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Research Article

Copper Photocatalyzed Divergent Access to Organic Thio- and Isothiocyanates

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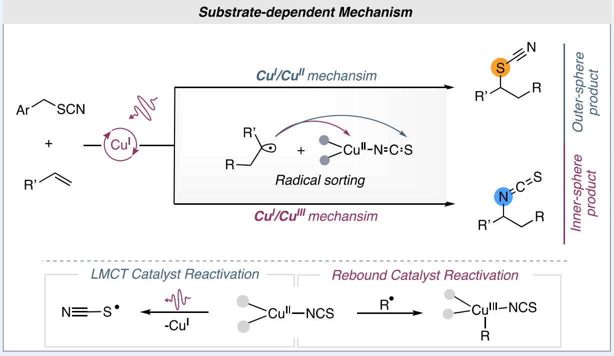
ABSTRACT: We disclose a copper-photocatalyzed strategy that enables selective access to organic thiocyanates and isothiocyanates using benzylic thiocyanates as ATRA reagents. The electronic nature of the aromatic system is a crucial factor defining the outcome of the reaction for forging either the kinetic C−S or the thermodynamic C−N bonds. Mechanistic investigations support a radical pathway initiated by a reductive C−S bond cleavage of the substrates followed by a divergent inner-/outer-sphere interaction with copper depending on the electronic density of the formed intermediates. The developed protocol proceeds with high regio- and chemoselectivity and can also be applied for late-stage functionalization of bioactive molecules. The utility of the products is highlighted by their facile conversion to several building blocks that are relevant to organic synthesis.



KEYWORDS: *copper, photocatalysis, ATRA, difunctionalization, thiocyanation*

Recent years have witnessed increasing efforts to improve the sustainability of photocatalytic approaches by using inexpensive and readily available metals (Fe, Co, Ni, Cu···) and appending atom-economical stratagems.[1−5] Within this context, the selective difunctionalization of alkenes has gained great attention. It represents a practical way to increase molecular complexity and access valuable molecules through the facile conversion of available feedstock chemicals. Atom-transfer radical additions (ATRA), pioneered by Kharasch et al.,[6,7] represent a unique way to trigger the reactivity of alkenes as it allows the difunctionalization of unsaturated moieties with high atom- and step-economy. Despite the significant progress in this area, reagents compatible with ATRA processes are mainly limited to organic halides.[4,8−10] Among the various photocatalysts that were discovered to promote ATRA processes, copper(I)-phenanthroline complexes are especially suitable given their ability to act beyond single-electron transfer (SET) reagents by engaging with substrates and thus promoting the forging of new chemical bonds with great efficiency.[8,9,11−15] Cu(I)-complexes initiate such transformations by reducing a substrate R-X, yielding a radical $R^\bullet$, which subsequently engages with an alkene (**a**). The simultaneously formed Cu(II)-complex **c** interacts with transient radical **b**, orchestrating the desired ATRA adduct **d** formation (Scheme 1a).

Nonetheless, the intricacies of the interaction between the radical entity **b** and the Cu(II)-complex **c** remain enigmatic, given the existence of three conceivable routes where **b** may either (i) rebind onto the Cu(II)-complex, traversing a Cu(III)-intermediate,[16,17] (ii) execute a SET with the Cu(II)-complex, regenerating the Cu(I)-catalyst alongside a carbocation intermediate, or (iii) abstract the counteranion through a radical-ligand transfer (RLT) mechanism[18,19] (Scheme 1b).

In pursuit of a more profound comprehension of the mechanism, we posited that the presence of an ambident nucleophile (Y = Z), with a defined coordination pattern at Cu(II), could serve as a discerning factor between inner-sphere and outer-sphere products. This differentiation is contingent upon the isomeric outcome obtained upon interaction with radical species **e** (Scheme 1c). We reasoned that the product outcome would comply with the philicity of the formed radical adding either onto the Cu(II)-center of the complex **f** or on its Z-end.[20] This dictates that electron-rich radicals, hence nucleophilic, will selectively engage with the electron-deficient Cu(II)-center, allowing the inner sphere product **g** to form, while electron-deficient radicals that tend to be electrophilic will associate with the nucleophilic Z-end of the complex leading to **h**.

Organic thiocyanates and isothiocyanates constitute important classes of molecules. They are valuable synthetic precursors that can readily interconvert into various functional

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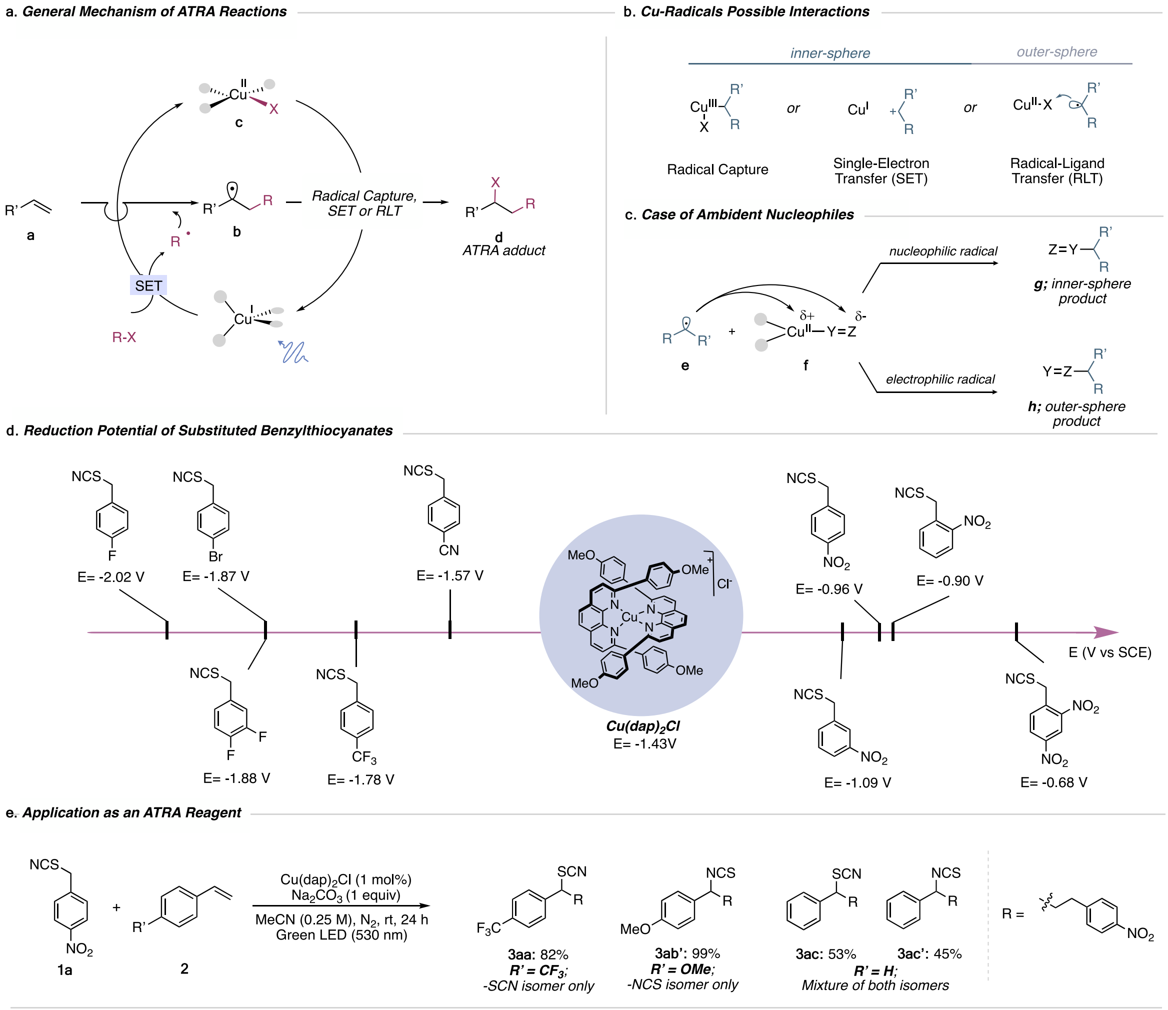
Scheme 1. (a) General Mechanism of an ATRA Reaction, (b) Potential Interactions between Cu(II) and Transient Radicals, (c) Reactivity of Cu(II) Bearing Ambident Nucleophiles with Organic Radicals, (d) Reduction Potential of Benzylthiocyanates, (e) Use of 4-Nitrobenzylthiicyanate as an ATRA Reagent with 4-Trifluoromethylstyrene (2a), 4-Methoxystyrene (2b), and Styrene (2c)



groups, such as thioureas, disulfides, and thiols.[21] Consequently, they have attracted much interest in the pharmaceutical domain and other areas.[21−24] There are many ways to incorporate thiocyanate moieties into molecules, such as nucleophilic addition/substitutions or addition of thiocyanate radicals to alkenes, alkynes, or aromatic systems, representing the main routes.[24−30]

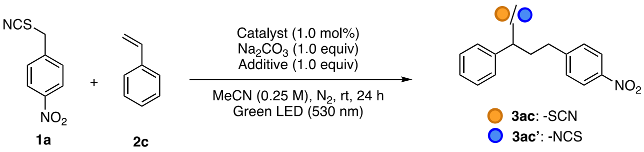
Based on Houmam's report on the selective cleavage of benzylic thiocyanates,[31] we envisioned that benzylthiocyanates can be amenable to current photocatalytic ATRA approaches due to their accessible reduction potentials and their ability to release the ambident thiocyanate anion. We, therefore, set out to investigate benzyl thiocyanates as a new class of ATRA reagents for the benzylthiocyanation of olefins using the unique features that copper photocatalysts offer.

Having determined the reduction potential of a series of benzyl thiocyanates (Scheme 1d), we settled on 4-nitrobenzyl thiocyanate (**1a**) as a model substrate being in the right range (E_{red} (**1a**) = −0.96 V vs SCE) for reduction by many reported copper-based photocatalysts. We began our investigations with the exposure of 4-nitrobenzene thiocyanate (**1a**), olefin (**2**), and Na_2CO_3 in the presence of catalytic amounts of $Cu(dap)_2Cl$ (dap = 2,9-bis(4-methoxyphenyl)-1,10-phenanthroline) to green LED irradiations. Indeed, reacting 4-substituted-styrene with a strong electron-withdrawing group, such as the trifluoromethyl moiety, led exclusively to the thiocyanate **3aa** while using a strong e-donor such as the methoxy group, selectively afforded the isothiocyanate **3ab′** in quantitative yield (Scheme 1e). However, subjecting the electron-neutral styrene (**2c**) to the aforementioned conditions delivered both thiocyanate **3ac** and isothiocyanate **3ac′** products with a 1.2:1 ratio.

We hypothesized that the low chemoselectivity for **3ac**/**3ac′** is due to the involvement of multiple mechanistic pathways (cf. Scheme 1a−c).[32,33] Thus, we questioned whether a thiocyanate source's presence can help drive the reaction's outcome toward a selective formation of one isomer over the other. Indeed, incorporating a stochiometric amount (for optimization details, see the SI) of sodium thiocyanate (entry 2) or related thiocyanates permitted access to thiocyanate **3ac** with much improved chemoselectivity. Alternatively, the Cu(II)-complex $Cu(dap)Cl_2$ (entry 3) that has been shown to form in situ Cu(I) by Cu−Cl homolysis[34] or $Cu(dmp)_2Cl$ (dmp = 2,9-dimethyl-1,10-phenanthroline, entry 4) as a more economical alternative[35] gave good, albeit somewhat inferior results. Changing to catalysts that operate through outer-sphere photoredox such as the more reducing Ir(ppy)$_3$ ($E_{1/2}$ = −1.73 V vs SCE) or the less reducing Ru(bpy)$_3$Cl$_2$ ($E_{1/2}$ = −0.81 V vs SCE) diminished the selectivity but also the overall yield (entries 5 and 6). The absence of base (Na_2CO_3) strongly negatively impacted the efficiency even when the reaction time was prolonged to 48 h, highlighting its role in protecting the copper catalyst from poisoning[8] (entry 7). Sodium thiocyanate can assume such a protective role, as reflected by a good overall yield with a high −SCN selectivity when this additive is employed, but Na_2CO_3 is omitted (entry 8). Attempting to promote the reaction using AIBN under thermal conditions resulted in a complete shutdown, suggesting that a radical chain pathway for this transformation is not probable (entry 9). Control experiments revealed that the copper catalyst and the light source are necessary components (entries 10 and 11).

With the optimized conditions in hand (Table 1, entry 2), we evaluated the scope of the transformation (Scheme 2).

Table 1. Optimization of the Reaction's Conditions[h]



Entry	Catalyst	Additive (equiv)	3ac[a] (%)	3ac'[a] (%)
1	Cu(dap)$_2$Cl	—	53	45
2	Cu(dap)$_2$Cl	NaSCN (1.0 equiv)	93	7
3	Cu(dap)Cl$_2$	NaSCN (1.0 equiv)	84	16
4[b]	Cu(dmp)$_2$Cl	NaSCN (1.0 equiv)	81	6
5[b]	Ir(ppy)$_3$	NaSCN (1.0 equiv)	56	12
6[b]	Ru(bpy)$_3$Cl$_2$	NaSCN (1.0 equiv)	26	6
7[c]	Cu(dap)$_2$Cl	—	10 (40)[d]	11 (40)[d]
8[e]	Cu(dap)$_2$Cl	NaSCN (1.0 equiv)	70	12
9[f]	AIBN	NaSCN (1.0 equiv)	n.r.	n.r.
10	—	NaSCN (1.0 equiv)	n.r.	n.r.
11[g]	Cu(dap)$_2$Cl	NaSCN (1.0 equiv)	n.r.	n.r.

[a] Yields determined by ^{1}H NMR using tetrachloroethane as an internal standard. [b] Irradiated by a 455 nm blue LED. [c] In the absence of Na_2CO_3. [d] After 48 h. [e] In the absence of Na_2CO_3. [f] Reaction performed at 80 °C. [g] In the absence of the light source. n.r.: no reaction. [h] Standard conditions: 4-nitrobenzylthiocyanate (**1a**, 0.25 mmol, 1.0 equiv), styrene (**2c**, 0.5 mmol, 2.0 equiv), Cu(dap)$_2$Cl (2.5 μmol, 1.0 mol %), sodium carbonate (0.25 mmol, 1.0 equiv), in MeCN (anh., degassed, 1.0 mL, 0.25 M) for 24 h under a N_2 atmosphere at room temperature.

Styrenes with weak electron-withdrawing or electron-donating substituents generally gave the products with a marked preference for the thiocyanates (**3ac**−**3ap**). Good functional group tolerance was observed, i.e., alkyl, halide, naphthyl, trimethylsilyl, and certain oxygen-based substituents in the arene moiety. The use of styrenes with much stronger electron-withdrawing groups, such as trifluoromethyl-, nitro-, or pentafluorostyrene, selectively afforded the thiocyanates (**3aa, 3aq**−**3as**) with no observable isothiocyanate isomer. In contrast, styrenes with a strong electron-donating alkoxy group resulted in a complete reversal of selectivity, furnishing exclusively the isothiocyanate products **3ab′** and **3at′**. This selectivity trend was also observed when α-methylstyrene and 2,3-dimethylbutadiene were employed, leading solely to the isothiocyanates **3au′** and **3av′**.

The thiocyanation protocol could also be demonstrated for the late-stage functionalization of some biologically active molecules. Subjecting theophylline- and vitamin E-derived substrates to the optimal conditions delivered the corresponding ATRA adducts (**3aw, 3ax**) with good yields. Nevertheless, the protocol was inefficient toward nonactivated olefins, Michael acceptors, and alkynes, reflecting the electrophilic character of the presumably formed 4-nitrobenzyl radical.[20] Trying to incorporate other benzyl thiocyanates was only successful in the case of 2-nitrobenzyl thiocyanate (**3bc**/**3bc′**), while other moieties such as *p*-cyanobenzylthiocyanate gave only trace amounts of product due to the higher reduction barrier (E_{red} = −1.57 V vs SCE) being out of reach for the copper photocatalysts employed (see SI). The observed chemoselectivity difference when using **1b** compared to **1a** may be attributed to the involvement of the nitro moiety in an inner-sphere chelation mechanism with copper (*vide infra*).

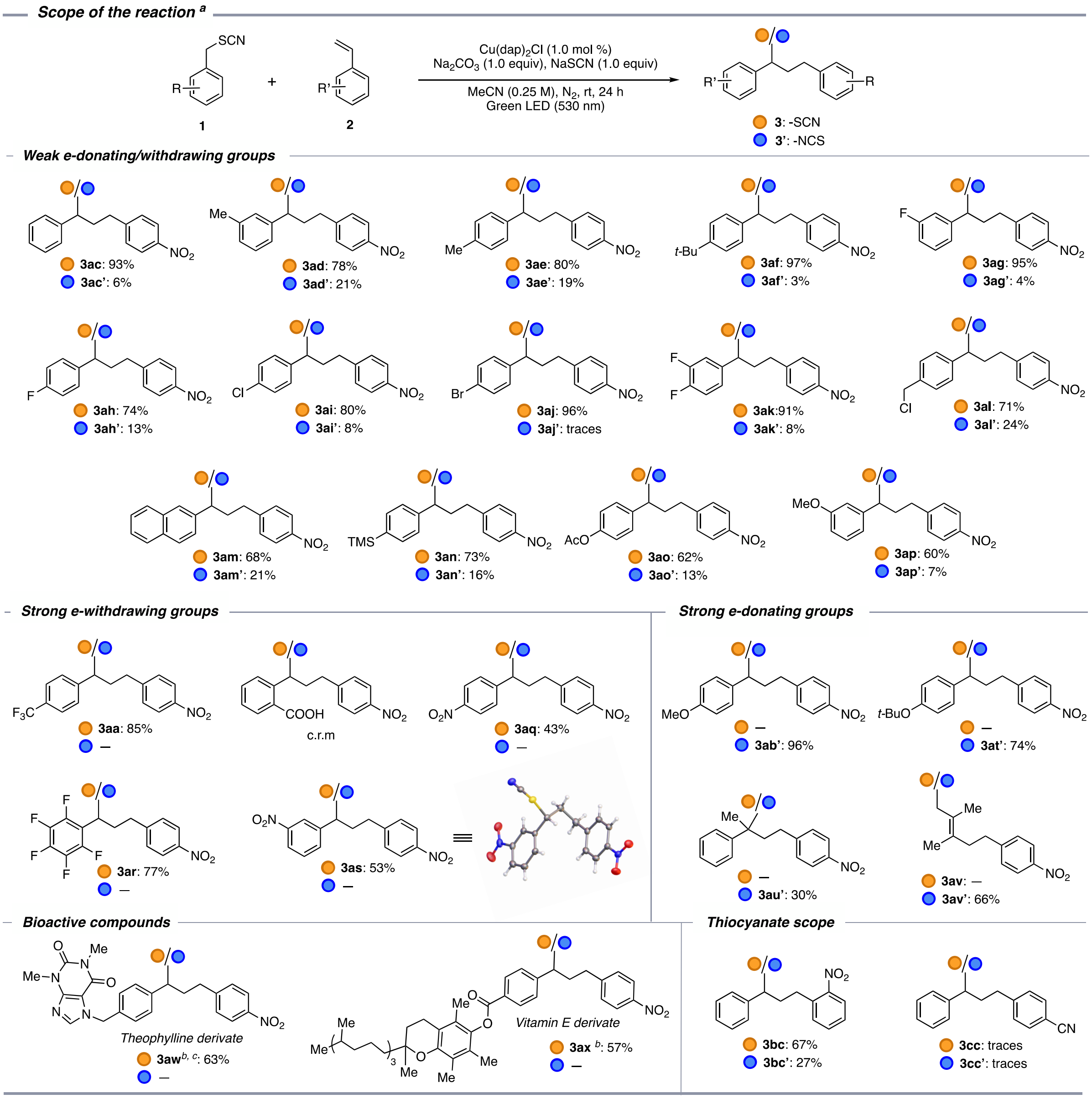
The chemoselectivity of the title transformation was assessed by incorporating competitive C−C unsaturated motifs within the same substrate. When both vinyl and ethynyl moieties were present, the vinyl group was selectively functionalized, affording the products **3ay** and **3ay′**. Furthermore, the simultaneous presence of the vinyl and allyl groups gave rise to **3az** with the allyl moiety remaining intact (Scheme 3).

To broaden the scope of this ATRA reaction, we sought to develop a protocol to access isothiocyanates in a subsequent reaction selectively. Given the presence of benzyl isothiocyanates in bioactive molecules and their importance as synthetic intermediates,[21,36−39] we targeted the design of a one-pot procedure encompassing sequential ATRA followed by a zinc-mediated isomerization.[40] Gratifyingly, zinc chloride was proven to be an efficient isomerization mediator, promoting one-pot access to isothiocyanates with good overall yields (Scheme 4a). Expanding this one-pot protocol by adding secondary amines gave direct access to thioureas **4a**−**4c**, representing common structural motifs with high relevance in many domains[41,42] (Scheme 4b).

In addition, thiocyanates **3** provide a robust synthetic platform to access different functionalities (Scheme 4c). For instance, the thiol **5a** was obtained by treatment of **3ac** with phosphorus pentasulfide, while the reduction of **3ac** using $NaBH_4$ delivered the disulfide **5b** through the corresponding S-CN cleavage followed by S−S homocoupling. Furthermore, trifluoromethylthioether **5c**, an attractive building block in medicinal chemistry due to its typical lipophilicity,[43,44] could be obtained by exposing **3ac** to trifluoromethyltrimethylsilane in the presence of cesium carbonate. Notably, upon the reduction of the nitro group in **3ac** with zinc the thiocyanate moiety is removed, yielding the aniline derivate **5d** in 72% yield. Thus, the thiocyanate can serve as a traceless directing group, allowing overall formal hydrobenzylation of styrenes.

Several experiments were carried out to gain deeper insights into the mechanism of this reaction. Upon addition of a stoichiometric amount of the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) to a reaction mixture of **1a** and **2c**, a complete shut-down of the benzylthiocyanation was observed. Instead, TEMPO adduct **6** was isolated, confirming the generation of the 4-nitrobenzyl radical upon the reductive cleavage of **1a** (Scheme 5a). In line with this, employing a radical clock reagent 7 under the standard conditions exclusively led to forming **8** through radical-initiated ring opening followed by a subsequent thiocyanation (Scheme 5b). In order to gain a deeper understanding of the

Scheme 2. Scope of the Reaction (Isolated Yields)[a]



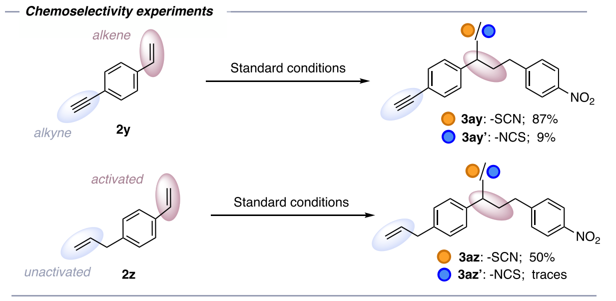
[a][a]Reaction conditions: benzylthiocyanate (**1**) (0.5 mmol, 1.0 equiv), olefin (**2**) (1.0 mmol, 2.0 equiv), Cu(dap)$_2$Cl (5.0 mmol, 1.0 mol %), sodium carbonate (0.5 mmol, 1.0 equiv), and sodium thiocyanate (0.5 mmol, 1.0 equiv) were irradiated by a 530 nm green LED in MeCN (anhydrous, degassed, 2.0 mL, 0.25 M) for 24 h under a N$_2$ atmosphere at room temperature. [b]DCM was used instead of MeCN. [c]Reaction conducted with a concentration of 0.125 M. [d]c.r.m = complex reation misture, "-" = not observed.

formation of the -SCN/-NCS isomers, we followed the evolution of **3ac** and **3ac′** over time, revealing their steady, independent development in the presence and absence of sodium thiocyanate as an additive (see SI). Furthermore, exposing either **3ac** or **3ac′** to the reaction conditions disproved a potential photomediated isomerization (Scheme 5c).[28]

To probe the role of Cu(II) for the thiocyanate delivery to the products, attempts to obtain a crystal structure of a Cu(II)(dap)-thiocyanate complex failed, but we were successful with the structurally more simple "dmp" ligand which confirmed that Cu(II) coordinates to the N-end of the thiocyanate anion (Scheme 6a) in line with literature precedent.[45−49] The decrease in the fluorescence intensity of the excited-state Cu(dap)$_2$Cl* in the presence of **1a** proved its interaction with the copper catalyst (Scheme 6b). Reacting Cu(dap)$_2$Cl with **1a** under green LED irradiation at room temperature resulted in the formation of the C−C coupled dimer **9** derived from the corresponding benzylic radicals along with a precipitate (green fine powder), which was identified as Cu(dap)(NCS)$_2$ (Scheme 6c, black spectra), and was confirmed by its independent synthesis (Scheme 6c, red spectra). It is to be noted, however, that Cu(dap)(NCS)$_2$ is the predominant, but not the sole, paramagnetic species after 24 h of irradiation.

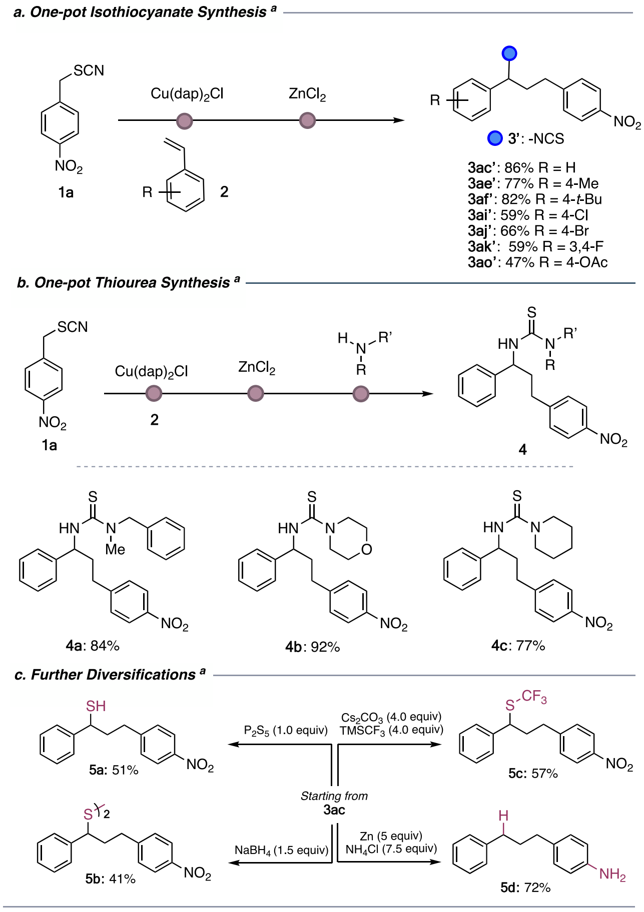
On the other hand, mixing **1a** with Cu(dmp)$_2$Cl led to no reaction at room temperature in the dark, as confirmed by ^{1}H NMR spectroscopy. However, when this mixture was subjected to blue light irradiation, the reddish solution turned orange, accompanied by the formation of an orange precipitate, which

Scheme 3. Chemoselectivity Experiments (Isolated Yields)[a]



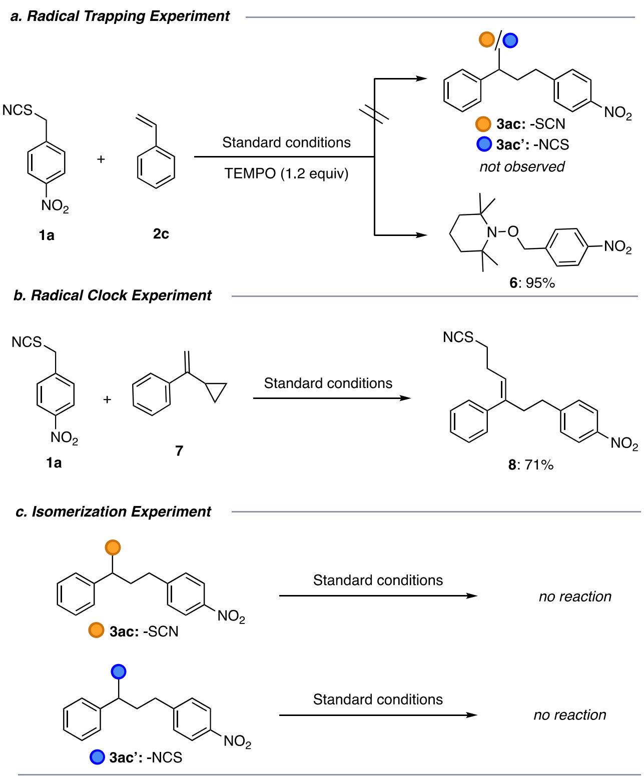
[a] Reaction conditions: 4-nitrobenzylthiocyanate (**1a**) (0.5 mmol, 1.0 equiv), olefin (**2**) (1.0 mmol, 2.0 equiv), Cu(dap)$_2$Cl (5.0 μmol, 1.0 mol %), sodium carbonate (0.5 mmol, 1.0 equiv), and sodium thiocyanate (0.5 mmol, 1.0 equiv) were irradiated by a 530 nm green LED in MeCN (anh., degassed, 2.0 mL, 0.25 M) for 24 h under a N$_2$ atmosphere.

Scheme 4. Thiocyanate Diversification: (a) Access to Isothiocyanates, (b) Access to Thioureas, (c) Further Diversifications[a]



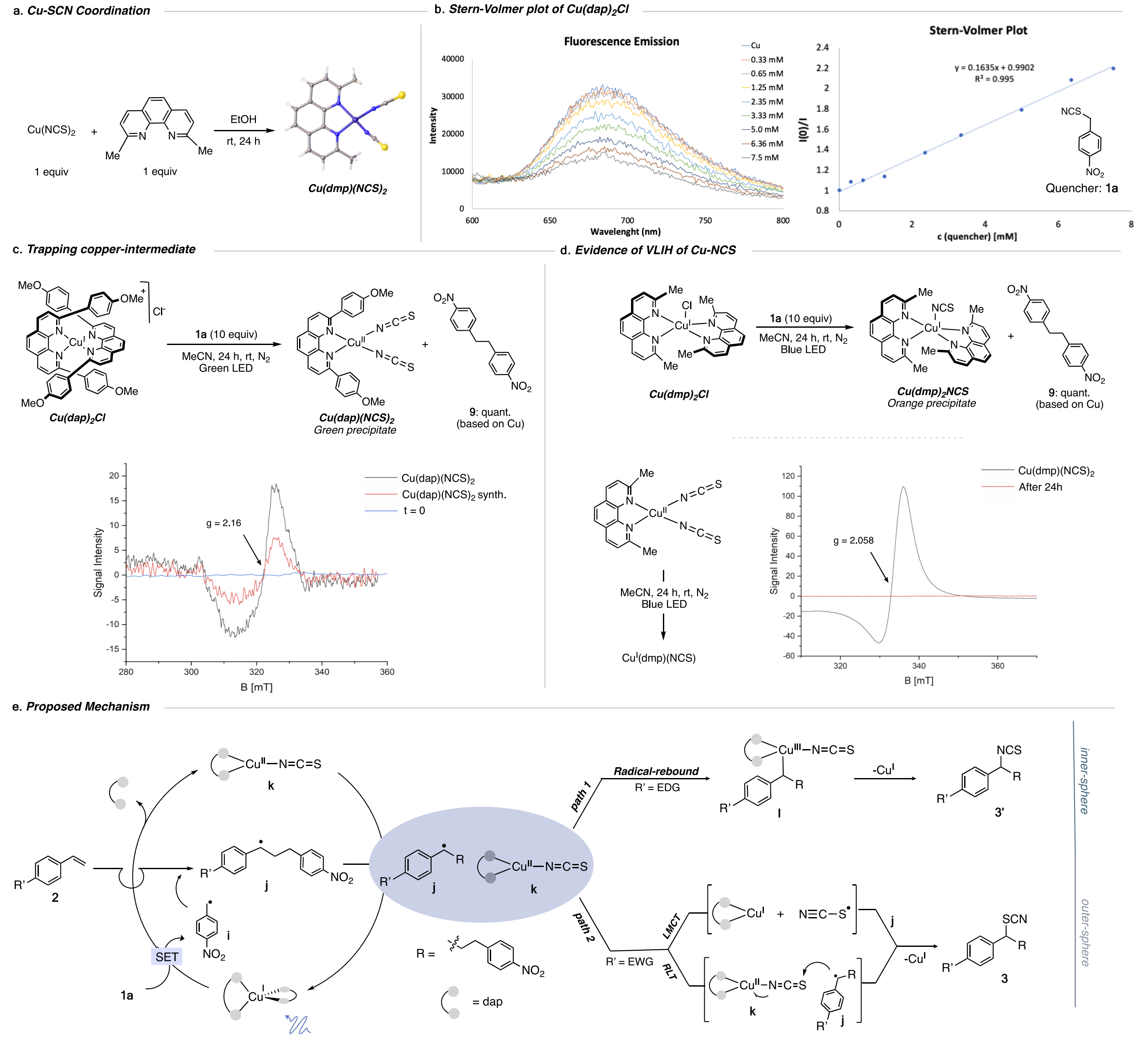
[a] Isolated yields.

Scheme 5. Mechanistic Investigations, (a) Radical Trapping Experiment, (b) Radical Clock Experiment, (c) Isomerization Experiments Starting from 3ac and 3ac′



was identified as Cu(dmp)$_2$NCS. Surprisingly, we could not detect any Cu(II)-species using EPR spectroscopy. To understand the obtention of Cu(dmp)$_2$NCS, we have attempted to probe a potential visible-light induced homolysis (VLIH) mechanism as we assumed that a Cu(II)-complex is transiently formed.[50] The irradiation of a solution of Cu(dmp)(NCS)$_2$ for 24 h led to the loss of the paramagnetic signal in the EPR spectra suggesting the formal reduction to Cu(I)-species through a ligand-to-metal charge transfer (LMCT) process accompanied by a release of a thiocyanate radical (Scheme 6d). The reactivity of the thiocyanate radical in the photoreduction reaction was not further examined. Notably, during our optimization studies, we observed 1,2-dithiocyanated styrene as a side-product. The formation of the latter can only be initiated through a [SCN]$^\bullet$ addition to the styrene (see SI).[51,52] However, unlike Cu(dmp)(NCS)$_2$, the poor solubility of Cu(dap)(NCS)$_2$ and rapid precipitation prevent its photoreduction to Cu(dap)NCS. This finding can serve as a rationale for the chemoselectivity improvement upon exogenous thiocyanate addition. We assume that the addition of the thiocyanate salt helps to drive the reaction toward a greater −SCN selectivity through a higher concentration of Cu(II)-NCS species and thus increasing the rate of the [SCN]$^\bullet$ formation (Scheme 6e, path 2, LMCT), especially since the copper speciation has been reported to have a strong influence on the VLIH quantum yields.[53]

Based on the mechanistic evidence, the pathway of the reaction is initiated by the formation of 4-nitrobenzyl radical **i** and Cu(II)-NCS species **k**, obtained from the reductive cleavage of **1a** by the photoexcited copper catalyst (Scheme 6e). The radical **i** adds to the olefin **2**, forming transient benzylic radical **j** interacting with **k**. The interaction between these depends on the philicity of C-centered radical **j**. In the case of a strong electron-donating substituent, where only the isothiocyanate isomer is observed (path 1), the −NCS moiety is transferred via an inner-sphere radical rebound mechanism initiated by a radical capture generating transient Cu(III)-complex **l** that forges the C−N bond in **3′** through a reductive elimination. On the other hand, electron-deficient radicals, Scheme 6. (a) Coordination Mode between Cu(II) and Thiocyanate Anions, (b) Fluorescene Quenching and Stem−Volmer Plot, (c) Intermediate Cu-NCS Species, (d) VLIH of Cu-NCS Bonds, and (e) Proposed Mechanism

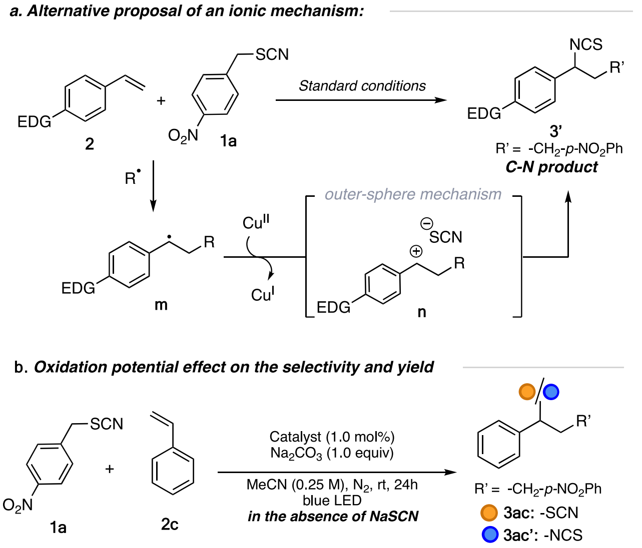


where only S-end compounds **3** are formed, react in an outer-sphere fashion via two probable mechanisms (path 2) in which **j** can either (i) perform a radical-coupling with the S-centered thiocyanate radical[54,55] [SCN]• issued from a LMCT in the Cu(II)-NCS bond,[50] comparably to the report by Stahl et al.[56] or (ii) abstract the −SCN ligand from the nucleophilic S-end[57] of **k** via an RLT mechanism.[58]

The path in which Cu(I) is regenerated through a SET is unlikely since the oxidation of the radical **m** would form the correspondent cation **n** that is relatively soft and is expected, following the HSAB theory, to lead to the C−S product instead of **3′** (Scheme 7a).[29,40,59,60] To further probe the possibility of a redox-cycle, we investigated the influence of the catalyst's oxidation potential for the chemoselectivity outcome of the reaction. Since Cu(II)-species are weaker oxidants than other commonly used photoredox catalysts, we expected that implementing catalysts able to convert the radical **m** to **n** would display a distinct selectivity toward the obtention of one major isomer. Reacting **1a** and **2c** in the absence of an exogenous thiocyanate source with a variety of catalysts with different oxidation potentials was less efficient (lower yields) in the case of outer-sphere photoredox catalysts (entries 2, 3, and 4, Scheme 7b) highlighting that an ionic mechanism is not optimal. Moreover, the **3ac**/**3ac′** ratio could be correlated with the increase of the catalysts' oxidation potential, suggesting that the passage through cationic intermediates favors the C−S product.

In summary, we have developed a copper-photocatalyzed benzylthiocyanation strategy using substituted benzylthiocyanates as novel ATRA reagents. This protocol permits access to thiocyanate and isothiocyanate derivatives in a highly chemo- and regioselective manner. The transformation was substrate dependent, and the selective delivery of the −SCN and −NCS isomers depending on the electronic properties of the substituted olefins. Mechanistic studies suggested that the reaction proceeds through distinct mechanistic pathways

Scheme 7. (a) Benzylic Isothiocyanation Following an Ionic Mechanism; (b) Correlation between the Catalysts' Oxidation Potential and the −SCN/−NCS Ratio



Entry	Catalyst	3ac[a]	3ac'[a]	Ratio
1	$Cu(dap)_2Cl$	53%	45%	1.17
2	$Ir(ppy)_3$	16%	12%	1.33
3	$Ru(bpy)_3Cl_2$	42%	8%	5.25
4	$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$	18%	5%	3.6

[a] yield determined by ^{1}H-NMR using tetrachloroethane as an internal standard

$Cu(dap)_2Cl$	$Ir(ppy)_3$	$Ru(bpy)_3Cl_2$	$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$
Cu(I)*/Cu(II) = -1.43 V	Ir(III)*/Ir(IV) = -1.73 V	Ru(II)*/Ru(III) = -0.81 V	Ir(III)*/Ir(IV) = -0.89 V
Cu(II)/Cu(I) = 0.61 V	***Ir(IV)/Ir(III) = 0.77 V***	***Ru(III)/Ru(II) = 1.29 V***	***Ir(IV)/Ir(III) = 1.69 V***

depending on the type of substrates. The incorporated thiocyanate and isothiocyanate functionalities were shown to be easily converted to various moieties of interest in the synthetic and pharmaceutical fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c00565.

Research details, experimental procedures, full characterization of products, and NMR spectra (PDF)
X-ray crystallographic data of 3-NO_2-product_3as (CIF)
X-ray crystallographic data of $Cu(dmp)(NCS)_2$ (CIF)
X-ray crystallographic data of $Cu(dap)_2[Cu_2(NCS)_3]$ (CIF)

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Notes

The authors declare no competing financial interest.

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