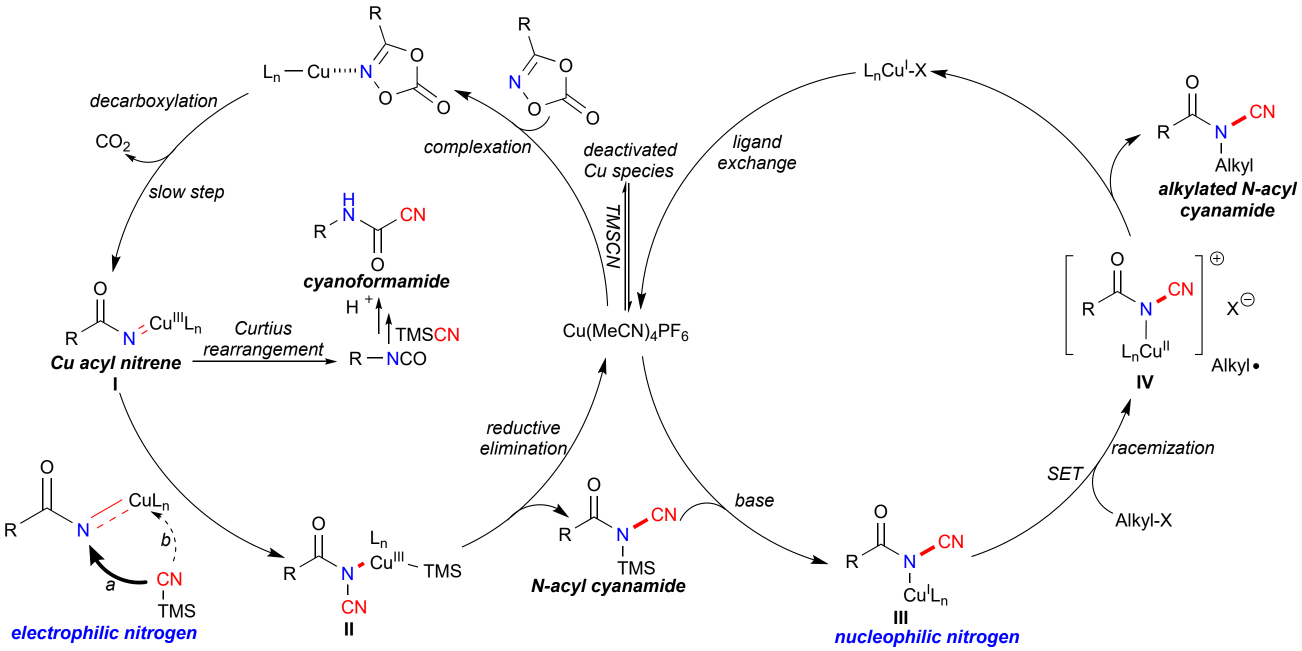

Figure 8. Proposed mechanism for the synthesis of alkylated *N*-acyl cyanamides via the combination of Cu-catalyzed nitrene transfer with Cu-catalyzed *N*-alkylation

two-step method merges a Cu-nitrenoid transfer (electrophilic nitrogen) with a Cu-catalyzed *N*-alkylation (nucleophilic nitrogen). We have also used nitrene transfer to develop a synthetic method for cyanoformamides. Our catalytic system is versatile, with broad scope and high functional-group tolerance. We suggest a proposed mechanism on the basis of nitrene trapping, kinetics experiments, radical clock, and radical racemization.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Jack R. Norton (jrn11@columbia.edu).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

This study did not generate any datasets.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.chempr.2024.04.020.

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AUTHOR CONTRIBUTIONS

J.R.N. and Y.W. conceived the project. J.R.N. directed the research. Y.W. designed, carried out, and analyzed most of the experiments of the main manuscript. H.K.Z. and J.Q. carried out some experiments and purified products. M.A.A. analyzed computational insight. J.R.N. and Y.W. composed the manuscript and the supplemental experimental procedures. All authors commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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