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Visible Light-Mediated Atom Transfer Radical Addition via Oxidative and Reductive Quenching of Photocatalysts

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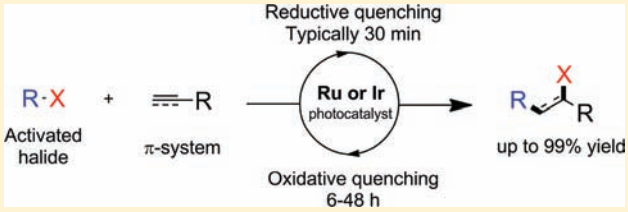
Supporting Information

ABSTRACT: Herein, the development of visible light-mediated atom transfer radical addition (ATRA) of haloalkanes onto alkenes and alkynes using the reductive and oxidative quenching of $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ and $[Ru(bpy)_3]Cl_2$ is presented. Initial investigations indicated that the oxidative quenching of photocatalysts could effectively be utilized for ATRA, and since that report, the protocol has been expanded by broadening the scope of the reaction in terms of the photocatalysts, substrates, and solvents. In addition, further modifications of the reaction conditions allowed for the efficient ATRA of perfluoroalkyl iodides onto alkenes and alkynes utilizing the reductive quenching cycle of $[Ru(bpy)_3]Cl_2$ with sodium ascorbate as the sacrificial electron donor. These results signify the complementary nature of the oxidative and reductive quenching pathways of photocatalysts and the ability to predictably direct reaction outcome through modification of the reaction conditions.



INTRODUCTION

With the combined efforts of several research groups,[1] atom transfer radical addition (ATRA) has been developed as a highly useful synthetic transformation. ATRA allows for efficient alkene or alkyne difunctionalization, typically through the use of radical initiators or transition metal catalysts.[2] Recent efforts have been aimed at replacing and improving these conventional radical initiator systems[3] with the eventual goal of developing an ATRA protocol with broad generality and scalability under mild conditions. We hypothesized that it would be possible to utilize visible light-active photocatalysts[4,5] to develop an ATRA protocol with the following features: simple reaction setup, mild reaction conditions, minimal side reactions, optimal catalytic efficiency, and straightforward purification.

Recently, we realized our goal of performing ATRA between activated halides and alkenes utilizing visible light photocatalysis.[6] This ATRA protocol provided high yields under mild reaction conditions. In terms of substrate scope, only activated bromides and iodides were susceptible to the reaction conditions, and reaction times varied from 6 to 48 h to achieve high conversions. In addition, the protocol was restricted to nonconjugated terminal olefins. Herein, we report the realization, the development, and the recent advancements of visible light-mediated photocatalytic ATRA in terms of the photocatalysts, substrates, and solvents (Figure 1). In particular, a remarkably efficient iodoperfluoroalkylation is presented as a viable alternative to classical methods to introduce perfluorinated tags onto alkenes and alkynes. Collectively, these results demonstrate that both reductive quenching, which can be achieved in the presence of an external electron donor, and oxidative quenching of photocatalysts can effectively be utilized for ATRA transformations. Furthermore, the possibility of radical chain propagation[1c] possessing productive termination events is presented as a probable parallel mechanism (Figure 2).

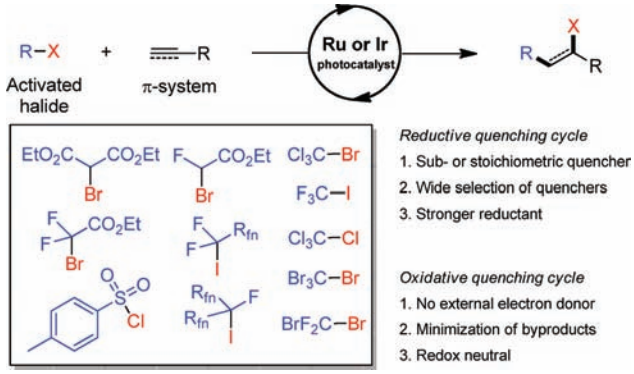


Figure 1. Scope and features of visible light-mediated ATRA.

RESULTS AND DISCUSSION

Initial Observation of Visible Light-Mediated ATRA.

The utilization of the oxidative quenching of $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**1**) for ATRA was prompted by earlier observations of ATRA products using the reductive quenching of $[Ru(bpy)_3]Cl_2$ (**2**) and $[Ir(ppy)_2(dtbbpy)]PF_6$ (**3**) (Figure 3).

Recently, we reported a reductive intramolecular radical cyclization of alkyl bromides onto unactivated π-systems,

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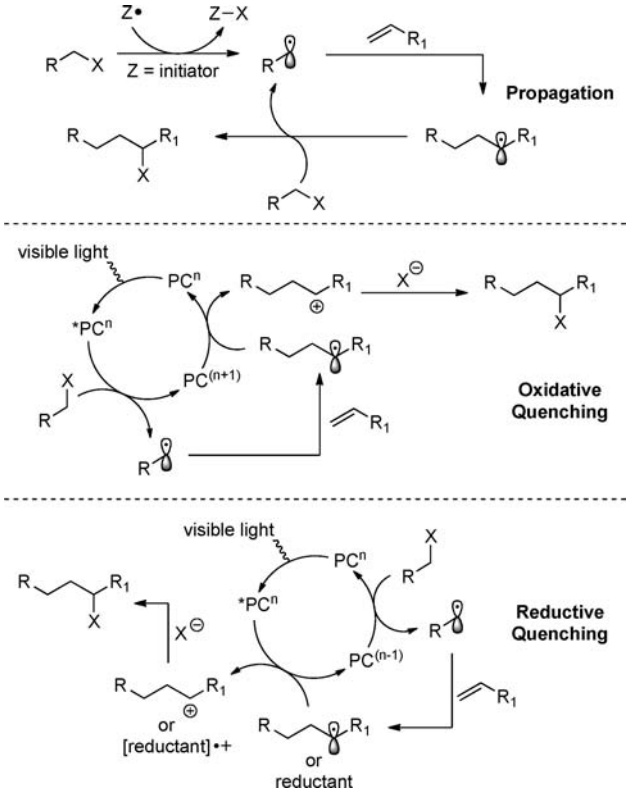


Figure 2. Mechanistic pathways toward ATRA.

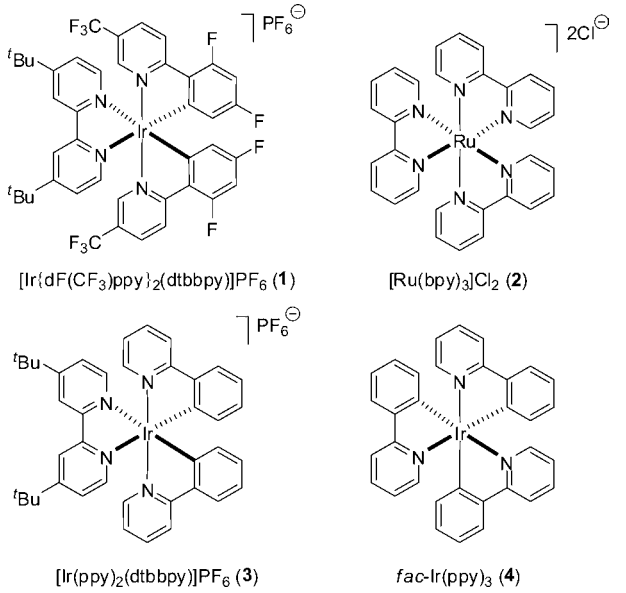
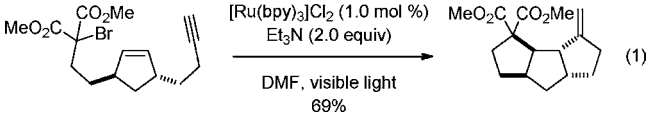


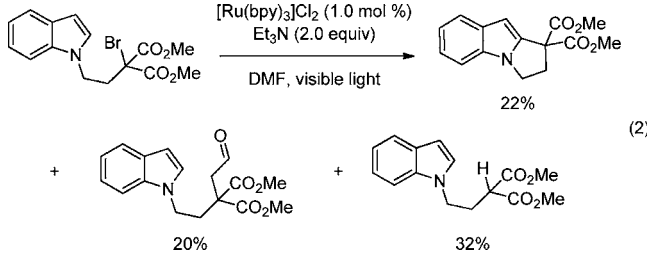
Figure 3. Photocatalysts commonly used for organic synthesis.

exemplified by the cascade radical cyclization in eq 1.[7] The reductive quenching of **2** and **3** using Et_3N as a stoichiometric



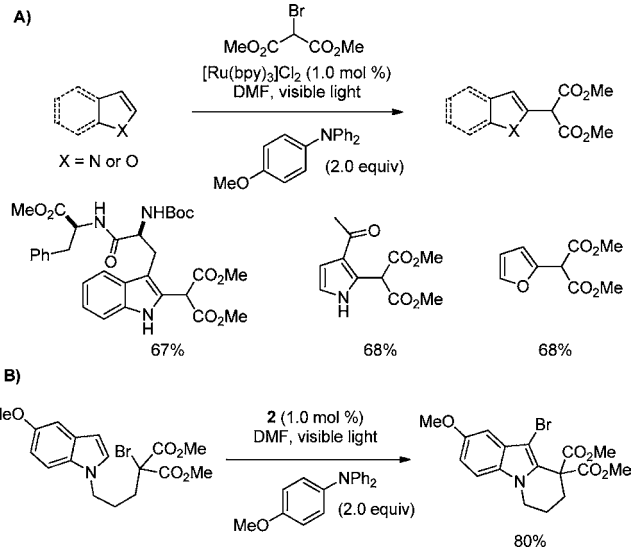
electron donor was found to provide cyclized products in good to excellent yields. However, only substrates containing an activated C−Br bond, such as bromomalonate derivatives, were susceptible to these conditions. In addition to this limitation, the protocol was shown to be restricted to intramolecular transformations when employing tertiary amines containing α-C−H bonds as electron donors.

For intermolecular reactions and unfavorable intramolecular cyclizations, the desired C−C coupling products are kinetically disfavored, as compared to hydrogen abstraction and enamine coupling, the two most prominent side reactions. Amines, such as Et_3N, produce ammoniumyl radical ions upon single electron oxidation. These radical cations are excellent hydrogen atom donors that can give rise to dehalogenated byproducts as illustrated by the formation of the reduced malonate derivative in eq 2. Furthermore, subsequent formation of iminium ions and enamines provides other nonproductive reaction pathways, as is evident from the acetaldehyde byproduct shown in eq 2.[8]



These shortcomings were successfully addressed using 4-methoxy-*N*,*N*-diphenylaniline (4-MeO-C_6H_4-NPh_2), an electron-rich aromatic amine lacking α-C−H bonds, as an electron donor for the efficient intermolecular C−H functionalization of indoles, pyrroles, and furans (Scheme 1A).[9] Although we were

Scheme 1. Utilizing 4-MeO-C_6H_4-NPh_2 as an Electron Donor



able to circumvent the issues highlighted by eq 2 using a mechanism-based analysis, the use of such amines is not ideal, because they are expensive and used in superstoichiometric quantities. In addition, their generality with respect to catalysts, solvents, and substrate scope appears to be limited.

While investigating the use of 4-MeO-C_6H_4-NPh_2 as an electron donor, we isolated an ATRA product while performing a 6-*exo*-trig cyclization of a bromomalonate derivative onto a tethered indole moiety as depicted in Scheme 1B. Even though

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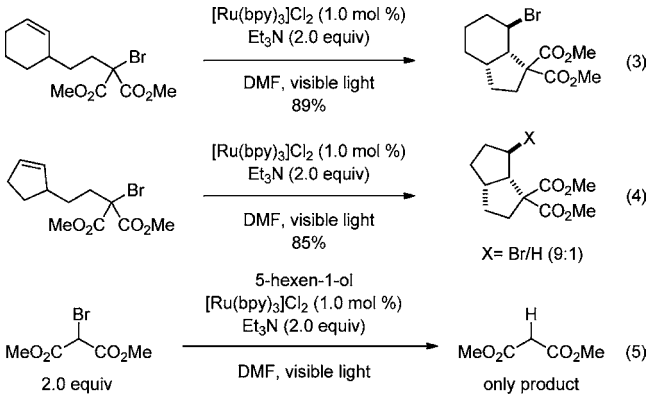
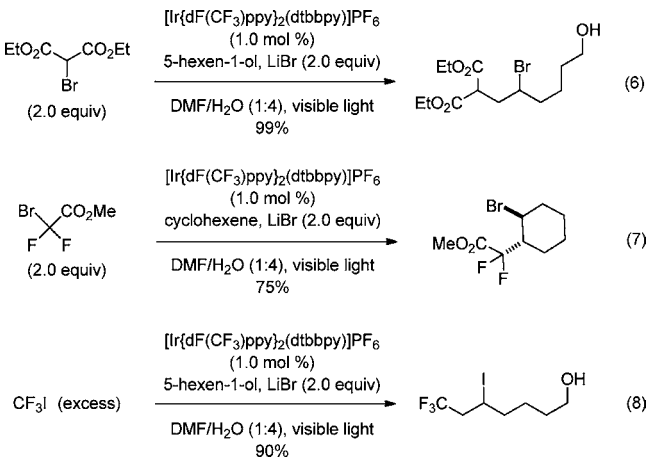
the mechanism for this transformation is still elusive, we realized that ATRA products could be obtained by means of our photocatalytic approach toward general C−C coupling reactions.

Visible Light-Mediated ATRA. We were pleased when we applied our visible light photoredox catalysis conditions and exclusively isolated the ATRA product from an intramolecular cyclization that provided a bromo bicyclo[4.3.0]nonane derivative (eq 3). The reaction was found to be very substrate



dependent and preferentially gave the cyclization−reduction product with terminal alkenes and alkynes, as illustrated in eq 1. The strong substrate dependence is emphasized by the reaction of the closely related cyclopentene substrate that gave a 9:1 mixture of a bromo bicyclo[3.3.0]octane derivative and the cyclization−reduction product, respectively (eq 4). Not surprisingly, all attempts to perform the intermolecular ATRA with these conditions resulted only in dehalogenation of starting material (eq 5).

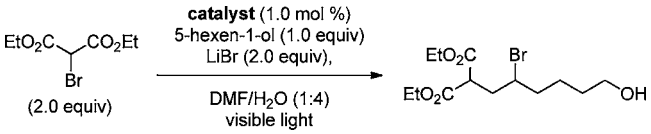
To avoid the problems associated with the use of stoichiometric amine electron donors, we opted to exploit the oxidative quenching of **1**.[10] In this case, the excited state of **1** would serve as the active single electron reductant, thereby eliminating the need for a sacrificial electron donor. With this strategy, we managed to conduct intermolecular ATRA reactions (eq 6−8) between various activated haloalkanes and



unactivated alkenes in high yields without detection of the reduced product. Of particular significance was the successful trifluoromethylation of terminal alkenes, because CF_3I (−1.52 V vs SCE)[11] appears difficult to reduce with the excited state of **1** (Ir^{4+}/Ir^{3+}* = −0.89 V vs SCE)[12] based solely upon the comparison of redox potentials (eq 8).[13] The protocol is characterized by mild conditions, high yields, and broad functional group tolerance.[6] Encouraged by the success of this atom transfer protocol, we sought to improve the overall conditions and expand the method to encompass a broader substrate scope.

Catalyst, Solvent, and Substrate Screening. Our first effort to improve the atom transfer protocol involved a more comprehensive screen of photocatalysts. Utilizing the conditions optimized for the intermolecular ATRA between diethyl bromomalonate and 5-hexen-1-ol with $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (**1**), we screened $[Ru(bpy)_3]Cl_2$ (**2**), $[Ir(ppy)_2(dtbbpy)]PF_6$ (**3**), and *fac*-$Ir(ppy)_3$ (**4**). The photocatalysts **2** and **3** both provided full consumption of starting material and high yields of the product after 24 h, although **2** provided slightly higher yields than **3**. On the contrary, the use of photocatalyst **4** resulted in incomplete consumption of the starting material, possibly due to the low solubility of **4** in the DMF/H_2O solvent system (Table 1). For reasons associated with accessibility and lower cost of **2** as compared with **1**, we chose to proceed with further studies employing photocatalyst **2**.[14]

Table 1. Catalyst Screening[a]



entry	catalyst	yield (%)[b]
1	none	0
2	**1**	99
3	**2**	99
4	**3**	93
5	**4**	35

[a]24 h reaction time. [b]Isolated yield (%) after purification by chromatography on SiO_2.

The generality of the atom transfer protocol was then evaluated with respect to the solvent (Table 2). Highly polar solvents such as DMSO, hexafluoroisopropanol (HFIP), MeCN, and H_2O all provided the atom transfer of diethyl bromomalonate onto 5-hexen-1-ol cleanly and in high yields (Table 2, entries 1−5). In particular, DMSO afforded full consumption of the starting material in the shortest time frame (Table 2, entry 2). Although MeOH did provide the desired product, the crude reaction mixture gave partial transesterification of the product, which resulted in a lower isolated yield of the desired product (Table 2, entry 9). Less polar solvents such as THF, EtOAc, and DCM typically gave complex reaction mixtures and lower yields; longer reaction times did not increase the yields significantly (Table 2, entry 6−8). With DMSO as the solvent, we observed that lowering the loading of the halogenated coupling partner from 2.0 to 1.2 equiv and LiBr from 200 to 10 mol % only slightly increased the reaction time but did not lower the yield (Table 2, entry 14). These new optimized conditions offer several advantages when compared to the original conditions: a nearly equimolar ratio of alkene and atom transfer coupling partner, a photocatalyst that is commercially available and more cost efficient to synthesize, reduced loading of Lewis acid additive to substoichiometric quantities, and a solvent system capable of overcoming most solubility issues. To evaluate the improved

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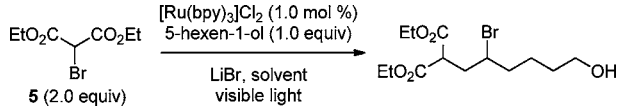
Table 2. Solvent Screening

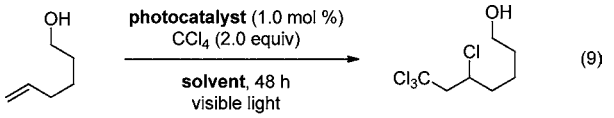


entry	solvent	5 (equiv)	LiBr (mol %)	time (h)	yield[a] (%)
1	DMF/H_2O (1:4)	2.0	200	10	99
2	DMSO	2.0	200	6	99
3	HFIP	2.0	200	7	93
4	MeCN	2.0	200	20	95
5	H_2O	2.0	200	7	95
6	THF	2.0	200	20	74
7	EtOAc	2.0	200	24	47[b]
8	DCM	2.0	200	24	28[b]
9	MeOH	2.0	200	12	72
10	DMSO	2.0	100	6	98
11	DMSO	2.0	50	6	96
12	DMSO	2.0	10	7	95
13	DMSO	1.5	10	7	94
14	DMSO	1.2	10	8	98

[a]Isolated yield (%) after purification by chromatography on SiO_2. [b]Full consumption of starting material not observed.

reaction conditions (1.0 equiv of alkene, 1.2 equiv of atom transfer agent, 10 mol % LiBr for α-bromo carbonyls, 2 mL DMSO/mmol alkene, and 1.0 mol % **2**) in terms of the substrate scope, we repeated several of our previously published coupling reactions. We observed that yields were comparable and, in some cases, even higher with our newly developed reaction conditions (Table 3).

In an effort to further broaden the substrate scope and thus achieve a high degree of generality of the ATRA protocol, we revisited substrates that were not compatible with our original conditions. Specifically, utilizing the oxidative quenching cycle of **1**, we were previously unable to effect the atom transfer onto styrene derivatives and 1,2-disubstituted alkenes (with the exception of cyclohexene in eq 7). In addition, we failed to couple CCl_4 to any of the olefins (eq 9), even though the



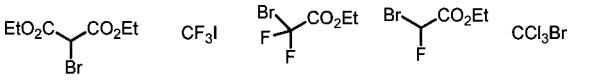
(9)

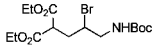
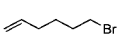
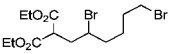
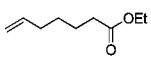
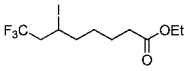
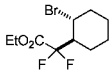
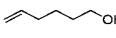
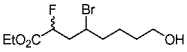
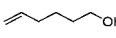
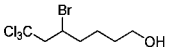
DMF/H_2O (1:4), [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$	No reaction
DMF/H_2O (1:4), [Ru(bpy)$_3$]Cl$_2$	No reaction
DMSO, [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$	82%
DMSO, [Ru(bpy)$_3$]Cl$_2$	24%

excited state reduction potential of **1** (Ir^{4+}/Ir^{3+*} = −0.89 V vs SCE)[12] should be sufficient to reduce CCl_4 (−0.78 V vs SCE).[15] We began this portion of our investigation using norbornene and β-pinene, because these strained alkenes are known to be more reactive than cyclohexene.[16]

Utilizing our originally optimized conditions, the ATRA of CCl_3Br to norbornene was sluggish, partly attributable to the low solubility of norbornene in DMF/H_2O. However, the newly optimized conditions utilizing DMSO and **2** provided a homogeneous reaction mixture and the atom transfer addition product in high yield (Scheme 2). Dibromodifluoromethane (CF_2Br_2)[17] and 4-toluenesulfonyl chloride (TsCl) with norbornene also provided the corresponding ATRA products in high yields, but the ATRA product of CCl_4 and norbornene

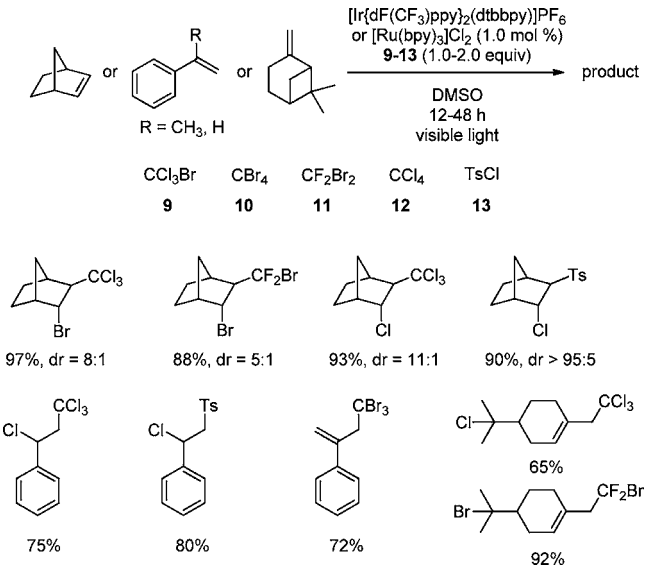
Table 3. ATRA Using Photocatalysis[a]



entry	RX	olefin	product	yield(%) with **1**[b,d]	yield(%) with **2**[c,d]
1	**5**			99	99
2	**5**			92	94
3[e,f]	**6**			81	90
4	**7**			75	88
5[g]	**8**			99[c]	99[c]
6[e]	**9**			87	95

[a]24 h reaction time unless otherwise noted. [b]Reactions conducted using 1.0 mol % **1**, 2.0 equiv of haloalkane or haloester, and 2.0 equiv of LiBr in H_2O/DMF (4:1). [c]Reactions conducted using 1.0 mol % **2**, 1.2 equiv of haloalkane or haloester, and 10 mol % of LiBr in DMSO. [d]Isolated yield (%) after purification on SiO_2. [e]No LiBr added. [f]48 h reaction time. [g]dr 1:1.

Scheme 2. Expansion of Photocatalytic ATRA via Oxidative Quenching[18]



could only be achieved in high yield when **1** was utilized in combination with the new conditions. We speculated that the successful atom transfer of CCl_4 onto norbornene was due to a combination of the inherent strain energy of norbornene and its increased solubility in DMSO. However, we subsequently observed the successful coupling of CCl_4 and 5-hexen-1-ol with either **1** or **2** in DMSO (eq 9), whereas neither catalyst gave the

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ATRA product in the DMF/H_2O solvent system in which solubility was not an issue. This indicates that DMSO is not only superior to the DMF/H_2O solvent system with regard to solubility but also with regard to promoting the ATRA process. In addition to norbornene, β-pinene, styrene, and α-methyl styrene were also successful coupling partners with several halogenated compounds; however, high yields for the ATRA of CCl_4 required the use of **1** rather than **2** in all cases (Scheme 2).

Motivated by our successful enhancement of the ATRA protocol, we next sought to develop a fluorous tagging protocol of alkenes and alkynes utilizing perfluoroalkyl iodides that would rival known protocols in terms of efficiency (reaction time and yield), mild reaction conditions, and functional group tolerance.

Introduction to Fluorous Tagging. The fluorous biphasic concept[19] was introduced to the field of organic synthesis in the mid-1990s, and since then, the special properties of perfluorinated carbons have been innovatively utilized for the synthesis of small molecules.[20] The introduction of perfluorinated tags in conjunction with solid-phase extraction (F-SPE) by Curran and co-workers[21] made an especially crucial impact on both industrial and academic research in the context of conventional, parallel, and combinatorial syntheses.[22,23] By temporary attachment or permanent affixation of a perfluorinated alkyl chain to reagents or reactants, product isolation in reactions that typically have been tedious and laborious are now promptly performed by either multiphasic solvent systems or by SPE techniques, utilizing either heavy (>60% fluorine by weight) or light (<40% fluorine by weight) perfluorous molecules, respectively. Even though several perfluorinated compounds of various sizes are commercially available, the development of novel methods for efficient and selective introduction of fluorinated motifs is a growing area of interest because of the expansion of its applications within the research fields of medicinal, synthetic, industrial, and agricultural chemistry.[24]

Perfluorinated motifs can be incorporated both under stoichiometric[25] and catalytic[26] conditions. Addition reactions of perfluoroalkyl iodides to alkenes and alkynes represent one of the most common means to synthesize fluorous compounds. This type of transformation can be accomplished photochemically (UV), thermally (>200 °C), electrochemically, or through a redox active system.[27] During our investigation of visible light-mediated ATRA of activated halides across double bonds utilizing the oxidative quenching catalytic cycle of **1**, we managed to access trifluoromethylated alkanes in high yields (Table 3, entry 3 and eq 8). However, a large excess of CF_3I, high boiling solvents (DMF or DMSO), and long irradiation times (48 h) were required for high conversions. These disadvantages encouraged us to further develop and expand our ATRA protocol within the field of fluorous chemistry (Figure 4).

A General Iodoperfluoroalkylation of Alkenes and Alkynes. Initially, we sought to apply the optimized conditions for the ATRA (Table 3, entry 3), mediated by the oxidative quenching of **1** or **2**, to the ATRA of a variety of perfluoroalkyl iodides. It is well-known that longer chain perfluoroalkyl iodides are more easily reduced (less negative reduction potentials) than CF_3I.[28] Therefore, we reasoned that the oxidative quenching of **1** and **2** would promote the ATRA of perfluoroalkyl iodides such as $C_8F_{17}I$ with high efficiency. Surprisingly, no conversion was observed after 24 h when

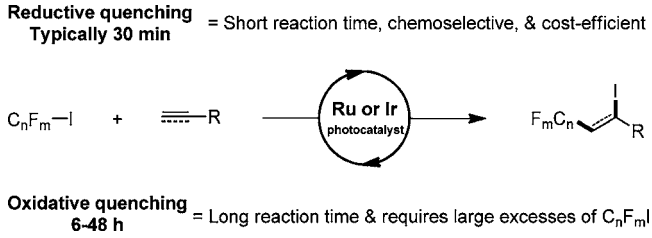
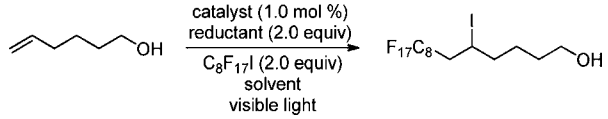


Figure 4. Photoredox-mediated ATRAs have been extended to perfluoroalkyl iodides onto alkenes and alkynes utilizing the reductive quenching cycle of $[Ru(bpy)_3]Cl_2$.

Table 4. Optimization of Reaction Conditions



entry	cat.	solvent	reductant	time (h)	yield[g] (%)
1	**1**	DMF		24	N.R.
2[a]	**2**	DMSO		5	95
3	**4**	DMF		216	43
4	**2**	MeCN	H.E.[f]	5	10
5	**2**	MeCN	$^iPr_2NEt$	5	73
6	**2**	MeCN	Bu_3N	5	58
7	**2**	MeCN	Na-ascorbate	5	25
8[b]	**2**	MeCN	Na-ascorbate	1.5	99
9	**2**	MeCN/MeOH[e]	Na-ascorbate	0.5	91
10[c]	**2**	MeCN/MeOH[e]	Na-ascorbate	0.5	99
11[d]	**2**	MeCN/MeOH[e]	Na-ascorbate	0.5	67

[a]Reaction conducted using $C_8F_{17}I$ (1.2 equiv). [b]Hexadecyltrimethylammonium bromide used as an additive. [c]1.3 equiv of perfluoroalkyl iodide and 0.35 equiv of sodium ascorbate were used. [d]1.3 equiv of perfluoroalkyl iodide and 0.05 equiv of sodium ascorbate were used. [e]4:3 mixture. [f]H.E. = Hantzsch ester (diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate). [g]Isolated yield (%) after purification by chromatography on SiO_2.

$C_8F_{17}I$ (−1.32 V vs SCE) and 5-hexen-1-ol were reacted with photocatalyst **1** (Table 4, entry 1). We then turned to our newly improved conditions utilizing **2** in DMSO, which generated the desired product in 95% yield within 5 h (Table 4, entry 2). However, we continued screening conditions with the expectation that we could lower the reaction time while maintaining high yields by using a catalyst with a stronger reducing capacity. When employing photocatalyst **3**, which has a much stronger excited state reduction potential (−1.73 V vs SCE) than **1** or **2**,[29] the desired product was isolated in only 43% yield after 9 days (Table 4, entry 3). These unsatisfactory results led us to revisit the reductive quenching cycle of **2**. Initially, we were uncertain about relying on the reductive quenching cycle due to the issues of prominent side reactions (vide supra). Nevertheless, the advantages of using **2** as the photocatalyst include its low cost and the relatively strong reductive power of $[Ru(bpy)_3]^+$ (−1.33 V vs SCE).[30]

Prompted by this reassessment, we screened various stoichiometric reductants for **2** (Table 4, entries 4−7), and the desired product was isolated in yields ranging from 10 to 73% after 5 h of irradiation. We observed low solubility of sodium ascorbate[31] in acetonitrile and consequently found that the addition of either a phase transfer catalyst, such as hexadecyltrimethylammonium bromide, or the use of MeOH as cosolvent led to significant improvements in both yield and

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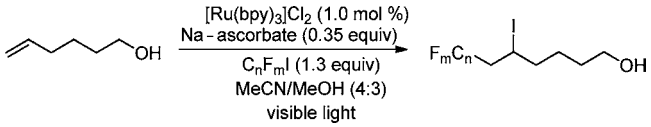
reaction time (Table 4, entries 8–9). Thorough optimization of the reaction conditions provided a 99% yield in just 0.5 h (Table 4, entry 10). The efficiency of the reaction was preserved in other polar solvents and was diminished in less polar solvents. No product formation was observed in the absence of catalyst or a visible light irradiation source.[32]

After the successful intermolecular ATRA of $C_8F_{17}I$ onto 5-hexen-1-ol, the reaction scope toward structurally diverse perfluoroalkyl iodides was examined. As expected, high to excellent yields were obtained for various perfluoroalkyl iodides (Table 5) with a small decrease in yield for shorter $C_6F_{13}I$

Table 5. ATRA of Various Perfluoroalkyl Iodides



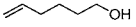
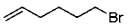
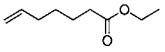
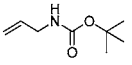
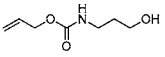
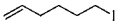
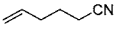
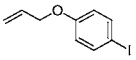
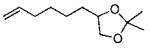
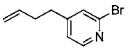
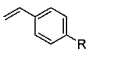
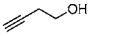
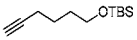
entry	substrate	time (h)	yield (%)[c]
1[a]	CF_3I	48	90
2[b]	$C_6F_{13}I$	0.5	81
3	$C_8F_{17}I$	0.5	99
4	$C_{10}F_{21}I$	0.5	97
5	$(CF_3)_2CFI$	0.5	81

[a]See eq 8. [b]2.0 equiv of both perfluoroalkyl iodide and reductant were used. [c]Isolated yield (%) after purification by chromatography on SiO_2.

(Table 5, entry 2) and branched $(CF_3)_2CFI$ (Table 5, entry 5). A plausible explanation for this drop in yield for $C_6F_{13}I$ is that shorter perfluoroalkyl iodides have a more negative reduction potential. In the case of $(CF_3)_2CFI$, the drop in yield probably stems from steric effects rather than redox properties.[33]

The scope and functional group compatibility of the optimized conditions of the intermolecular ATRA between $C_8F_{17}I$ and various terminal alkenes and alkynes were also evaluated (Table 6). In general, yields were high to excellent for a wide variety of substrates with the exception of styrene derivatives. Although the addition of perfluoroalkyl radicals onto styrene derivatives has been performed using radical initiators,[34] electron neutral, poor, and rich styrenes all produced complex reaction mixtures from which the corresponding product could not be isolated (Table 6, entry 11). Side reactions, such as polymerization, might arise from reduction or oxidation of either product or alkene starting material by the catalyst. However, nonconjugated alkenes substituted with electron-deficient aromatics, such as 2-bromo-4-(but-3-en-1-yl)pyridine (Table 6, entry 10), as well as alkenes substituted with nonconjugated electron-rich aromatics (Table 6, entry 8) afforded the product in high yields. Of significant importance is that both aromatic and alkyl bromides and iodides are compatible with these mild reaction conditions (Table 6, entries 2, 6, 8, and 10). Alkenes containing allylic *N*- and *O*-carbamate functionalities, frequently utilized as fluorous-tagged protecting groups for amines and alcohols, gave high to excellent yields, as did acetals (Table 6, entries 4, 5, and 9). Multigram scale reactions were performed without a significant decrease in yields within the optimized reaction time of 0.5 h (Table 6, entries 1 and 10). Furthermore, on a large scale (40 mmol), only 0.01 mol % of **2** was needed to obtain a yield of 96% for ATRA with $C_8F_{17}I$ and 5-hexen-1-ol.[35] Alkynes are also suitable partners in this ATRA protocol. However, the optimized conditions that provided exclusive ATRA products

Table 6. Substrate Scope

entry	substrate	t (h)	yield (%)[g]
1		0.5	99 (96%)[a]
2		0.5	93
3		0.5	94
4		0.5	96
5		0.5	79
6		0.5	94
7		0.5	90
8		4	99
9		0.5	91[b]
10		2	88 (85%)[c]
11	 R = H, OMe, C(O)OEt, PPh_2, $POPh_2$	0.5 - 24	0[d]
12		0.5	96[e]
13		0.5	94[f]

[a]Yield in parentheses is for a preparative reaction (4.0 g, 40 mmol) using 0.010 mol % catalyst. [b]1:1 dr. [c]Yield in parentheses is for a preparative reaction (1.6 g, 7.5 mmol) using 0.10 mol % catalyst. [d]Partial consumption of starting material. For all substrates, a complex reaction mixture was obtained, or the targeted product was unstable and thus not successfully isolated. [e]1.8:1 dr. [f]2:1 dr. [g]Isolated yield (%) after purification by chromatography on SiO_2.

for alkenes gave significant quantities of reduced byproducts for all alkynes investigated. This problem was successfully addressed by changing the solvent system from MeCN/MeOH to *t*-BuOH/H_2O providing the corresponding perfluorovinyl iodides in high yields (Table 6, entries 12 and 13). Assuming that propagation is a nonactive mechanistic component (vide infra), the turnover number (TON) of the catalyst is $\sim 10^4$, and the turnover frequency (TOF) is >5.3 s^{-1}.

The high efficiency and broad functional group compatibility of this system prompted an investigation of its potential for the strategic introduction of perfluorinated tags in the synthesis of structurally complex molecules. Curran and co-workers introduced the concept of fluorous scavenging to facilitate small molecule synthesis as a general strategy for product isolation.[36] Similarly, post-transformational introduction of perfluorinated tags to alkene-functionalized protecting groups or reagents via the present protocol would circumvent possible solubility issues and/or other impeding properties imposed by perfluorinated tags. In addition, this method also provides the possibility to tune the fluorous nature of substrates and catalysts. The validity of this hypothesis was evaluated by

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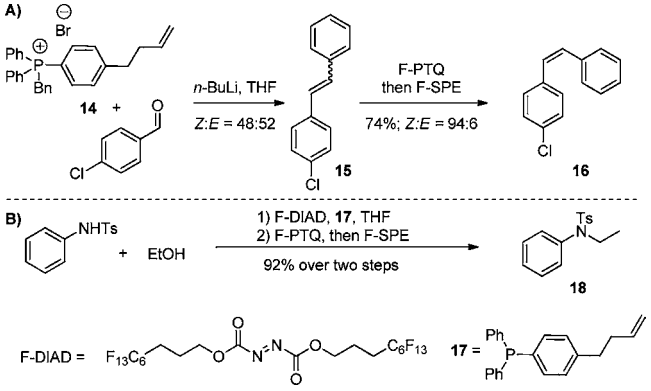
fluorous post-transformational quenching (F-PTQ) of alkene-functionalized phosphine reagents in both Wittig (Scheme 3A)

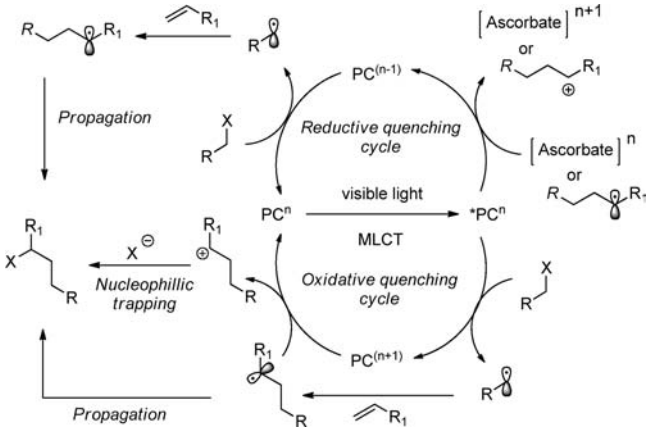
Scheme 3. Fluorous Post-Transformational Quenching



and Mitsunobu reactions (Scheme 3B). Both transformations are known to produce byproducts that are problematic during product isolation. Several strategies have been employed to address this issue,[37] including fluorous techniques,[38] which suggested that they would be suitable test systems for the evaluation of the general applicability of this protocol. For the Wittig reaction, phosphonium salt **14** was treated with *n*-BuLi, followed by *p*-chlorobenzaldehyde, providing a crude reaction mixture consisting of stilbene derivative **15** and a phosphine oxide functionalized with a terminal alkene. Subjecting the crude reaction mixture to F-PTQ with a prolonged irradiation time, followed by F-SPE,[32] allowed for the isolation of the pure product **16** in 74% yield (94:6 dr). As a consequence of excited state quenching (energy transfer) of the catalyst by the stilbene derivative, a longer reaction time was needed for full consumption of the phosphine oxide. In addition, because the (*E*)-stilbene has a smaller HOMO−LUMO gap than (*Z*)-stilbene, the excited state quenching also explains the high diastereoselectivity toward the (*Z*)-diastereoisomer.[39] For the Mitsunobu reaction, *N*-tosylaniline and EtOH were treated with phosphine **17** and fluorous-tagged DIAD (F-DIAD) providing a crude reaction mixture consisting of product **18**, excess phosphine **17**, phosphine oxide from **17**, excess F-DIAD, and fluorous tagged hydrazine. The crude mixture was once again subjected to F-PTQ to tag the excess phosphine and phosphine oxide. After 2.5 h, the reaction was subjected to F-SPE to provide the pure product in 92% yield.

Discussion of Plausible Reaction Mechanisms. Both the reductive and the oxidative quenching cycles are initiated by activation of the photocatalyst by visible light absorption to produce the ^{3}MLCT state of the catalyst (Scheme 4). In the presence of an electron donor, the excited state is reductively quenched providing a reduced catalyst ($*PC^n/PC^{n-1}$, PC = photocatalyst). For the fluorous tagging protocol, $*[Ru(bpy)_3]^{2+}$ is reduced to $[Ru(bpy)_3]^+$ using sodium ascorbate as the electron donor. $[Ru(bpy)_3]^+$ has a sufficiently strong reduction potential (−1.33 V vs SCE) to effectively convert perfluoroalkyl iodides (−1.0 to −1.5 V vs SCE) to electrophilic free radicals. The radical then undergoes addition to the alkene or alkyne. The ATRA product can subsequently be formed via two different routes: either by propagation or by oxidation to the cation followed by nucleophilic trapping in accordance with the oxidative quenching pathway as outlined in Scheme 4. The oxidation potential of secondary radicals (0.47 V vs SCE)[40]

Scheme 4. Proposed Mechanism for Photocatalytic ATRA



renders them prone to oxidation by the photocatalyst, consequently initiating another catalytic cycle. Nucleophilic trapping with iodide, possibly preassociated as a counterion to the catalyst, provides the ATRA product. For ATRA using classical radical initiators, propagation has been shown to be an operative mechanism and can also be a viable mechanistic component in this catalytic system. For either route, sodium ascorbate acts only as an initiator to provide the initial $[Ru(bpy)_3]^+$ species. This is corroborated by the fact that only small amounts of sodium ascorbate (0.05 mol %) are needed for nearly complete consumption of the starting material (Table 4, entry 11).

In the redox neutral oxidative quenching pathway, the photocatalyst reduces the halogenated substrate directly from its excited state to produce an oxidized photocatalyst ($*PC^n/PC^{n+1}$) and an electrophilic radical that undergoes addition to an alkene. The addition produces a radical that can be oxidized to a carbocation by the catalyst to complete the catalytic cycle and subsequently generate the product by nucleophilic trapping of a halide, or the radical can participate in a propagation chain to also produce the ATRA product.

Our previous report,[6] as well as new experimental evidence, provides support for the radical-polar crossover[41] mechanism proposed for the oxidative quenching of photocatalysts (Scheme 4). When the ATRA of diethyl bromomalonate (1.2 equiv) was performed with 4-penten-1-ol, LiBr (1.2 equiv), and $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (1.0 mol %) in DMF/H_2O, the tetrahydrofuran byproduct **20** was isolated in 10% yield (Scheme 5A). When the atom transfer product **19** is resubjected to the reaction conditions or refluxed in toluene, the formation of **20** is not observed. In addition, the treatment of **19** with base generated cyclopropane **21** as the only product. These observations strongly indicate that **20** is not generated from **19** but rather from the nucleophilic trapping of a carbocation intermediate by the tethered alcohol. Further support for a radical-polar crossover mechanism was obtained through an intermolecular trapping experiment in which carbon tetrachloride (2.0 equiv) and 5-hexen-1-ol were subjected to the newly developed conditions, using $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (1.0 mol %) and DMSO in the presence of excess KBr (2.5 equiv) (Scheme 5B). After 24 h of irradiation, a mixture of the corresponding chloride and bromide ATRA products, **22** and **23**, respectively, was isolated in 35% yield in a 2.5:1 molar ratio favoring the chloride product **22**. Neither the resubjection of **22** to the reaction conditions nor the presence of 18-crown-6 to increase the nucleophilicity

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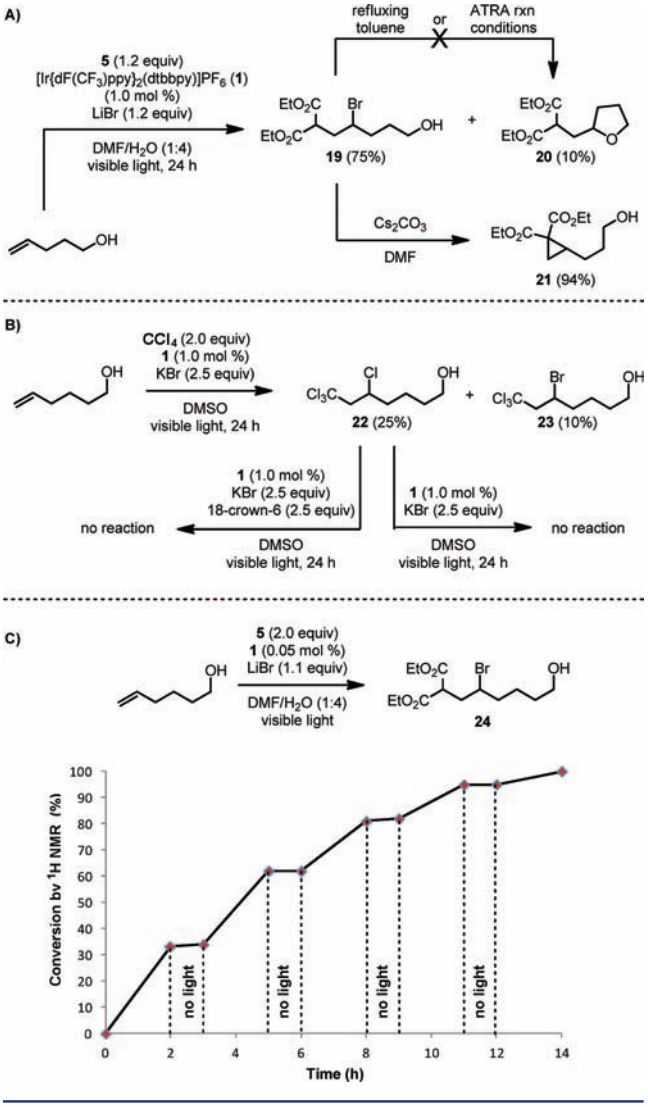
Scheme 5. Evidence for a Radical-Polar Crossover Mechanism

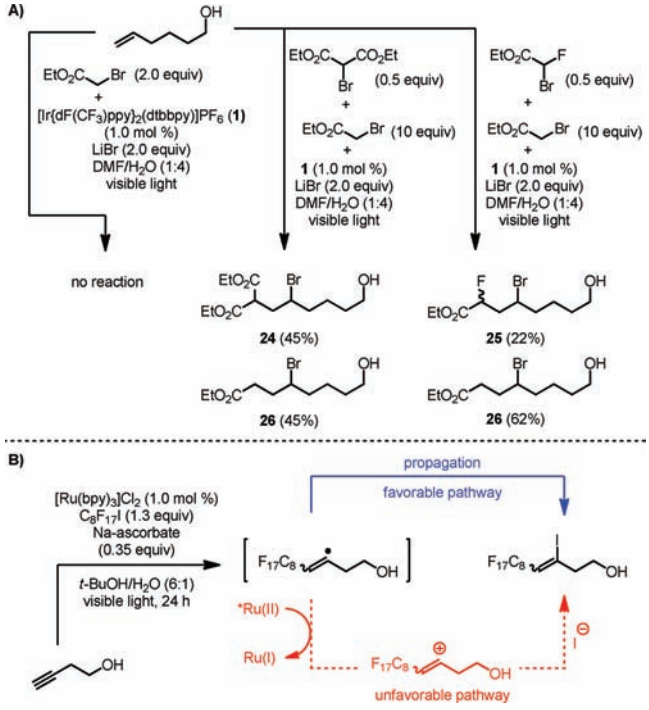


of bromide produced detectable amounts of **23**, which further suggest that the formation of **23** is the result of nucleophilic trapping rather than a displacement reaction of the secondary chloride of **22** with bromide.

In addition to the trapping investigations, we performed an experiment designed to verify the necessity of light to maintain the ATRA reaction. A mixture of diethyl bromomalonate (2.0 equiv), 5-hexen-1-ol, LiBr (1.1 equiv), and [Ir{dF(CF_3)-ppy}$_2$(dtbbpy)]PF_6 (0.05 mol %) in DMF/H_2O was stirred for 14 h, alternating between 2 h periods of visible light irradiation and 1 h periods of complete lack of visible light irradiation until consumption of 5-hexen-1-ol was judged to be complete (Scheme 5C). It was observed that the reaction progressed steadily with visible light irradiation, but consumption of the alkene abruptly stalled when the light source was removed. The results of this experiment neither definitively confirm a radical-polar crossover mechanism nor definitively negate a radical chain propagation mechanism, although it is clear that visible light is a necessary component of the reaction. However, if propagation is an active mechanistic component, it is evident that the propagating chain reactions are short-lived. Therefore, it is reasonable to assume that when using only 0.05 mol % of catalyst, regeneration of the catalyst via oxidation of an alkyl radical to an alkyl cation to initiate the short chain propagation is necessary for full consumption of the alkene. This oxidation constitutes closure of the catalytic cycle and serves as a productive formal termination step.

Although the intra- and intermolecular trapping experiments in combination with the indirect evidence obtained from the "light/dark" experiment provide strong evidence for a radical-polar crossover mechanism (vide supra), propagation cannot be ruled out as a competing parallel mechanism. To assess if propagation can be an active mechanistic pathway, we identified an effective probe for propagation, ethyl bromoacetate (Scheme 6A). Ethyl bromoacetate does not undergo ATRA via oxidative

Scheme 6. Evidence for Propagation Mechanism



quenching with our reaction conditions when **1** is utilized as the catalyst. Therefore, the addition of ethyl bromoacetate to a reaction mixture of ethyl bromofluoroacetate, **1**, 5-hexen-1-ol, LiBr, and DMF/H_2O should only lead to the formation of **25** if a radical-polar crossover mechanism is the only operative mechanism. However, if a propagation mechanism is operative, then it may be possible to observe the ATRA product of ethyl bromoacetate. In fact, the ATRA product of ethyl bromoacetate (**26**) was indeed obtained as a mixture with the ATRA product of ethyl bromofluoroacetate (**25**) in 84% yield as a 1:2.8 molar ratio favoring **26**. Similarly, adding ethyl bromoacetate to a reaction mixture of diethyl bromomalonate, **1**, 5-hexen-1-ol, LiBr, and DMF/H_2O gave a product mixture of **24** and **26** in 90% yield with a 1:1 molar ratio. These two experiments unambiguously demonstrate that propagation can occur when oxidative quenching of photocatalysts is utilized, although the differing product ratios illustrate the substrate dependence on the degree of propagation. An illustrative example in which propagation is most likely completely operative is the successful ATRA of perfluoroalkyl iodides onto alkynes. In this case, propagation is a much more likely reaction pathway than the

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thermodynamically unfavored oxidation of a vinyl radical to a vinyl cation (Scheme 6B).

A plausible mechanistic rationale for the oxidative quenching of **1** and **2** involves visible light-mediated initiation of a chain propagation that provides the ATRA product. Termination of the propagation via oxidation of the radical to the carbocation by the catalyst, thus completing a photocatalytic cycle, provides the ATRA product by nucleophilic trapping and also regenerates the ground state catalyst (PC^n). Therefore, the use of a photocatalyst as an initiator for ATRA contrasts with traditional radical initiators in that the termination process is a productive event. To which extent radical propagation or radical-polar crossover contribute to the overall yield is most likely highly dependent on the nature of the substrates and the conditions used (i.e., which catalyst and which solvents are employed) and if the reductive or oxidative quenching pathway is utilized.

Although both quenching pathways lead to the same product, there are essential differences worth noting. The reduction potentials for $*[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]^+$ and $*[Ru(bpy)_3]^{2+}$ are −0.89 and −0.86 V vs SCE, respectively, for oxidative quenching, whereas the reduction potential of $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]$ is −1.37 V vs SCE and −1.33 V vs SCE for $[Ru(bpy)_3]^+$ for reductive quenching. Because of the nature of these metal-centered complexes, the reduction potential for a photocatalyst when applying the oxidative quenching pathway is less negative than when utilizing the reductive quenching pathway. This is illustrated by the longer reaction times and the requirement of using Lewis acid additives (i.e., LiBr) when α-bromo carbonyls are used for ATRA via oxidative quenching. In this case, the Lewis acid coordination makes the carbon−halogen bond more prone to reduction and, therefore, to free radical formation.[6] In contrast, the reductive quenching cycle utilizes a reductive quencher to access a stronger reductant (PC^{n-1}) to achieve the reduction of the carbon−halogen bond without the need for a Lewis acid. This ability to effect the same transformation by carefully optimizing the reaction conditions for either oxidative or reductive quenching of a photocatalyst illustrates the complementary nature of the two quenching pathways.

CONCLUSION

During our pursuit to develop efficient reductive cyclization and intermolecular coupling reactions by means of visible light photocatalysis, we observed the formation of ATRA products. As a consequence of these observations, we realized that redox neutral coupling products might be obtained by our photocatalytic approach toward general C−C coupling reactions. The reductive quenching conditions optimized for reductive coupling and cyclization reactions with tertiary amines as stoichiometric electron donors did not produce efficient and general ATRA transformations. We consequently turned to the oxidative quenching pathway and successfully employed $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ in the photocatalytic ATRA between various activated halides and alkenes. Even though this protocol efficiently mediated the ATRA between terminal alkenes and activated alkyl bromides and iodides, the reaction conditions were not amenable to activated alkyl chlorides, 1,2-disubstituted alkenes, or styrene derivatives. However, these limitations were resolved by utilizing $[Ru(bpy)_3]Cl_2$ or $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ in DMSO instead of a DMF/H_2O mixture.

By utilizing the oxidative quenching cycle of the photocatalyst, reactions originating from sacrificial electron donors are avoided. However, this somewhat restricts the reductive ability of the catalyst and limits the substrate scope. These shortcomings were addressed successfully during the development of a highly efficient and mild protocol to effect fluorous tagging of both alkenes and alkynes. By utilizing sodium ascorbate as an inexpensive substoichiometric electron donor, we managed to bypass shortcomings associated with the use of tertiary amines as electron donors. The ATRA reaction has a broad functional group tolerance and is competent with structurally diverse perfluorinated alkyl iodides. Yields are high to excellent, and reaction times are typically 0.5 h. Furthermore, the capability of the protocol in post-transformational quenching was illustrated by fluorous tagging of an alkene-functionalized triphenylphosphine derivative in both Wittig and Mitsunobu reactions.

The development of ATRA via the oxidative and reductive quenching of photocatalysts has been firmly established as a reliable and versatile methodology. In particular, the ability to predictably direct the reaction outcome by careful selection and modification of the catalysts, additives, and solvents has been presented. Further investigations of photocatalytic ATRA and the synthetic applications of this methodology will be reported in due course.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectroscopic data of all new compounds, and a comprehensive description of reaction setup. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Kharasch, M. S.; Skell, P. S.; Fischer, P. *J. Am. Chem. Soc.* **1948**, *70*, 1055. (b) Curran, D. P.; Kim, D.; Ziegler, C. *Tetrahedron* **1991**, *47*, 6189. (c) Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* **2001**, *66*, 7776. (d) Weidner, G. K.; Giroult, A.; Panchaud, P.; Renaud, P. *J. Am. Chem. Soc.* **2010**, *132*, 17511.

(2) Muñoz-Molina, J. M.; Belderrain, T. M.; Pérez, P. J. *Eur. J. Inorg. Chem.* **2011**, *21*, 3155.

(3) (a) Baugley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3072. (b) Quebatte, L.; Thommes, K.; Severin, K. *J. Am. Chem. Soc.*

2006, *128*, 7440. (c) Eckenhoff, W. T.; Garrity, S. T.; Pintauer, T. *Eur. J. Inorg. Chem.* **2008**, *4*, 563. (d) Taylor, M. J. W.; Eckenhoff, W. T.; Pintauer, T. *Dalton Trans.* **2010**, *39*, 11475. (e) Fernández-Zúmel, M. A.; Buron, C.; Severin, K. *Eur. J. Org. Chem.* **2011**, *12*, 2272.

(4) For recent reviews on photoredox catalysis, see (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Teply, F. *Collect. Czech. Chem. Commun.* **2011**, *76*, 859. (c) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617.

(5) (a) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77. (b) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886. (c) DeClue, M. S.; Monnard, P. A.; Bailey, J. A.; Maurer, S. E.; Collis, G. E.; Ziock, H. J.; Rasmussen, S.; Boncella, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 931. (d) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756. (e) Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 10875. (f) Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 14604. (g) Koike, T.; Akita, M. *Chem. Lett.* **2009**, *38*, 166. (h) Borak, J. B.; Falvey, D. E. *J. Org. Chem.* **2009**, *74*, 3894. (i) Dai, C.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nature Chem.* **2011**, *3*, 140. (j) Pham, P. V.; Nagib, D. A.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 6119. (k) Ischay, M. A.; Lu, Z.; Yoon, T. P. *J. Am. Chem. Soc.* **2010**, *132*, 8572. (l) Andrews, S. R.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2010**, *49*, 7274. (m) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 1162. (n) Rueping, M.; Villa, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360. (o) Chen, Y.; Damlet, A. S.; Steinman, J. B.; Liu, D. R. *Nature Chem.* **2011**, *3*, 146. (p) Andrews, S. R.; Becker, J. J.; Gagné, M. R. *Org. Lett.* **2011**, *13*, 2406. (q) Larraufie, M. H.; Pellet, R.; Fensterbank, L.; Goddard, J. P.; Lacote, E.; Malacria, M.; Ollivier, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 4463. (r) Hurtley, A. E.; Cismesia, M. A.; Ischay, M. A.; Yoon, T. P. *Tetrahedron* **2011**, *67*, 4442. (s) Lu, Z.; Shen, M.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 1162. (t) Du, J.; Espelt, L. R.; Guzei, I. A.; Yoon, T. P. *Chem. Sci.* **2011**, *2*, 2115. (u) McNally, A.; Prier, C. K.; MacMillan, D. W. C. *Science* **2011**, *334*, 1114.

(6) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160.

(7) Tucker, J. W.; Nguyen, J. D.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Chem. Commun.* **2010**, *46*, 4985.

(8) Tucker, J. W.; Narayanam, J. M. R.; Krabbe, S. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 368.

(9) Furst, L.; Matsuura, B. S.; Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3104.

(10) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A., Jr.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712.

(11) Andrieux, C. P.; Gelis, L.; Medebielle, M.; Pinson, J.; Saveant, J. M. *J. Am. Chem. Soc.* **1990**, *112*, 3509.

(12) Incorrectly estimated to be −1.21 V vs SCE in ref 10.

(13) For the trifluoromethylation of arenes initiated by the reduction of CF_3SO_2Cl, see Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224.

(14) $[Ru(bpy)_3]Cl_2$ is synthesized in one step from $RuCl_3$ (5.0 g for $140.00 from Sigma Aldrich), whereas $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ is synthesized in three steps from $IrCl_3$ (5.0 g for $472.50 from Sigma Aldrich). Also, at the time of submission, the cost of 1.0 g of $[Ru(bpy)_3]Cl_2$ (Sigma Aldrich) was $74.10.

(15) Mitani, M; Kiriyama, T; Kuratate, T. *J. Org. Chem.* **1994**, *59*, 1279.

(16) Dunbar, R. C.; Hays, J. D.; Honovich, J. P.; Lev, N. B. *J. Am. Chem. Soc.* **1980**, *102*, 3951.

(17) For a recent difluoromethylation protocol initiated by $Zn(SO_2CF_2H)_2$, DFMS, see Fujiwara, Y; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *134*, 1494.

(18) Efficient ATRA of CCl_4 requires the use of catalyst **1**. In all other cases, the use of catalyst **1** typically gives comparable results within a shorter reaction time.

(19) Horvath, I. T.; Rabai, J. *Science* **1994**, *266*, 72.

(20) Gladysz, J. A.; Curran, D. P.; Horvath, I. T. *Handbook of Fluorous Chemistry*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2004.

(21) Curran, D. P. *Synlett* **2001**, 1488.

(22) Curran, D. P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1175.

(23) Curran, D. P.; Luo, Z. Y. *J. Am. Chem. Soc.* **1999**, *121*, 9069.

(24) (a) Filler, R.; Kobayashi, Y. *Biomedical Aspects of Fluorine Chemistry*; Kodansha Ltd.: Tokyo, 1982. (b) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (c) Kirsh, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; John Wiley & Sons: New York, 2004. (d) Uneyama, K. *Organofluorine Chemistry*; Blackwell Publishing Ltd.: Ames, IA, 2006.

(25) Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Stuart, A. M.; Wood, D. R. W. *Polyhedron* **1999**, *18*, 2913.

(26) (a) Kainz, S.; Koch, D.; Baumann, W.; Leitner, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 1628. (b) Xiao, J. L.; Chen, W. P.; Xu, L. J.; Hu, Y. L.; Osuna, A. M. B. *Tetrahedron* **2002**, *58*, 3889. (c) Sanford, M. S.; Loy, R. N. *Org. Lett.* **2011**, *13*, 2548.

(27) (a) Haszeldine, R. N. *J. Chem. Soc.* **1953**, 3565. (b) Hauptchein, M.; Braid, M.; Lawler, F. E. *J. Am. Chem. Soc.* **1957**, *79*, 2549. (c) Lu, X.; Ma, S.; Zhu, J. *Tetrahedron Lett.* **1988**, *29*, 5129. (d) Cirkva, V.; Ameduri, B.; Boutevin, B.; Kvicala, J.; Paleta, O. *J. Fluorine Chem.* **1995**, *74*, 97. (e) Ryu, I.; Kerimerman, S.; Niguma, T.; Minakata, S.; Komatsu, M.; Luo, Z.; Curran, D. P. *Tetrahedron Lett.* **2001**, *42*, 947. (f) Iizuka, M.; Yoshida, M. *J. Fluorine Chem.* **2009**, *130*, 926.

(28) Koshechko, V. G.; Kiprianova, L. A. *Theor. Exp. Chem.* **1999**, *35*, 18.

(29) Flamigni, L.; Barbieri, A.; Sabatini, C.; Ventura, B.; Barigelletti, F. *Top. Curr. Chem.* **2007**, *281*, 143.

(30) Kalyanasundaram, K. *Coord. Chem. Rev.* **1982**, *46*, 159.

(31) See ref 3d for the use of ascorbic acid as an electron donor to regenerate initiators.

(32) See the Supporting Information for details.

(33) Dolbier, W. R. *Chem. Rev.* **1996**, *96*, 1557.

(34) (a) Guo, X. C.; Chen, Q. Y. *J. Fluorine Chem.* **1999**, *93*, 81. (b) Yoshida, M.; Ohkoshi, M.; Aoki, N.; Ohnuma, Y.; Iyoda, M. *Tetrahedron Lett.* **1999**, *40*, 5731. (c) Barata-Vallejo, S.; Postigo, A. *J. Org. Chem.* **2010**, *75*, 6141.

(35) One gram of $[Ru(bpy)_3]Cl_2$ is capable of converting 14 mol (1.4 kg of 5-hexen-1-ol) of substrate based on the results from preparative reactions described herein.

(36) (a) Curran, D. P.; Hadida, S.; Studer, A.; He, M.; Kim, S. Y.; Luo, Z.; Larhed, M.; Hallberg, M.; Linclau, B. Fluorous Synthesis: A User's Guide. In *Combinatorial Chemistry: A Practical Approach*; Fenniri, H., Ed.; Oxford Univ Press: Oxford, 2000; Vol. 2; pp 327−352. (b) Curran, D. P. Fluorous Techniques for the Synthesis of Organic Molecules: A Unified Strategy for Reaction and Separation. In *Stimulating Concepts in Chemistry*; Wiley-VCH: Weinheim, 2000; pp 25−37. (c) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766.

(37) Dandapani, S.; Newsome, J. J.; Curran, D. P. *Tetrahedron Lett.* **2004**, *45*, 6653.

(38) (a) Zhang, Q. S.; Luo, Z. Y.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866. (b) Dandapani, S.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3855.

(39) Wrighton, M.; Markam, J. *J. Phys. Chem.* **1973**, *77*, 3042.

(40) Wayner, D. D. M.; Houmam, A. *Acta Chem. Scand.* **1998**, *52*, 377.

(41) Murphy, J. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH Verlag GmbH: Weinheim, Germany, 2001; pp 298−315.