Triplet Energy Transfer Mechanism in Copper Photocatalytic *N*– and *O*–Methylation

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Abstract: Methylation reactions are chemically simple but challenging to perform under mild and non-toxic conditions. Photochemical strategies merged with copper catalysis enable rapid reaction times and broad applicability to *N*-heterocycles and aromatic carboxylic acids in high yields and good functional group tolerance. Detailed mechanistic investigations revealed a triplet-triplet energy transfer mechanism between hypervalent iodine reagents and readily available photosensitizers.

Introduction

The combination of metal catalysis and photochemistry has received considerable attention over the last decade and holds great promise for milder and more sustainable organic syntheses.[1] This rising field, termed metallaphotoredox catalysis and pioneered by the MacMillan group, enables diverse transformations utilizing oxidative or reductive excited state quenching mechanisms to form transient organic radicals from readily available starting materials.[2] Additionally, employed photosensitizers can undergo energy transfer (EnT) processes and thus enable an alternative activation mechanism in light-mediated catalysis holding great promises in future synthetic applications.[3]

Naturally occurring carboxylic acids are an ideal and abundant substrate to undergo reductive or oxidative quenching during metallaphotoredox catalysis. When activated, carboxy radicals are formed which rapidly liberate carbon dioxide in a highly exergonic reaction (–23.2 kcal mol^{-1}), to form a carbon-centered radical.[4] This approach, when combined with metal catalysis, has enabled various new kinds of C–C and C–N bond formation reactions.[5] A suitable activation method for carboxylic acids are hypervalent iodine(III) reagents, such as phenyliodo diacetate (PIDA), which are well known sources for aliphatic radicals[6] and have been activated with photochemistry in chain reactions.[7] On the one hand, single-electron transfer (SET) or reduction of PIDA can occur from highly reducing excited state photocatalysts (PC, Figure 1). On the other hand, access to triplet states of PIDA is feasible due to the heavy-atom effect of iodine and can be reached *via* direct Dexter-type energy transfer of long-lived triplet excited states of the photocatalyst. However, the operating mechanism is debated in the literature: In a seminal report by Liang *et al.* on the copper-catalyzed *N*-alkylation, oxidative quenching of the photocatalyst and subsequent reduction of PIDA was described as the initial step in the reaction mechanism to form a carboxy radical, which rapidly decarboxylates to form the active alkyl radical.[8] For most substrates, light activation was not necessary and thermal copper-catalyzed coupling between *N*-nucleophiles and alkyl fragments was broadly achieved. The proposed photocatalytic mechanism was recently investigated by Mane *et al.* with DFT calculations shining light on the sequence of intermediate reaction steps.[9] In a more complex scenario, the MacMillan group developed a radical sorting mechanism of unsymmetrical hypervalent iodine-derived radicals with nickel catalysis which operated under an energy transfer mechanism with thioxanthone (TXO) and a SET mechanism with 2,4,5,6-tetrakis(9*H*-carbazol-9-yl)isophthalonitrile (4CzIPN) as photocatalysts respectively.[10] To this end, it is not clear how distinct this differentiation can be made. In 2023, the group of Murakami reported a detailed study where they found switching behavior of mechanisms with hypervalent iodine reagents.[11] Following SET reactivity, an ionic pathway led to decarboxylative esterification, whereas EnT resulted in radical-radical homo-dimerization.

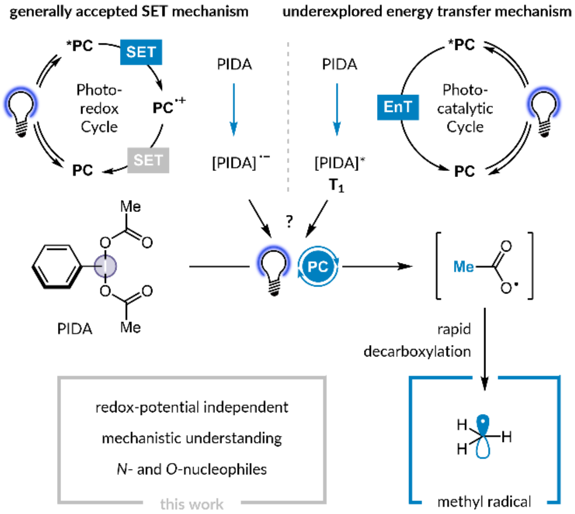

Figure 1: Methyl radical formation from hypervalent iodine reagents (*e.g.*, PIDA) can follow single electron transfer (SET) or energy transfer (EnT) mechanisms.

Merging the mechanistic diversity of hypervalent iodine reagents with copper catalysis is scarce[12] and will be applied to the radical methylation reaction. In particular methyl radicals are significantly destabilized compared to commonly employed primary or secondary radicals (relative radical stabilization energy, ΔRSE(1°) ~ –3.2 kcal mol^{-1}, ΔRSE(2°) ~ –5.6 kcal mol^{-1}) rendering methyl radicals a more difficult target.[13] The combination of metal catalysis and photochemistry is envisioned to extend methylation reactions beyond nucleophilic substitution reactions. Methylation of organic molecules is a general strategy to influence their

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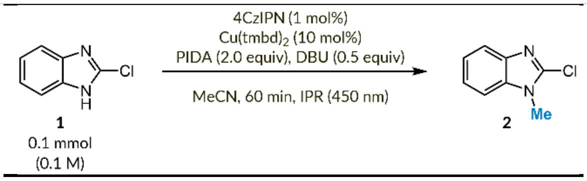
properties[14] and found tremendous applications in drug design coined the “magic methyl-effect”.[15] In particular, *N*-heterocycles are common targets for methylation reactions and commonly methyl iodide or dimethyl sulfate are used under basic conditions. However, both reagents are known carcinogens.[16] Catalytic, non-toxic, and mild alternatives thus remain of considerable interest and have transformative potential for pharmaceutical syntheses.

In the study by Liang *et al.* only two examples were described to undergo successful methylation reaction.[8a] Inspired by this study, we were wondering whether the differentiation between SET and EnT mechanisms can be applied to copper-catalyzed methylation reactions. We were aiming to develop a purely light-controlled process which yields methylated *N*-heterocycles. Followed by a detailed mechanistic understanding the underlying copper-catalyzed mechanism should enable us to derive general reaction conditions, which can be expanded to additional weaker nucleophiles.

Results and Discussion

We started our investigations with copper photo-catalytic conditions and PIDA for methylation reactions.[8] Initially, using 2-chlorobenzimidazole (**1**) as substrate, a quick optimization gave reproducible results and high yields using readily available reagents and benign reaction conditions (see Scheme S1-5). *N*-Methyl-2-chlorobenzimidazole (**2**) was obtained in close to quantitative yield (Table 1, Entry 1).

Table 1. Control experiments of the *N*-methylation reaction.

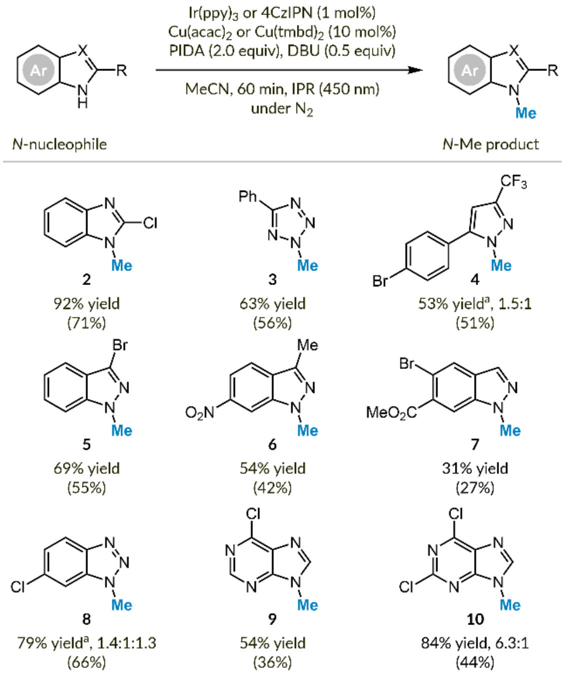


Entry	Deviation	Yield[a]
1	**none**	**98%**
2	air as atmosphere	43%
3	no 4CzIPN	0%
4	shielded from light	0%
5	no $Cu(tmhd)_2$	3%
6	no DBU	20%
7	KOAc instead of DBU	53%
8	NHPI–Ac instead of PIDA	10%

[a] ^{1}H-NMR yields of *N*-methylated product vs. mesitylene as internal standard in $CDCl_3$ under nitrogen atmosphere. tmhd: tetramethyl-3,5-heptanedione; DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene; IPR: integrated photoreactor.

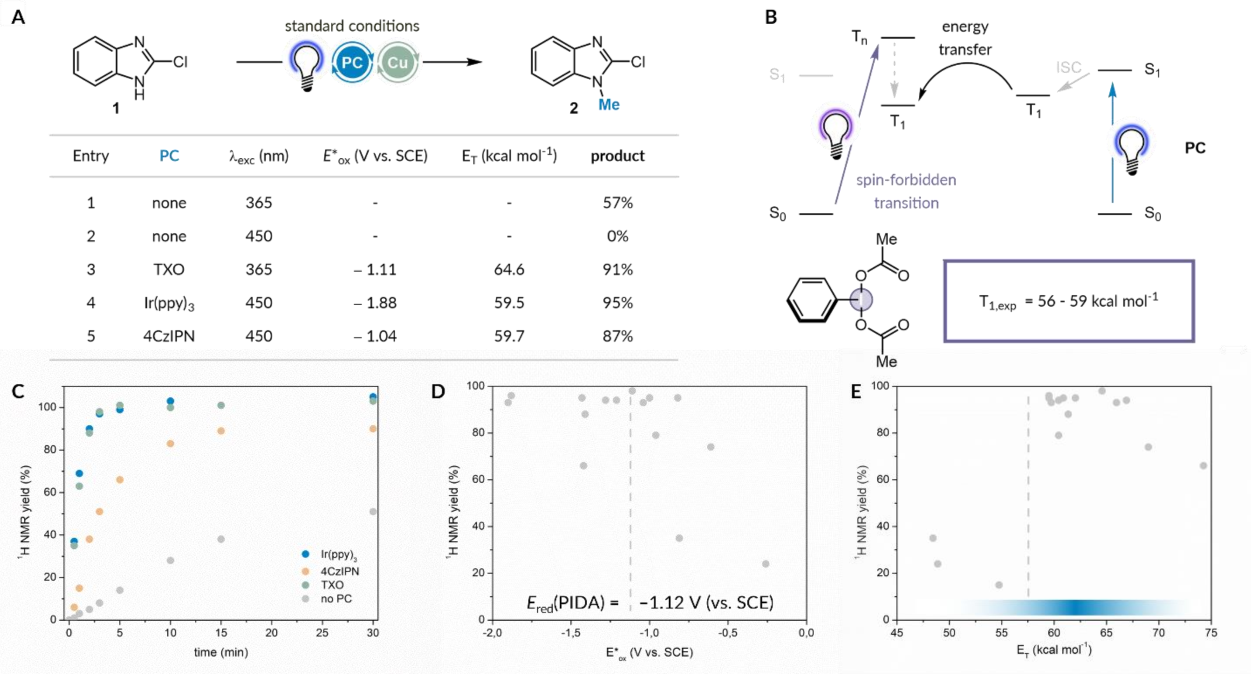
Control reactions revealed that the reaction conditions require inert atmosphere, as oxygen from air hampers the conversion (Table 1, Entry 2). All reaction components were crucial, as omitting them individually resulted in negligible to minimal product formation (Table 1, Entries 3–6). Shielding from light inside the integrated photoreactor (IPR) resulted in no product formation excluding a thermal background reaction (Table 1, Entry 4). Without base, the product formation decreased to 20% (Table 1, Entry 6). However, DBU is required, as substitution with acetate as base, which can be leveraged during the reaction, resulted in a lower yield of 53% (Table 1, Entry 7). By using redox-active ester *N*-hydroxyphthalimide acetate (NHPI–Ac) as methyl radical source only 10% yield was obtained indicating SET as an unlikely mechanism (Table 1, Entry 8).

With the optimized conditions in hand, we investigated the applicability of the reaction and found various *N*-heterocycles to be amenable under our reaction conditions. *N*-Heterocycles like benzimidazole, tetrazole, pyrazole, indazole, benzotriazole, and purine performed smoothly under the optimized conditions (Scheme 1). Many functional groups within the products **2** to **10**, like alkyl, aryl, halide, and even nitro, are tolerated respectively. Most substrates gave competitive isolated yields between 36% and 71% compared to classical methylation with toxic methyl iodide or dimethylsulfate (see experimental section in the SI). In some cases, better regioselectivity was achieved. In our hands, electron-poor heterocycles gave higher yields and several additional substrates gave only low yields as confirmed by ^{1}H NMR analysis (Scheme S13). Concerning the copper source, copper(II)acetylacetonate ($Cu(acac)_2$) and the tert-butyl analogue (tmbd) gave similar conversions (Scheme S5).



Scheme 1: Scope of the methylation reaction. ^{1}H NMR yields given and isolated yields in parentheses on 0.5 mmol scale. Isomer ratios given and major regioisomer is shown (see SI). ^{a} 2.0 equiv. DBU were used.

To gain mechanistic insights we envisioned different scenarios and investigated unsensitized as well as sensitized conditions using TXO, homoleptic tris(2-phenylpyridine)iridium(III) ($Ir(ppy)_3$), and 4CzIPN as



Entry	PC	λ_{exc} (nm)	E^*_{ox} (V vs. SCE)	E_T (kcal mol^{-1})	product
1	none	365	-	-	57%
2	none	450	-	-	0%
3	TXO	365	– 1.11	64.6	91%
4	Ir(ppy)$_3$	450	– 1.88	59.5	95%
5	4CzIPN	450	– 1.04	59.7	87%

Figure 2: Comparison of background reaction and sensitized reactions with selected photocatalysts (A). For details check SI. Proposed triplet energy transfer mechanism (B). Kinetic reaction profiles of Entries 1 and 3-5 (C), plot of excited state oxidative quenching potentials (D, reduction potential of PIDA highlighted) and triplet state energies of photosensitizers vs. reaction yield (E). ^{1}H-NMR yields of *N*-methylated product vs. mesitylene as internal standard in $CDCl_3$.

photocatalysts, where energy-transfer and electron-transfer processes are plausible respectively. We probed the background reaction under UV (365 nm) and visible light excitation (450 nm) and observed that product formation was moderate with the high-energy UV light, whereas no reaction took place with blue light (Figure 2A, C). Recently, the Nakalima and Nemoto groups investigated the direct excitation of hypervalent iodine species and found evidence for the spin-forbidden transition from the ground state (S_0) to a high-lying triplet state (T_n, Figure 2B).[17] The groups could show the experimental utility of this approach in various group transfer reactions and is in line with our observation. To the best of our knowledge, this strategy has not been applied to copper catalysis to date. When we added photosensitizers to the reaction, a significant boost in conversion was observed and high product formation was found for TXO, 4CzIPN, and Ir(ppy)$_3$ within a few minutes (Figure 2A). The kinetic profiles for each case reveal significant rate enhancement for the sensitized cases (Figure 2C). TXO enhances the UV light background reaction, and the quantitative formation of **2** is achieved after 5 minutes. For the other two sensitizers the kinetic difference likely originates from lower quenching efficiency of 4CzIPN compared to Ir(III) as determined by Stern-Volmer experiments (Figure S1-2).[10]

The triplet state quantum yields of all three photocatalysts are available from the literature (Φ(TXO) = 0.12 in MeOH at 298 K,[18] Φ(Ir(ppy)$_3$) = 0.97 in 2-Me-THF at 298 K,[19] and Φ(4CzIPN) = 0.18 in MeCN at 300 K).[20] The respective quantum yields or efficiencies of the quenching process were determined to be 0.021 for TXO, 0.016 for Ir(ppy)$_3$ and 0.005 for 4CzIPN (see SI). The quenching efficiency is largest for TXO and Ir(ppy)$_3$, which is in line with the observations from reaction kinetics (Figure 2C, see SI). Next, we probed for the likeliness of excited state single electron transfer (SET), and we screened a variety of photocatalysts and -sensitizers (Table S1). When the formation of **2** was plotted against the ground and excited state redox potentials, no correlation was observed, which suggests that a mechanism *via* single electron transfer is unlikely (Figure S6). For the expected oxidative quenching event (Figure 2D and S6C) even sensitizers which are lower in excited state oxidation potential than the necessary E_{red}(PIDA) = –1.12 V vs. SCE[21] performed well under the optimized conditions. However, plotting the triplet state energies of the photosensitizers against reaction progress shows a clear cut-off between 55 and 60 kcal mol^{-1} (Figure 1E). Only a limited number of acridinium and ruthenium sensitizers were available below this threshold (Table S1). Based on the behavior displayed in Figure 1E we estimate the triplet state energy of PIDA to be around 56-59 kcal mol^{-1}, which is in good agreement with 58.6 kcal mol^{-1} obtained from DFT calculations (B3LYP D3/def 2 level of theory, Table S2). With these results in hand a triplet-triplet energy transfer mechanism (TTEnT) is reasonable and likely the main operating mechanism for quenching of hypervalent iodine reagents in photocatalysis (Figure 1B, right).[22]

Therefore, we propose a catalytic cycle which starts with excitation of a photosensitizer (PS) with (visible) light (Figure 3A). After intersystem crossing, the long-lived triplet state (τ(TXO) = 0.76 μs, τ(4CzIPN) = 5.1 μs, τ(Ir(ppy)$_3$) = 1.9 μs)[23] undergoes triplet energy transfer to hypervalent iodine(III) to populate the T_1 excited state. Fragmentation and loss of CO_2 leads to the formation of active methyl radical (**I**), acetate (*vide infra*), and either neutral phenyl iodide or the iodanyl radical cation ($PhI^{\bullet+}$).[24] The formation of methyl radical (**I**) was confirmed by addition of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO, 2.0 equiv) as the respective radical adduct **II** formed in 165% ^{1}H NMR yield, whereas the coupling

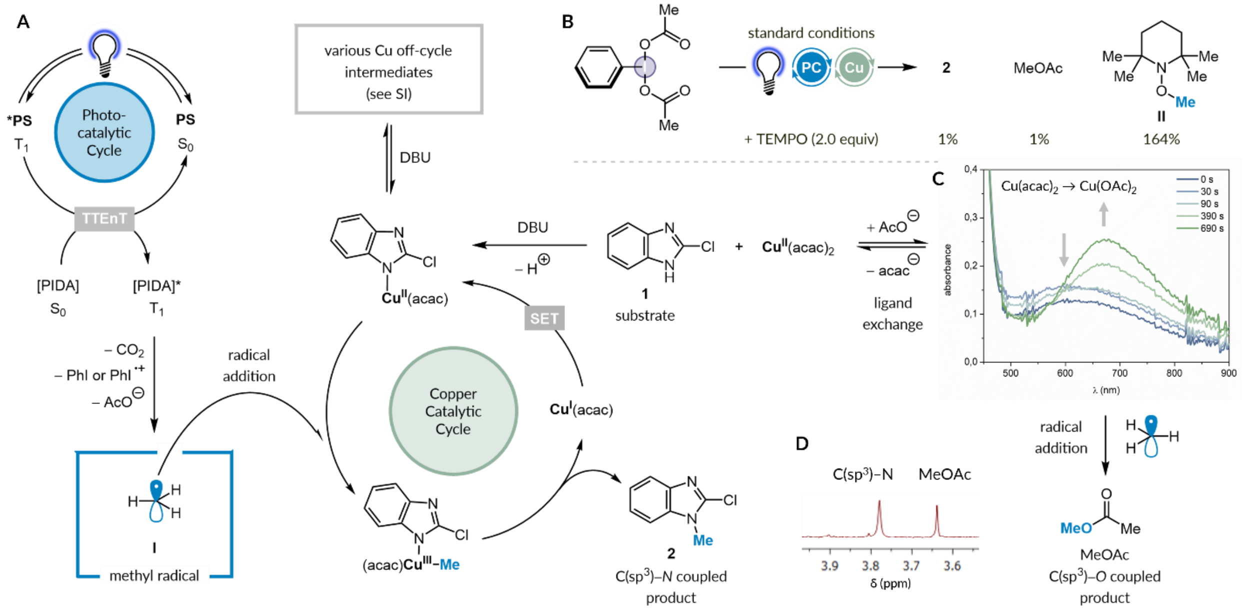


Figure 3: A) Proposed mechanism featuring triplet energy transfer activation of hypervalent iodine species merged with copper catalysis. B) Radical trapping experiments with TEMPO confirm the formation of methyl radical (**I**). C) Ligand exchange with free acetate was followed by UV/Vis experiments over the course of the reaction. D) Copper(II) acetate can trap methyl radical and form methyl acetate upon reductive elimination, which was confirmed by ^{1}H NMR.

reaction was completely suppressed (Figure 3B). Radical addition to Cu(II) intermediates occurs fast (k ~ 10^{-9} s),[25] and forms Cu(III) species which readily undergo reductive elimination, forming the desired product **2**. The resulting Cu(I) intermediate (E_{red} (Cu(acac)$_2$) = –1.65 V vs. SCE)[26] can be oxidized by PIDA or iodanyl radical cation and in the presence of *N*-nucleophile regenerates Cu(II) closing the catalytic cycle. This oxidation is further supported by the need for two equivalents of PIDA for high conversions (Figure S9). The role of DBU as non-nucleophilic base was investigated by direct aprotic injection experiments in a quadrupole MS instrument (Figure S10-11). In the negative mode many di- and trinuclear copper species were identified, which are likely off-cycle intermediates as known from conventional Chan-Lam coupling reactions (Figure 3A).[27] Thereof, DBU seems to be crucial in returning these intermediates back onto the catalytic cycle.[28] The active nature of copper(acac)$_x$–DBU complexes in the catalytic cycle are further supported by the recent theoretical study of Mane *et al.*.[9]

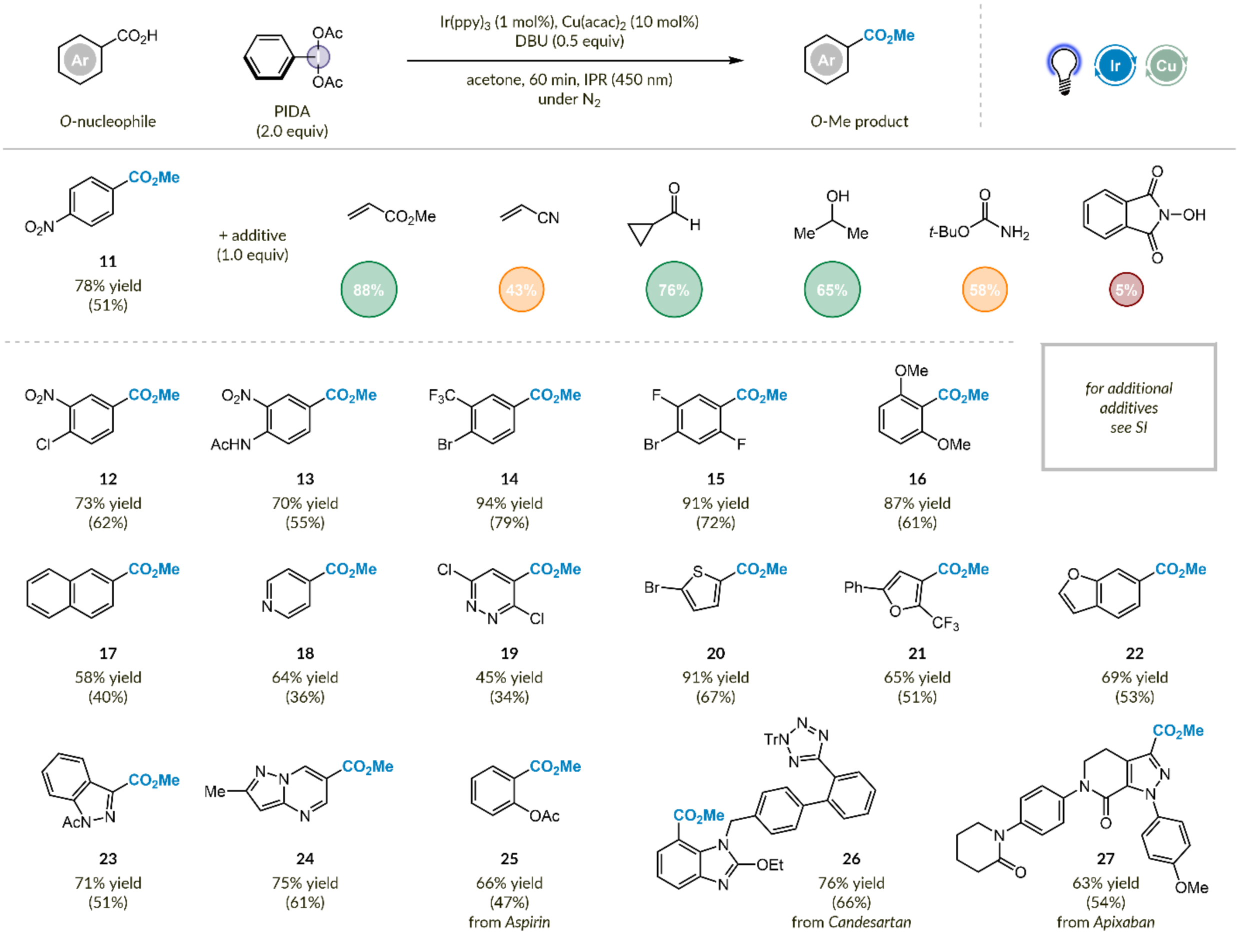
In line with the base dependency of the reaction described above, we conducted a UV/Vis study to follow changes of the copper catalyst with each component as well as over time and irradiation (see SI). A broad peak around 620 nm from Cu(acac)$_2$ is observed under normal reaction conditions (Figure S12). Upon irradiation of the reaction with 440 nm LEDs a bathochromic shift to 670 nm occurs (Figure S13), which builds up over the initial 10 minutes of reaction time and can be assigned to the formation of copper(II) acetate in the presence of PIDA. This equilibrium is in line with the literature for the fast exchange between acac$^-$ and $^-$OAc ligands (Figure 3C).[29] Additionally, energy transfer from the sensitizer can further induce the dissociation of acac ligands after photoexcitation.[30] After initial photoinduced acac dissociation, stronger *O*-nucleophiles, such as acetate, can ligate copper.[31] Combined with the MS results (*vide supra*), acetate seems to assist as base to fulfil the overall reaction stoichiometry. Without addition of photocatalyst, no change in absorption behavior is observed (Figure S15, left) confirming the nature of the photochemical process. Based on literature precedence, large excess of *N*-nucleophiles is required to induce formation of adducts with Cu(acac)$_2$, which may explain the small change in the UV/Vis (Figure S15, blue graphs).[32]

Alongside the formation of the desired *N*-methylated product, methyl acetate formed at similar rates with a minor initial lag phase (Figure S7-8). The addition of methyl radicals to copper(II) acetate was described to form a Cu(III) species (Figure S14), which upon fast reductive elimination liberates methyl acetate showing a distinct shift in the ^{1}H NMR at around 3.65 ppm (Figure 3D).[33] Additionally, indazoles show the formation of *N*-acetylated products. We probed the origin of the acetyl group and concluded it must arise from direct reaction of *N*-nucleophiles with PIDA, since neither methyl acetate nor Norrish-type fragmentation of the ligand on copper led to the *N*-acetyl indazole (Scheme S6). Acyl transfer from PIDA to nucleophiles is unusual but plausible,[34] and may enable intriguing redox active ester-type reactivity in the future. Likewise radical addition or coupling with the substrate was anticipated, since a highly stabilized α,α-amine radical intermediate would form (Scheme S7). Therefore, 2-cyclopropylbenzimidazole (**S1**) was synthesized and subjected to the standard conditions. No radical clock ring opening product **S2'** was obtained and only the desired product **S2** was obtained in 29% yield, indicating that no intermediate tertiary radical within the heterocycle was formed (Scheme S8).

With a solid mechanistic understanding provided by the combination of NMR, GC, luminescence quenching, UV/Vis spectroscopy, and aprotic MS experiments we were wondering whether weak nucleophiles, which are not readily methylated with common reagents like methyl iodide, are amenable to copper-catalyzed energy transfer catalysis. The direct photoexcited fragmentation of 1-butoxy 1-λ³-benzo[*d*][1,2]iodaoxol-3(1*H*)-one (IBB) in the presence of aliphatic acids was reported by Itami and Murakami and resulted in intramolecular *O*-benzylated products with 2-iodobenzoic acid *via* a polar SET mechanism.[35] Thermal decomposition of PIDA combined with copper catalysis was used by the group of Zhang in the methylation of mostly mono-substituted benzoic acids.[36] After quick solvent optimization we were pleased to see efficient reactivity of various benzoic acids upon combination of copper and energy transfer catalysis. In particular aprotic polar solvents performed well, and acetone was chosen due to the highest yields across diverse electronic substrates (Figure S16). Many benzoic acids were compatible with our protocol and even showed competitive yields across the board (see experimental section in the SI). Mono-, di-, and tri-substituted benzoates were applicable and the respective products **11** to **17** were obtained in isolated yields of up to 79% (Scheme 2). All reaction components are required for high performance rendering a purely light-driven process (Scheme S11) and shows high robustness toward the addition of various additives (Scheme S12). Secondary alcohols, imides, anhydrides, amines, olefins, alkynes, aryl bromides, and even carbonyl and nitro groups are well tolerated with only minor decrease in yield (Scheme S12, green). Only limited functionalities show inhibition of the reaction towards **11** such as *N*-hydroxy phthalimide (see SI). Multiple electron-rich and electron-poor heterocycles like pyridine, pyrazine, thiophene, furan, indazole, or pyrazolo-pyrimidine gave good conversion and up to 91% yield was obtained for products **18** to **24**. Competition experiments show that electron-withdrawing groups increase the yield and *N*-heterocycles are generally detrimental (Scheme S13-14). Last we subjected smaller and larger active pharmaceutical intermediates (APIs) as substrates to show the broad application and mild nature of this copper-catalyzed energy transfer mechanism. *Aspirin*, *Candesartan*, and *Apixaban* performed all well and methylated products **25**-**27** were obtained in 47%, 66%, and 54% isolated yield, respectively, displaying the outstanding potential of this method.

Conclusion

In conclusion we investigated the radical methylation reaction using hypervalent iodine(III) merged with copper photocatalysis. Although redox chemistry by single electron transfer cannot be ruled out completely, we emphasize that triplet-triplet energy transfer is far more likely operational between excited photosensitizer and hypervalent iodine(III) reagent. Quantum yields between 0.5 to 2.1% were obtained for different sensitizers,



Scheme 2: Scope of the methylation reaction. ¹H NMR yields vs. mesitylene as internal standard given and isolated yields in parentheses on 1.0 mmol scale.

confirmed by kinetic analysis, and the triplet state energy of PIDA was estimated to be around 58 kcal mol^{-1}. We could show that methyl acetate formation is a key side reaction under radical control, and this method is comparable with conventional methylation conditions. Various heterocycles and carboxylic acids can be methylated effectively in good to high yields and investigations into more challenging nucleophiles are currently ongoing. The triplet energy transfer reactivity of hypervalent iodine reagents opens new avenues in organic methodology in the future due to the broad availability of I(III) reagents, copper catalysts, and the mild nature of the underlying mechanism.

Supporting Information

Supplementary material can be found online. Characterization data and spectra are reported and the authors have cited additional references within the Supporting Information.

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Keywords: copper catalysis • photocatalysis • energy transfer • methylation • hypervalent iodine

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