

Photoredox/Copper Catalyzed Enantioselective Synthesis of Chiral β -Difluoroalkyl Nitriles Involving CF_3 Group Activation

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Abstract

Chiral β -difluoroalkylated nitriles are valuable fluorinated building blocks in medicinal chemistry. Their catalytic asymmetric synthesis, however, remains challenging because it requires stereochemical control over highly reactive, conformationally flexible radical intermediates while maintaining compatibility with C–F bond activation. Current asymmetric methods rely on costly, preactivated difluoroalkyl precursors. Here we report the first asymmetric defluorinative cyanodifluoroalkylation of alkenes using readily available aryl trifluoromethyl (ArCF_3) compounds as direct CF_2 surrogates and TMSCN as the cyanide source, enabled by dual photoredox/copper catalysis. Visible-light excitation of a reducing photocatalyst, assisted by a chiral copper complex, promotes single-electron reduction of the inert C–F bond of ArCF_3 to generate a difluorobenzyl radical, which adds to an alkene and is intercepted by a chiral Cu–CN species to enantioselectively forge the C–CN bond. This protocol accommodates diverse styrenes and trifluoromethylarenes, delivering chiral nitriles in high yields with excellent enantioselectivities (up to 99% ee), and enables late-stage modification of bioactive scaffolds and access to difluorinated analogue of chiral amine antiarrhythmic agent.

Introduction

The incorporation of fluorinated groups has become a cornerstone of modern drug discovery, as it finely modulates physicochemical properties, metabolic stability, and bioavailability.^{1–3} Among these motifs, the difluoromethylene (CF_2) unit is a particularly versatile bioisostere, which is capable of replacing carbonyl, methylene, ether, thioether, and sulfone functionalities while retaining or improving biological performance (Fig. 1A).^{4–7} This is well illustrated by UT-B inhibitors, where the benzylic CH_2 to CF_2 replacement reduced metabolism over 94% to only 4% in vitro, while preserving inhibitory activity.⁴ Chiral molecules bearing a CF_2 unit adjacent to a stereocenter are especially valuable, as the interplay between fluorine's electronic effects and three-dimensional chirality can offer new opportunities for fine-tuning molecular recognition and biological activity. Nitriles represent another privileged functional group, valued not only for their presence in drugs and agrochemicals but also as versatile precursors to carboxylic acids, amides, amines, and nitrogen heterocycles (Fig. 1B).^{8–10} Since many bioactive scaffolds contain sites amenable to CF_2 substitution (Fig. 1A, right), integrating a CF_2 unit with a nitrile group into a single chiral scaffold would yield especially versatile fluorinated building blocks, motivating the pursuit of enantioselective routes to chiral β -difluoroalkylated nitriles.

Transition-metal-catalyzed asymmetric cyano functionalization of alkenes is a reliable strategy for preparing enantio-enriched β -substituted nitriles.^{11–16} Particularly, copper-catalyzed radical relay processes enables the trap of carbon radical with chiral Cu–CN complexes.^{13–16} Liu and co-workers pioneered this approach using Togni's reagent for trifluoromethylcyanation of vinylarenes, and subsequent studies extended it to polyfluoroalkyl iodides and iododifluoroacyl ketones (Fig. 1B, left).^{17–21} More recently, Zhang's group developed a nickel-catalyzed umpolung strategy for the difluoroalkylation of imine-derived 2-azaallyl anions with difluoroalkyl halides, providing racemic access to β -

difluoroalkylated amines.²² Despite these advances, existing methods generally rely on preactivated fluoroalkylated precursors. These reagents can be costly, require additional preparation, and limit the structural diversity of accessible CF₂-containing products. To address this gap, we wonder if a direct asymmetric synthesis of chiral β -aryl-difluoromethylated nitriles could be realized from simple and readily available feedstocks.

Aryl trifluoromethyl compounds represent an especially attractive solution to this problem (Fig. 1B, right). These reagents are abundant, bench-stable, inexpensive, and require no prior functionalization, making them ideally suited for late-stage diversification of complex molecules.^{23–26} Selective cleavage of a single C–F bond within the CF₃ group would directly unmask an ArCF₂ radical fragment, offering a straightforward entry to gem-difluoromethylene containing building blocks. However, the strength of the C(sp³)–F bond (BDE $\approx$ 119 kcal/mol) renders its selective activation within ArCF₃ systems a persistent challenge.²⁷ Recent advances in photoredox catalysis have opened new avenues for C–F bond activation.^{28–31} Photoexcited catalysts can generate reactive radical intermediates capable of selectively removing one or more fluorine atoms from CF₃ groups.^{32–42} Nevertheless, applying ArCF₃ motifs to asymmetric cyanodifluoroalkylation remains unexplored and poses several challenges, including activation of strong C(sp³)–F bonds, suppression of unproductive radical pathways,^{29,43} compatibility between photoredox and copper catalysis, and enantiocontrol in radical C–CN bond formation.

Based on our sustained research interest in defluoro-functionalization,⁴⁴ we herein disclose the first asymmetric cascade three-component defluorinative cyanodifluoroalkylation of alkenes with aryl trifluoromethyl compounds and TMSCN enabled by dual photoredox and copper catalysis (Fig. 1C). This method provides direct access to chiral β -aryl-difluoromethylated nitriles from ArCF₃ feedstocks under mild conditions. The reaction shows broad substrate scope, good functional group tolerance, and excellent enantioselectivity, and can be applied to the late-stage modification of complex molecules. Moreover, the nitrile products are readily diversified into a range of enantioenriched CF₂-containing derivatives, underscoring the value of this strategy for the synthesis of chiral fluorinated molecules relevant to medicinal chemistry.

Results and Discussion

Reaction conditions screening. We selected the three-component reaction of 4-phenylstyrene (**1a**), 1,3-bis(trifluoromethyl)benzene (**2a**), and TMSCN (**3**) to evaluate whether single C–F bond activation could be coupled with catalyst-controlled asymmetric radical cyanation. Using PTH-1 as the photocatalyst, Cu(MeCN)₄PF₆ as the copper source, and chiral bisoxazoline ligand **L1** in DMF under 410 nm irradiation afforded **4a** in 52% yield with 92% ee (Table 1, entry 1), and its (*R*)-configuration was confirmed by X-ray single crystallography (Figure S10). Ligand evaluation revealed that enantio-induction was highly sensitive to the architecture of the chiral copper complex. Bisoxazoline ligand **L1** provided the optimal balance of reactivity and stereocontrol, whereas increasing the linker-ring size reduced both yield and ee (Table 1, left). Structurally distinct oxazoline and bisphosphine ligands afforded little or no enantio-

induction. This pronounced ligand dependence indicates that the chiral copper catalyst does not merely serve as a cyanide carrier but creates the organized asymmetric environment required for facially selective interception of the benzylic radical. The simultaneous changes in reaction efficiency and enantioselectivity further suggest that ligand structure influences both copper reactivity and the stereochemistry-determining C–CN bond-forming sequence. With **L1** fixed, Cu(MeCN)₄PF₆ proved superior to the other copper salts examined, including CuCN, CuOAc, CuBr, CuTc, and Cu(MeCN)₄BF₄ (Table S2), illustrating that the copper precursor and its coordination environment also affect productive radical cyanation. Photocatalyst screening showed that *fac*-Ir(ppy)₃ and 4-CzIPN led predominantly to [2 + 2] photodimerization of **1a**, whereas PTH-1 favored the desired three-component coupling. Thus, high enantioselectivity alone is insufficient. Productive asymmetric catalysis requires kinetic compatibility among radical generation, alkene addition, and capture by the chiral copper–cyanide species. Changing the solvent to MeCN/DMF (3:1, v/v) increased the yield to 73% without compromising the 92% ee. Only trace hydrocyanation (< 5%) was detected. Under the optimized conditions, **4a** was obtained in 73% isolated yield with 92% ee. Control experiments established that copper, **L1**, light, and PTH-1 were all indispensable. In the absence of **L1**, the yield and enantiocontrol were substantially diminished.

Table 1 Reaction conditions optimization.^a

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Screening of ligands ^a		Screening of conditions	
Entry	Variation from above conditions ^b	Yield (4a %) ^c	ee % ^d
1	[Cu(MeCN) ₄]PF ₆	52	92
2	other Cu instead of [Cu(MeCN) ₄]PF ₆	<52	<92
3	<i>fac</i> -Ir(ppy) ₃	n.d.	n.d.
4	4-CzIPN	n.d.	n.d.
5	other Phenoxazines instead of PTH-1	<43	≤94
6	MeCN	11	90
7	DMAc	35	91
8	MeCN:DMF=3:1	73 (65)^e	92
9	390 nm	37	91
10	430 nm	21	91
11	no Cu	n.d.	n.d.
12	no L1	32	n.d.
13	no PC	n.d.	n.d.
14	in dark	n.d.	n.d.
15	blue LED	n.d.	n.d.

L1, n = 1, 52%, 92% ee

L2, n = 2, 38%, 46% ee

L3, n = 3, 37%, 15% ee

L4, n = 4, 47%, n.d.

L6, 38%, n.d.

L8, 36%, n.d.

L5, 39%, 2% ee

L7, 33%, n.d.

PTH-1

^a Conditions: **1a** (0.1 mmol), **2a** (0.2 mmol), **3** (0.15 mmol), PTH-1 (10 mol%), [Cu(MeCN)₄]PF₆ (2.5 mol%), and chiral ligand (3.0 mol%) in DMF [0.05 M] were stirred, irradiation with 20 W 410 nm LEDs at room

temperature for 24 h under an Ar atmosphere. ^b **L1** as the optimal ligand. ^c Yields were detected by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard. ^d Determined by HPLC analysis on a chiral stationary phase. ^e Isolated yield.

Substrate scope. With the optimal conditions established, we next examined the substrate scope with respect to the alkene component on a 0.2 mmol scale (Fig. 2). A diverse range of structurally varied and functionalized styrene derivatives proved to be compatible with this protocol. For vinylbiphenyl substrates bearing a 4-phenyl group with either electron-donating (methyl, methoxy) or electron-withdrawing (methoxycarbonyl, fluoro, trifluoromethyl) substituents at the *para*-position, the desired products **4b–f** were obtained in moderate to good yields (31 to 68%) with high enantioselectivities (89 to 92% ee). Substrates bearing 2-naphthyl or 2-thienyl substituents at the *para*-position of the phenyl ring (**4g**, **4h**) were also well tolerated. Steric and substitutional variation of the biphenyl framework was likewise tolerated, and products **4i–m** were formed with 90 to 95% ee. Particularly noteworthy was the double cyanodifluoroalkylation of 4,4'-divinyl-1,1'-biphenyl, which generated two stereogenic centers in **4n** (7:1 dr), and the major diastereomer was obtained with 99% ee. This result demonstrates that the chiral copper catalyst maintains effective stereochemical control over sequential radical C–CN bond-forming events. Furthermore, alkenes bearing an internal alkyne, variously functionalized alkyl chains, heteroatoms, or heteroaromatic rings at the distal end were well accommodated, giving the corresponding products **4o–s** in moderate yields with excellent enantioselectivities (89–94% ee).

We next turned our attention to the scope of trifluoromethylarene substrates, using 4-phenylstyrene **1a** as the alkene partner (Fig. 3). Bis(trifluoromethyl)benzene derivatives proved to be excellent substrates; regardless of the relative positions of the CF₃ groups, products **4ah** and **4ai** were obtained in moderate yields with high enantioselectivities. A series of 5-substituted 1,3-bis(trifluoromethyl)benzene derivatives were then evaluated, and a wide range of functional groups, including alkyloxy (**4aj**, **4ak**), alkyl chlorides and fluorides (**4al**, **4ap**), terminal alkyne (**4am**), cyclopropane (**4an**), alkene (**4aq**), primary alcohol (**4ar**), ester (**4as**), and acetal (**4at**), were well tolerated, affording the desired products in moderate to good yields with high enantiomeric excesses (88% to 96% ee). Notably, free phenol and aniline groups remained intact under the reaction conditions (**4av**, **4aw**), underscoring the mildness of this protocol. Furthermore, by increasing the catalyst loading to 10 mol% and switching to 390 nm irradiation, the strategy could be extended to heteroaryl–CF₃ substrates such as pyridine and *N*-methylbenzimidazole derivatives, delivering products **4ax–4bb** with maintained enantioselectivity, albeit in modest yields. These results highlight the broad functional-group tolerance and compatibility of our protocol with structurally diverse and functionally dense architectures. To demonstrate the utility of this protocol in complexed molecules, we examined several alkene-tethered derivatives of biologically active molecules. A non-chiral alkene derivative of fluoxetine, which is the widely prescribed antidepressant, was smoothly converted to the desired product **4bc** in moderate yield with 84% ee, albeit as a 1:1 mixture of diastereomers. Chiral alkene substrates derived from menthol, diacetone glucose, and aprepitant were also competent coupling partners. These reactions generated products **4bd–4bf** with useful levels of catalyst-controlled diastereoselectivity, demonstrating that the chiral copper catalyst can differentiate

the two faces of the intermediate benzylic radical even in the presence of pre-existing stereogenic elements. These results highlight the robust stereochemical compatibility of our catalytic system with structurally complex, and underscore its potential for the enantioselective diversification of pharmacologically relevant molecules.

Derivatization of chiral cyanodifluoroalkyl products. The value of an asymmetric catalytic method is determined not only by the ee of the initially formed product but also by whether the catalyst-installed stereochemical information can be preserved and exploited in subsequent synthesis. We therefore investigated the derivatization of **4a** to establish the nitrile group as a stereochemically reliable platform for accessing diverse chiral CF₂-containing structures (Fig. 4A). A gram-scale reaction was first conducted, delivering **4a** in 52% isolated yield with 92% ee (1.25 g). The nitrile moiety in **4a** proved to be a highly adaptable synthetic handle, enabling a range of transformations that proceeded with excellent preservation of enantiopurity unless otherwise noted. Under strong acidic conditions, the nitrile group was alcoholized to the corresponding fluorinated ester **5** in good yield without erosion of ee. Two selective reduction pathways were accomplished. Complete reduction to the primary amine **6** was achieved using BH₃·SMe₂ in THF, affording the product in 80% yield with 93% ee. Meanwhile, treatment with NiCl₂/NaBH₄ in MeOH selectively furnished secondary amine **7** in 85% yield with maintained enantioselectivity. Partial reduction with DIBAL-H at – 78°C, however, gave aldehyde **8** as a racemate. Pd-catalyzed hydration of the nitrile with acetaldoxime delivered the chiral amide **9** in excellent yield. Cycloaddition with TMSN₃ under *n*Bu₃SnO catalysis efficiently produced the 5-substituted tetrazole **10** in 72% yield with 94% ee. Furthermore, a Rh-catalyzed [2 + 2+2] cycloaddition of **4a** with a diyne afforded the chiral pyridine derivative **11** in 68% yield and 92% ee. Collectively, these transformations highlight the synthetic potential of our enantioselective defluorinative cyanation reaction for the rapid construction of structurally diverse chiral fluorinated molecules. This approach also enables rapid access to difluorinated analogue **14** of a chiral amine antiarrhythmic agent (Fig. 4B).⁴⁵ The parent compound was previously reported to overcome the major limitations of mexiletine, namely the need for repeated administration and a narrow therapeutic window. Notably, amine **14** can be obtained by reductive conversion of the nitrile product **12** and the followed rearrangement, further illustrating the synthetic utility of our method.

Mechanistic studies. To elucidate the mechanism of this enantioselective cyanodifluoroalkylation of alkenes, a series of mechanistic experiments were conducted (Fig. 5). Initially, when the radical scavenger TEMPO or BHT was introduced to the model reaction mixture, formation of defluorocyanation product **4a** was completely suppressed. In the case of BHT, the desired product was detectable in only 15% yield. Meanwhile, the corresponding α,α-difluorobenzylic radical adducts trapped by TEMPO and BHT (**15** and **16**, respectively) were identified by HRMS-ESI analysis (Fig. 5A). In addition, the radical clock substrate **17** participated in the reaction under standard conditions to afford the cyclopropyl ring-opened product **18** (Z/E = 8:1) in 64% yield with 71% ee (Fig. 5B), further supporting the involvement of radical intermediates. To gain further insight into the defluorination process of trifluoromethylarenes, we conducted the Stern–Volmer fluorescence quenching experiments (Fig. 5C). Consistent with our

expectations, **2a** + Cu salt/**L1** mixture quenched the excited state PTH-1 significantly faster than other reagents, such as **2a** or Cu salt/**L1** ($k_3 > k_2 + k_1$), indicating Cu salt/**L1** complex could facilitate the challenging SET reduction of trifluoromethylarenes by the excited photocatalyst. Light on/off experiments indicated that continuous photo-irradiation is essential for the reaction to proceed (Figure S8). The quantum yield was determined as $\Phi = 0.06\%$, suggesting that a radical chain pathway could be less likely involved (for details, see SI). Because the central objective of this study is catalyst-controlled stereoselective radical cyanation, we next examined the relationship between ligand chirality and product enantiopurity. A linear correlation was observed between the ee of **L1** and that of **4a** (Fig. 5D). This absence of a nonlinear effect is consistent with a catalytically relevant monomeric copper species containing one chiral bisoxazoline ligand.

Catalytic cycle. On the basis of these experimental observations and literature precedents^{17,46} a plausible catalytic cycle is proposed in Fig. 6. The cycle involves two intertwined catalytic loops, including a photoredox cycle and a copper catalytic cycle. Photoexcitation of PTH-1 generates the excited-state photocatalyst PTH-1*, which reduces trifluoromethylarene **2** with the assistance of the copper complex *via* a SET event. This process affords the key α,α -difluorobenzyl radical **I** along with a fluoride anion and the oxidized photocatalyst [PTH-1]⁺. Radical **I** then adds to alkene **1** to generate the prochiral benzylic radical intermediate **II**. Concurrently, ligand exchange between the **L1**/Cu(I) complex and TMSCN gives a Cu(I)–CN species. This species is oxidized by [PTH-1]⁺, followed by capture of a second cyanide equivalent, to form the higher-valent **L1**/Cu(II)(CN)₂ complex. This step concurrently regenerates the ground-state photocatalyst, closing the photoredox cycle. Finally, the **L1**/Cu(II)(CN)₂ complex traps radical **II**. The resulting Cu(III) intermediate **III** undergoes reductive elimination to deliver the enantioenriched product **4** and regenerate the **L1**/Cu(I)CN species, thereby completing the copper catalytic cycle.

CONCLUSIONS

In summary, we have developed a visible-light-mediated dual photoredox/copper catalytic system for the enantioselective defluorinative cyanation of alkenes with trifluoromethylarenes, using TMSCN as the cyanide source. This protocol operates under mild conditions and accommodates a broad range of alkenes and trifluoromethylarenes, providing straightforward access to enantioenriched β -difluoroalkyl nitriles. The synthetic utility of this method is further demonstrated by the late-stage functionalization of drug derivatives and bioactive molecules, as well as diverse transformations of the nitrile moiety into other valuable functional groups. Collectively, this work not only offers a practical and efficient entry to chiral fluorinated building blocks but also highlights the potential of merging photoredox catalysis with asymmetric copper catalysis for the functionalization of otherwise inert C(sp³)–F bonds.

Method

General procedure for the synthesis of chiral cyanodifluoroalkyl products

In a flame-dried 10.0 mL Schlenk quartz tube equipped with a magnetic stir bar was charged sequentially with $\text{Cu}(\text{MeCN})_4\text{PF}_6$ and **L1** under Ar atmosphere, followed by the addition of super dry *N,N*-dimethylformamide (1.0 mL). Then the mixture was stirred at room temperature for 30 min. To the resulting mixture was added PTH-1 or PTH-8 (0.02 mmol, 10 mol%), alkene **1** (0.2 mmol, 1.0 equiv), trifluoromethylarenes **2** (0.4 mmol, 2.0 equiv), **3** (0.3 mmol, 1.5 equiv) and super dry acetonitrile (3.0 mL) under Ar. The mixture was stirred at a distance of 2 ~ 3 cm from a 390–410 nm LEDs at 25 °C for about 10–48 h until the reaction was completed, as monitored by TLC analysis. The mixture was diluted with water (10 mL) and then extracted with ethyl acetate (10 mL×3), dried over anhydrous Na_2SO_4 , and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to give the product.

Declarations

Author contributions

Competing Interests

The authors declare no competing interests.

Additional information

Supplementary Information

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Data Availability

The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information Files as well as from the corresponding authors on request. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 2533995 (for **4a**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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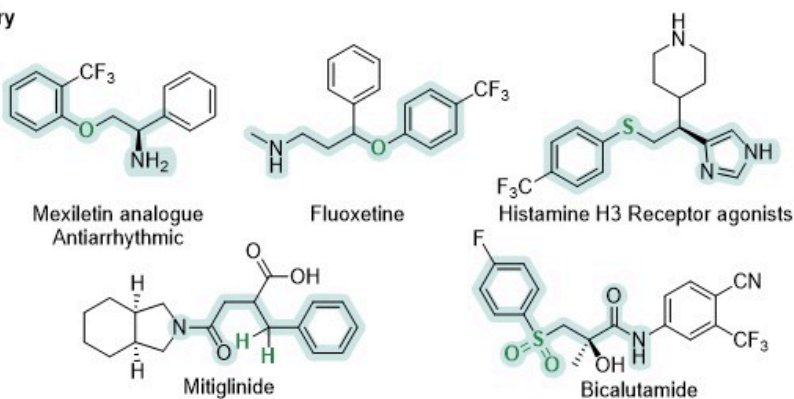
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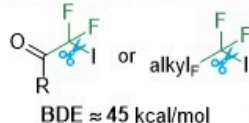
Figures

Cc1ccc(cc1S(=O)(=O)c2nc3c(ncn3c4ccccc4NCC5=CC=CC=C5S)S(=O)(=O)c2)R

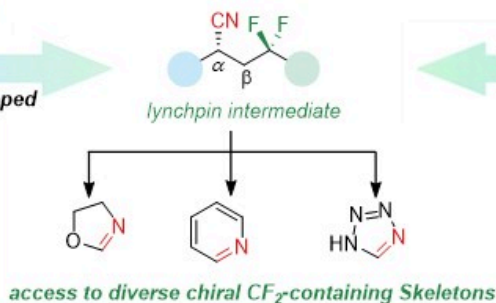
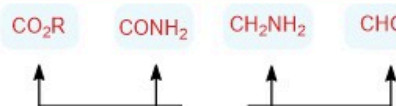
R=	CH ₂	O	CF ₂
IC ₅₀ (nM)	11	104	15
Metab (%)	>95	94	4



*preactivated
difluoroalkyl precursors*



inaccessible to β -aryl- CF_2 -substituent
pre-preparation/expensive



- activation of inert C(sp³)-F bond
- competition of alkene radical anion
- stereoselective control

68 examples
up to 99% ee

- activation of inert C(sp³)-F bond

■ enantioselective

enable late-stage functionalization

diverse transformations

State-of-the-art strategies for CF₃ group activation enabling enantioselective cyanodifluoroalkylation of alkenes.

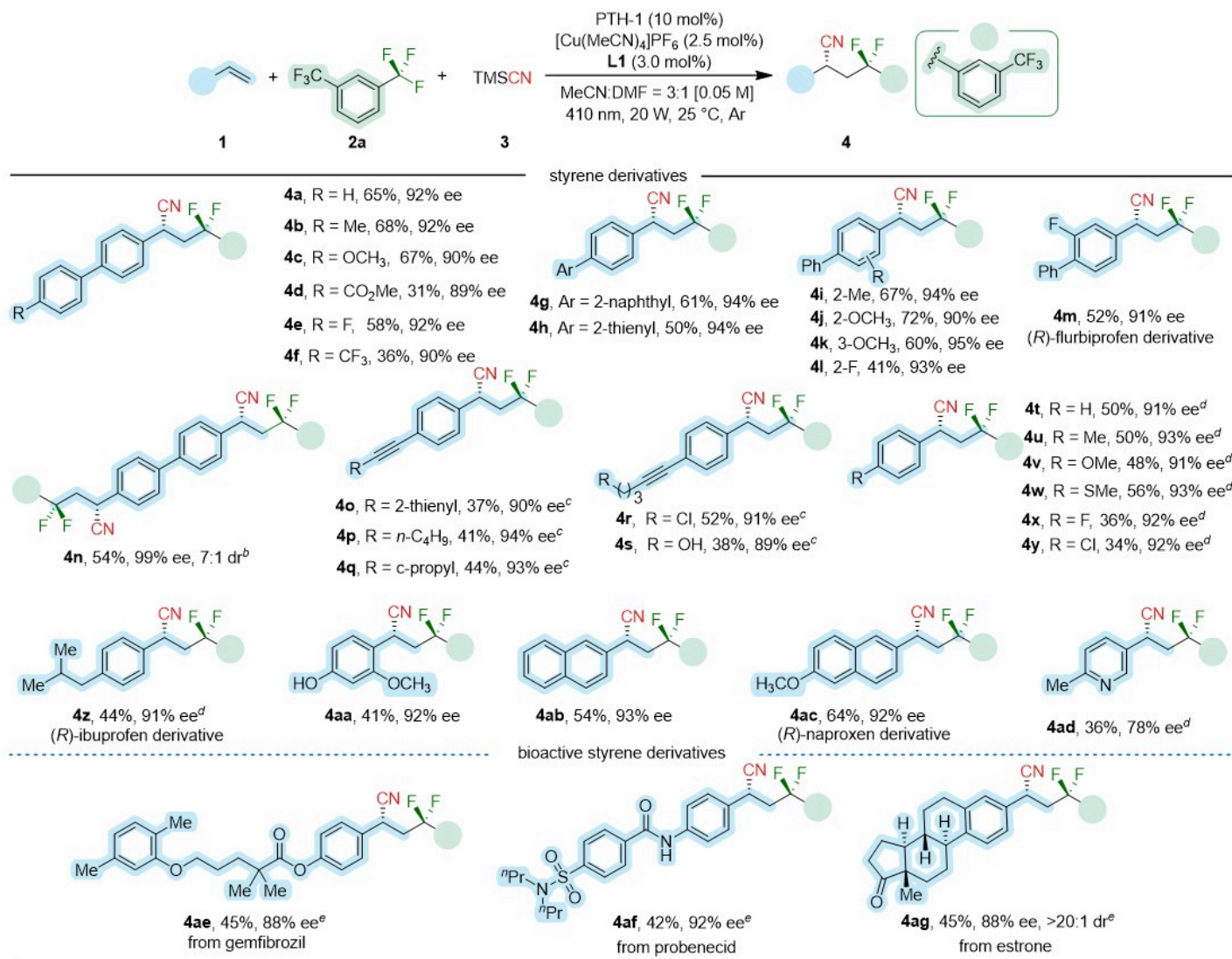


Figure 2

Scope of alkenes.^a Conditions: alkene (0.2 mmol), **2a** (0.4 mmol), **3** (0.3 mmol), PTH-1 (10 mol%), [Cu(MeCN)₄]PF₆ (2.5 mol%), and **L1** (3.0 mol%) in V_{MeCN}: V_{DMF} = 3: 1 [0.05 M] were stirred, irradiation with 20 W 410 nm violet LEDs at room temperature for 24 h under argon atmosphere. ^b With [Cu(MeCN)₄]PF₆ (5.0 mol%) and **L1** (6.0 mol%), **2a** (0.8 mmol) and **3** (0.6 mmol) for 34 h. ^c 34 h. ^d [Cu(MeCN)₄]PF₆ (5.0 mol%) and **L1** (6.0 mol%) irradiation with 20 W 390 nm for 10 h. ^e 48 h.

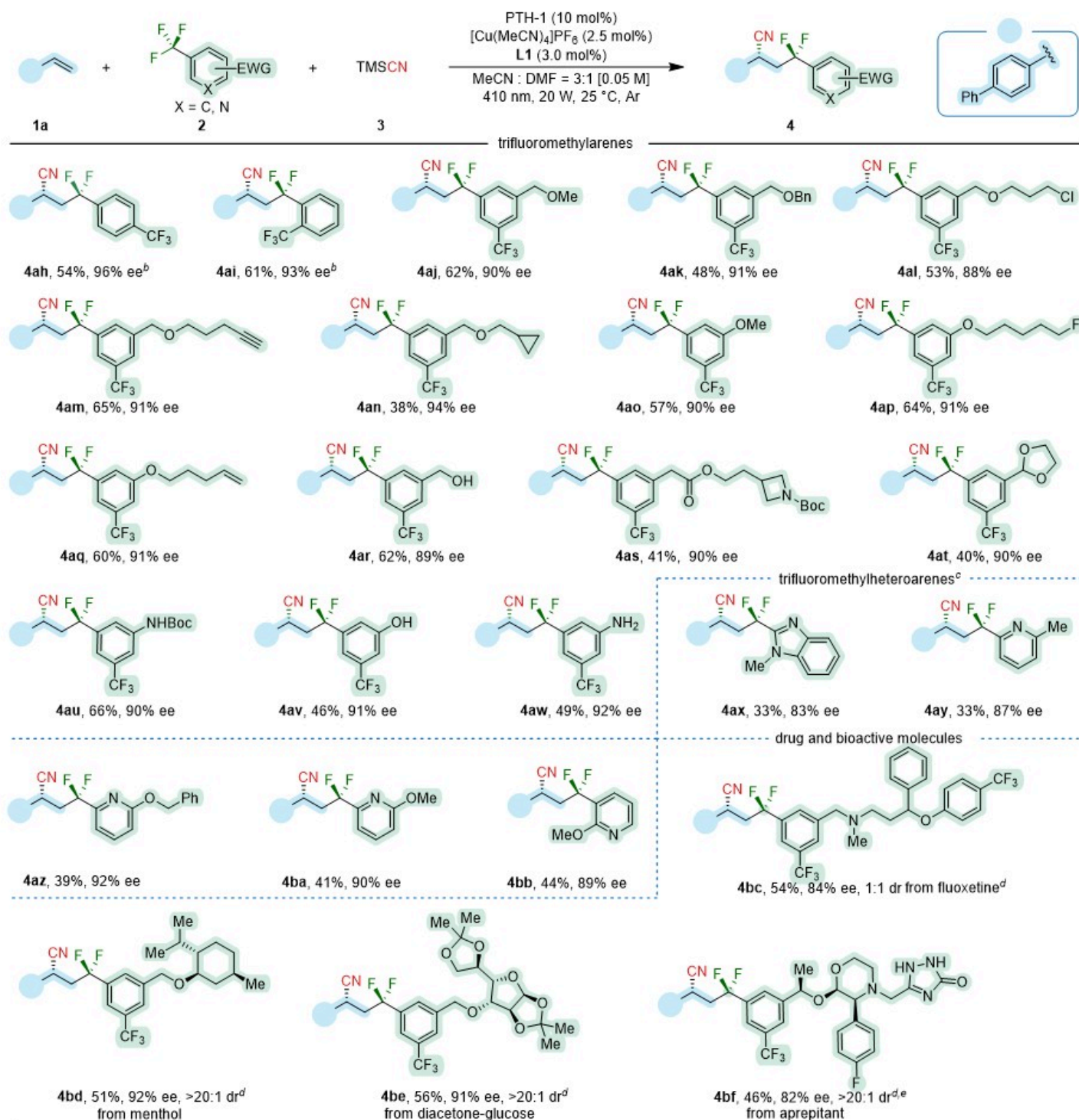


Figure 3

Scope of trifluoromethylarenes.^a Conditions: **1a** (0.2 mmol), **2** (0.4 mmol), **3** (0.3 mmol), PTH-1 (10 mol%), [Cu(MeCN)₄]PF₆ (2.5 mol%), and **L1** (3.0 mol%) in V_{MeCN}: V_{DMF} = 3: 1 [0.05 M] were stirred, irradiation with 20 W 410 nm violet LEDs at room temperature for 40 h under argon atmosphere. ^b 10-phenylphenoxazine instead of PTH-1, irradiation with 20 W 390 nm for 10 h. ^c With [Cu(MeCN)₄]PF₆ (10

mol%) and **L1** (12 mol%), irradiation with 20 W 390 nm for 10 h. ^d 48 h. ^e **1a** (0.2 mmol), ArCF₃ (0.1 mmol), **3** (0.15 mmol).

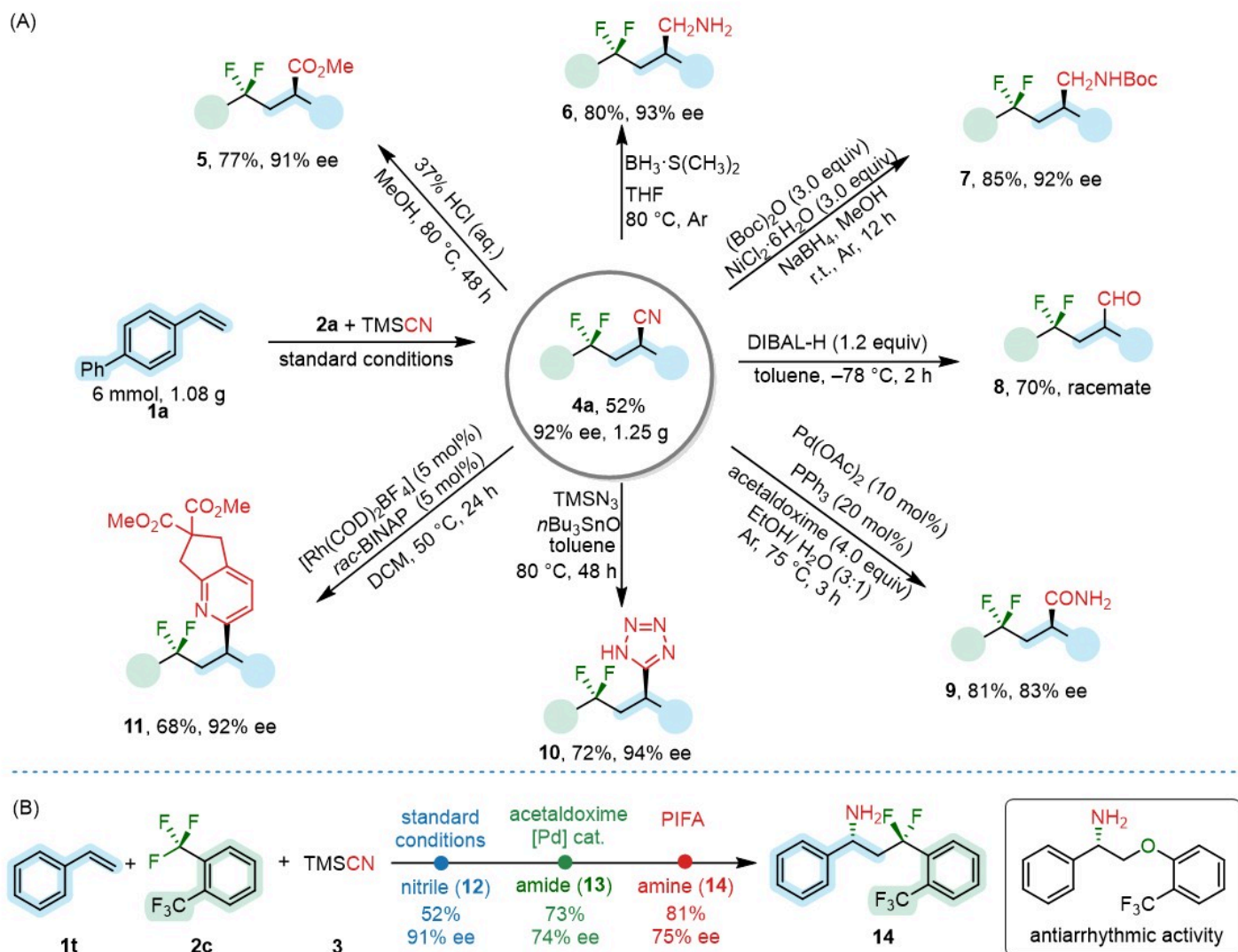


Figure 4

Derivatization of chiral cyanodifluoroalkyl products. Please see SI for the experimental details.

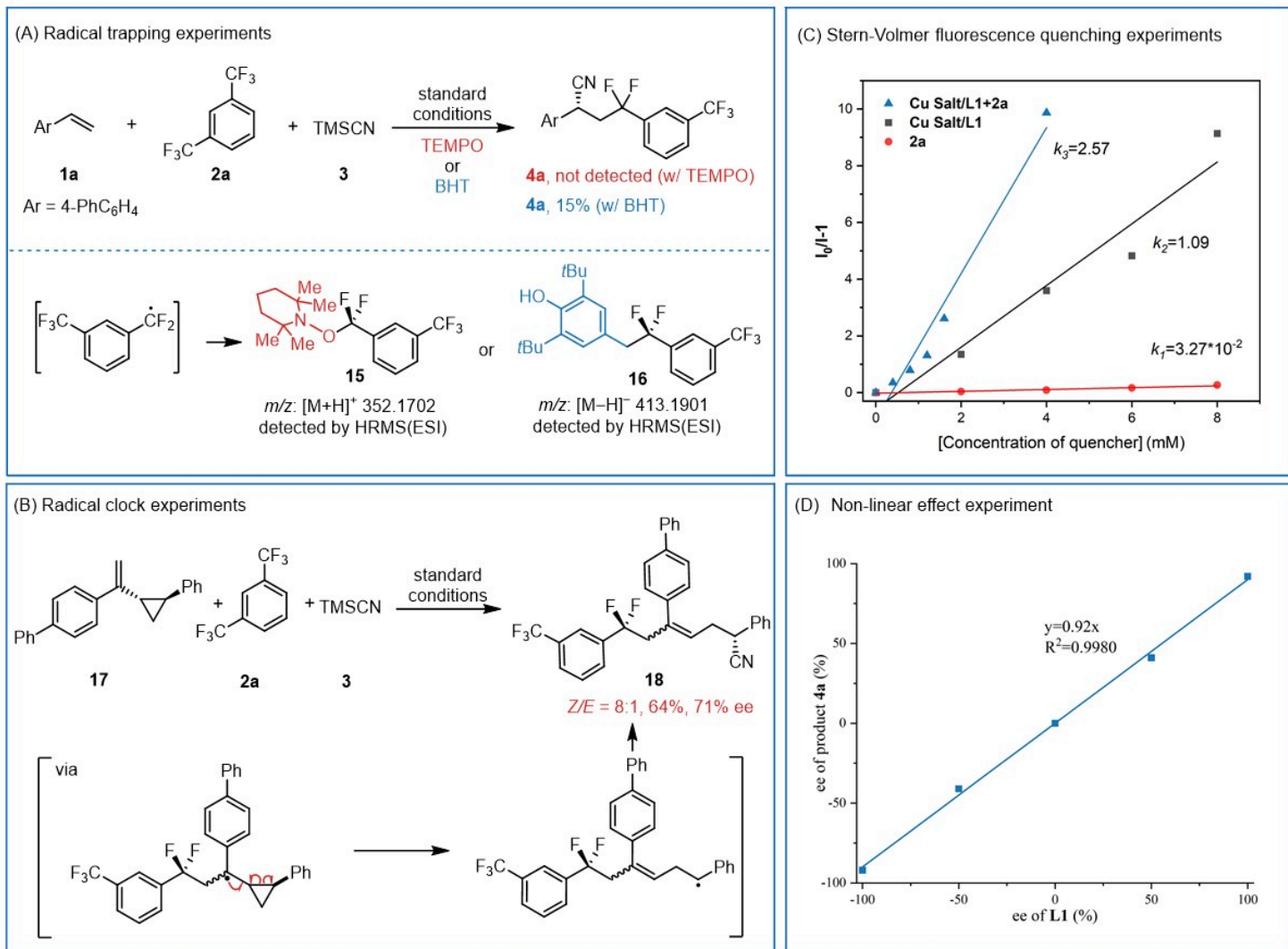


Figure 5

Mechanistic studies. Please see SI for experimental details.

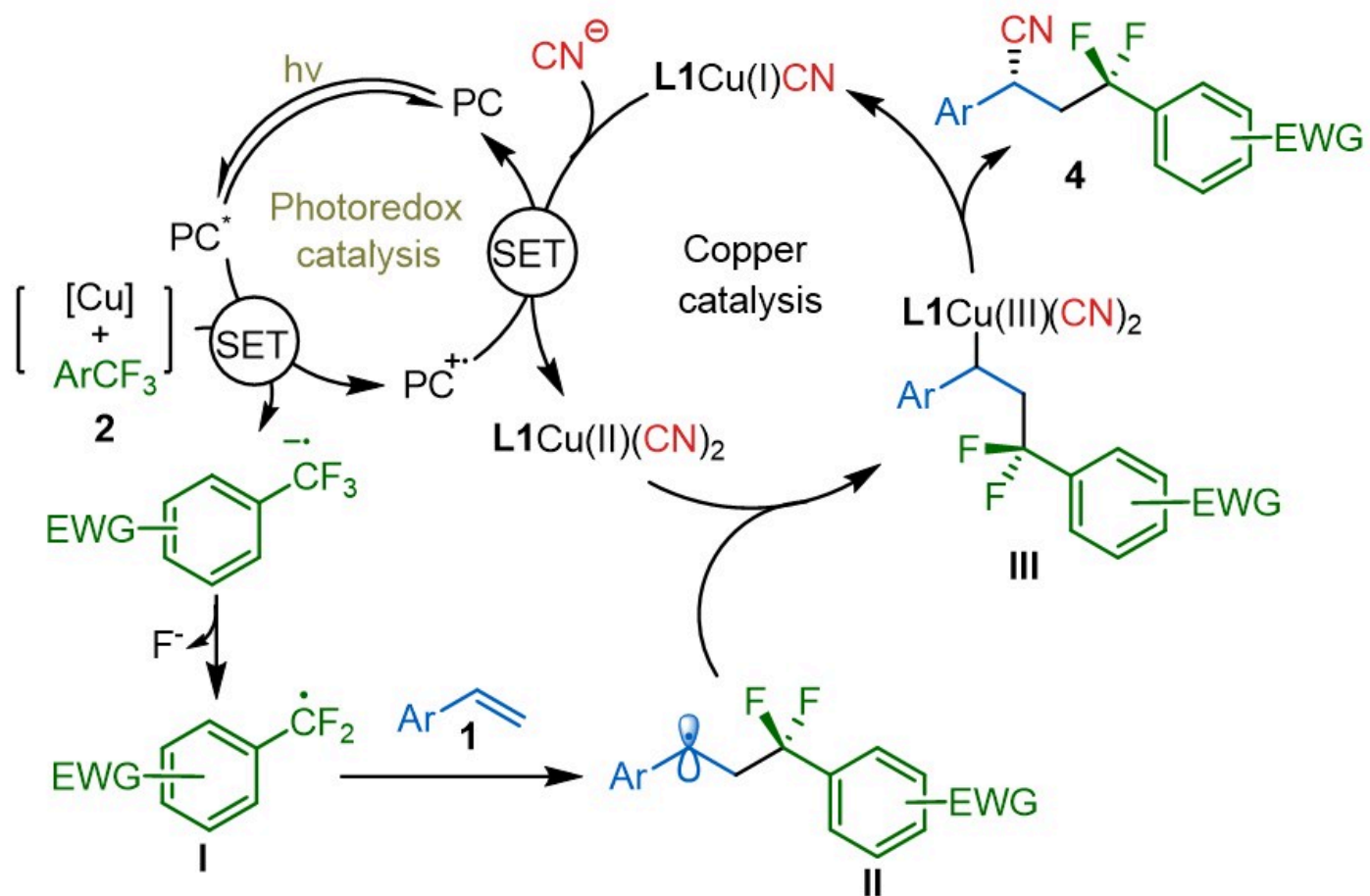


Figure 6

Proposed catalytic cycles.

Supplementary Files

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