Fluoroalkylation

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Gold-Catalyzed Highly Selective Photoredox C(sp^2)–H Difluoroalkylation and Perfluoroalkylation of Hydrazones

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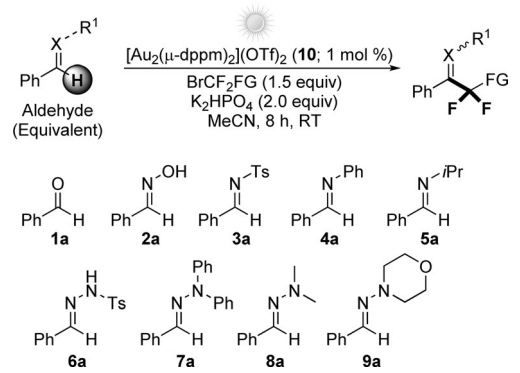
Abstract: *The first gold-catalyzed photoredox C(sp^2)–H difluoroalkylation and perfluoroalkylation of hydrazones with readily available R_F–Br reagents is reported. The resulting gem-difluoromethylated and perfluoroalkylated hydrazones are highly functionalized, versatile molecules. A mild reduction of the coupling products can efficiently produce gem-difluoromethylated β-amino phosphonic acids and β-amino acid derivatives. In mechanistic studies, a difluoroalkyl radical intermediate was detected by an EPR spin-trapping experiment, indicating that a gold-catalyzed radical pathway is operating.*

Owing to its unique properties, the difluoromethylene group (CF_2) is a very useful and valuable structural motif in organic synthesis, drug discovery, and life science.[1] It can serve as an effective functional group to improve biological activity[2] and as a bioisostere for an oxygen atom or a carbonyl group.[3] Therefore, the development of efficient difluoromethylation methods has attracted considerable attention,[4] and many transition-metal-mediated difluoromethylations of aryl boron[5] and organohalogen[6] compounds as well as other substrates[7] have been developed. Aromatic aldehydes and their synthetic equivalents, such as imines, hydrazones, and oximes, are versatile building blocks and important intermediates for the synthesis of fine chemicals and the pharmaceutical industry. To the best of our knowledge, the direct C(sp^2)–H difluoroalkylation of benzaldehyde or its synthetic equivalents is unexplored,[8] but could complement existing strategies.

The exploitation of solar energy in current organic synthesis represents a promising approach to mimic photosynthesis.[9] Recently, the use of gold(I) complexes in photoredox catalysis has gained considerable attention.[10,11] Both Barriault[10a,b] and co-workers and our group[10c] have shown that $[Au_2(\mu\text{-dppm})_2]^{2+}$ is an efficient photocatalyst to readily generate active carbon-centered radicals from organic halides. We have now examined the possibility of a direct C–H difluoroalkylation of benzaldehyde (**1a**) and its synthetic equivalents (oxime **2a**, imines **3a**–**5a**, and hydrazones **6a**–**9a**)



Scheme 1. Screening for an effective difluoromethylation. Reaction conditions: $[Au_2(\mu\text{-dppm})_2](OTf)_2$ (1 mol%), **1**–**9** (0.1 mmol), "CF_2" reagent (1.5 equiv), K_2HPO_4 (2 equiv), MeCN (0.3 mL), sunlight, RT, 8 h.

with diethyl (bromodifluoromethyl)phosphonate and ethyl 2-bromo-2,2-difluoroacetate by using $[Au_2(\mu\text{-dppm})_2](OTf)_2$ (**10**) as the photocatalyst in sunlight[12] (Scheme 1).[13] The results demonstrate that hydrazones **8a** and **9a** can undergo a difluoroalkylation reaction in moderate yields with excellent stereo- and regioselectivities.[14] Even though the copper-catalyzed trifluoromethylation of *N,N*-dialkyl hydrazones with Togni's reagent is known,[15] a transition-metal-catalyzed C–H difluoro- and perfluoroalkylation of hydrazones by photocatalysis with inexpensive and readily available R_F–Br reagents is unprecedented.

Owing to the potential of the *gem*-difluoroalkylation of *N,N*-dialkyl hydrazones, an optimization of the reaction conditions of the coupling of hydrazone **9a** with (bromodifluoromethyl)phosphonate **11a** was conducted by variation of the bases, the photocatalyst loading, the light source, and the reaction time (see Table 1 and also the Supporting Information for details). Whereas sunlight is the preferred light source, its replacement with a UVA light source substantially improved the yields. The optimized reaction conditions entailed the use of 2 mol% of **10** with 3 equivalents of 2,6-lutidine as a base (to neutralize the HBr formed during the reaction) and irradiation with UVA light (315–400 nm) for about 24 hours (76% yield, entry 1). Other available photocatalytic systems delivered no, or only traces of, product (entries 2–5). Irradiation with harder UV light ($\lambda = 254$ nm)

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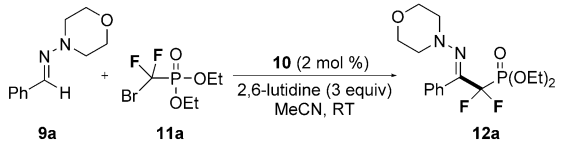
Table 1: Representative examples from the optimization of the reaction conditions.[a,13]



Entry	Catalyst (mol%)	Light source	Yield[b] [%]
1	$[Au_2(\mu\text{-dppm})_2](OTf)_2$ (**10**; 2)	UVA (315–400 nm)	76
2	$[Ru(bpy)_3]Cl_2$ (2)	blue LEDs	0
3	$[Ir(ppy)_3]$ (2)	blue LEDs or CFL	trace
4	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (2)	blue LEDs or CFL	0
5	eosin Y (2)	blue LEDs	0
6	**10** (2)	UV (254 nm)	0
7	–	UVA	0
8	**10** (2)	in the dark	0
9[c]	$Pd(OAc)_2$ (10)	–	0
10[c]	$[Ni(glyme)Cl_2]$ (10)	–	0

[a] Reaction conditions: **9a** (0.2 mmol), **11a** (2 equiv), 2,6-lutidine (3 equiv), MeCN (0.6 mL), room temperature, 24 h. [b] Yields of isolated products. [c] 80 °C. CFL = compact fluorescent light bulb.

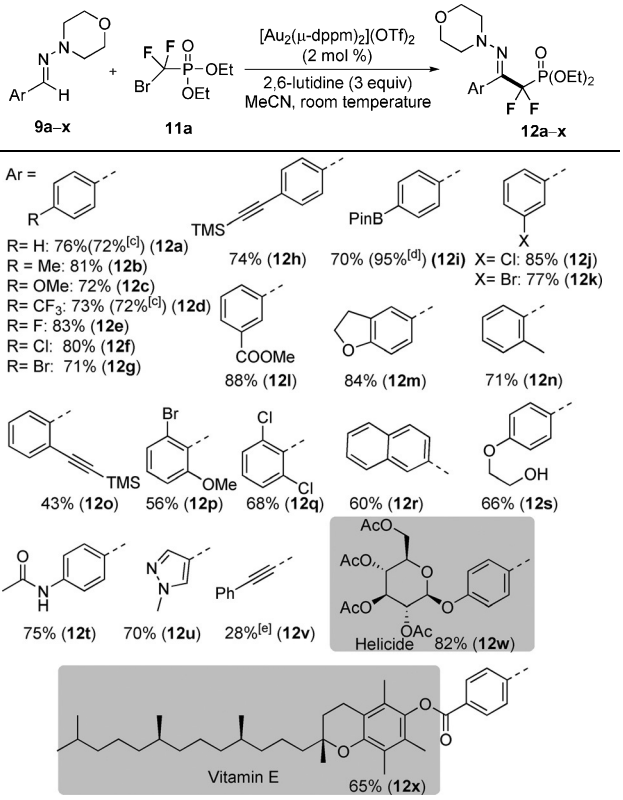
did not lead to the formation of **12a** (entry 6). Control experiments showed that the phosphonyldifluoromethylation does not proceed in the absence of either light or the gold photocatalyst (entries 7 and 8). With $Pd(OAc)_2$ and $[NiCl_2(glyme)]$ as the catalyst system, only the decomposition of both **9a** and **11a** was observed at 80 °C (entries 9 and 10).

With the optimized conditions in hand, the scope of the phosphonyldifluoromethylation of *N*-morpholine hydrazones was explored (Table 2). The method has a very broad substrate scope and displayed excellent chemoselectivity. The desired products **12a**–**12x** were obtained in moderate to good yields, and the corresponding phosphonyldifluoromethylated arenes were not formed. Versatile functional groups, such as halogens, ethers, esters, boronic esters, alcohols, amides, and alkynes, were tolerated. The possibility of a late-stage modification was explored with medically important helicide and vitamin E derivatives (**12w** and **12x**). The C=N bond of the products **12** is exclusive formed in *E* configuration (confirmed by NMR studies, DFT calculations, and X-ray crystal-structure analysis[16] of **12r**).[13] Propiolaldehyde hydrazone gave the desired product only in moderate yield (**12v**, 60% starting material recovery).

Then, the scope of the reaction was explored by studying the reactions of various benzaldehyde hydrazones with ethyl bromodifluoroacetate (**11b**).[13] Although the difluoroacetylation reaction also proceeded smoothly with $[Ir(ppy)_3]$ as the photocatalyst, the *E*/*Z* selectivity of the difluoromethylated product **13a** was much lower than when gold complex **10** was used (2.5:1 vs. 8:1, Scheme 2). $[Ir(ppy)_3]$ enables the isomerization of the *E*-configured product to the less stable *Z* product, and its use thus resulted in low *E*/*Z* selectivity,[17] which highlights another advantage of the gold photocatalyst. During the screening of different *N*,*N*-dialkyl hydrazones (**13a**–**13c**), we found that when *N*,*N*-dimethyl hydrazone was used as the starting material in the presence of the gold catalyst, the C=N bond was exclusively formed in *E* configuration. A variety of aromatic aldehyde hydrazones were converted (Table 3). All investigated substrates underwent the difluoroacetylation reaction, yielding the difluoroacetylated products **13a**–**13t** in 42–83% yield, including the heterocyclic aldehyde hydrazones **13s** and **13t**.

Given the importance of perfluoroalkyl groups, we examined the possible incorporation of such groups into hydrazones. As shown in Table 4, with perfluoroalkyl bromides, perfluoroalkylated hydrazones could be obtained in moderate to good yields. In sunlight, the trifluoromethylated hydrazones **14g** and **14h** could be isolated in satisfactory yields when trifluoroiodomethane was used as an inexpensive

Table 2: Substrate scope with regard to phosphonyldifluoromethylation.[a,b]

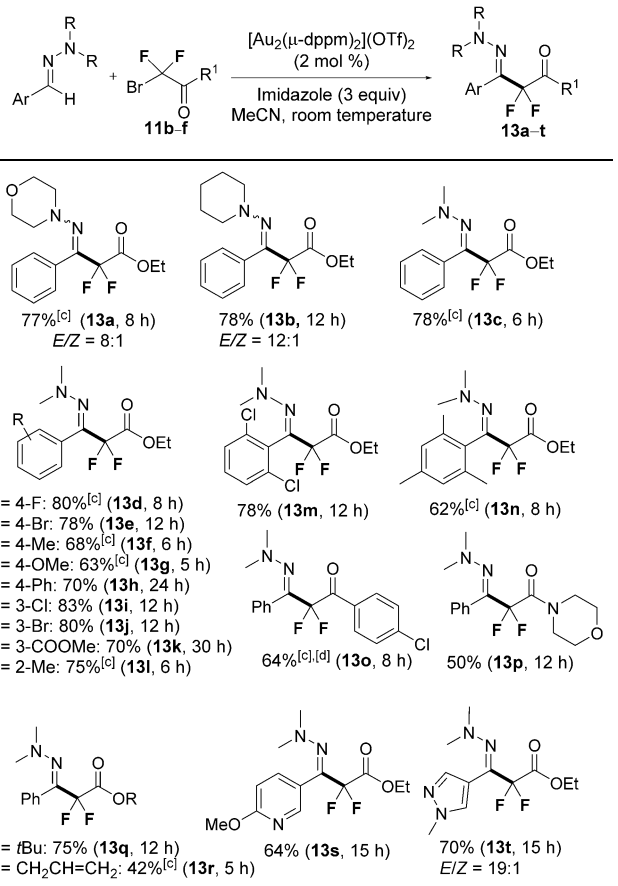


[a] Reaction conditions as mentioned in Table 1, 24–30 h. [b] Yields of isolated products. [c] 1 mmol scale. [d] Yield determined by ^{19}F NMR spectroscopy. [e] Imidazole (3 equiv) was used instead of 2,6-lutidine.

$[Au_2(\mu\text{-dppm})_2](OTf)_2$	Sunlight	77%; *E*/*Z* = 8:1
$[Au_2(\mu\text{-dppm})_2](OTf)_2$	UVA	76%; *E*/*Z* = 8:1
$Ir(ppy)_3$	Blue LEDs	77%; *E*/*Z* = 2.5:1
Eosin Y	Blue LEDs	No Reaction
$[Au_2(\mu\text{-dppm})_2](OTf)_2$	No Light	No Reaction
No Photocatalyst	Sunlight	No Reaction

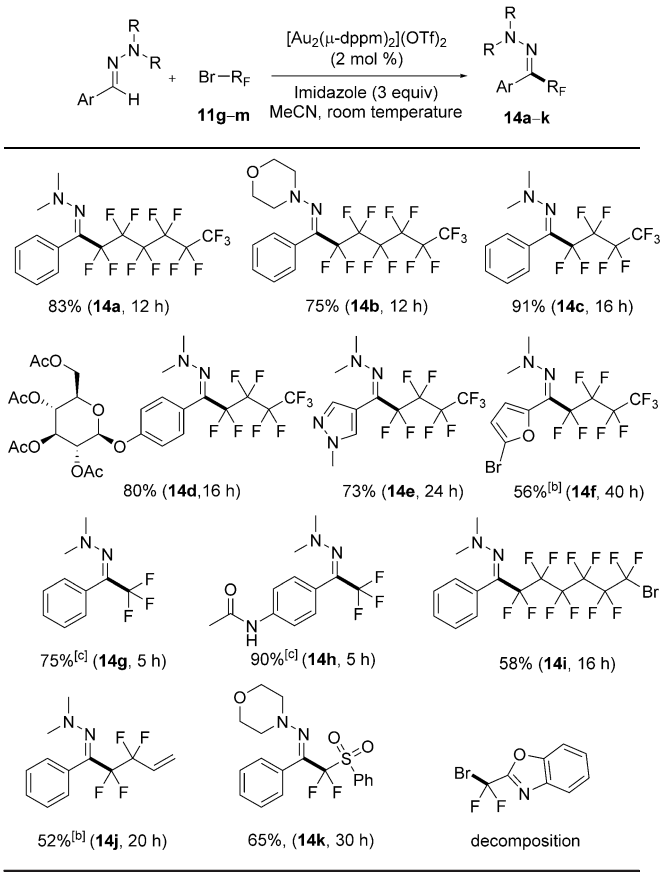
Scheme 2. *E*/*Z* selectivities achieved with different photocatalysts. The isomeric ratios were determined by ^1H NMR analysis.

Table 3: Substrate scope of the difluoroacetylation of hydrazones.[a,b]



[a] Reaction conditions: hydrazone (0.2 mmol), $[Au_2(\mu\text{-dppm})_2](OTf)_2$ (**10**; 2 mol%), $BrCF_2EWG$ (2 equiv), imidazole (3 equiv), MeCN (0.6 mL), RT, UVA light (315–400 nm). [b] Yields of isolated products. [c] Reaction irradiated with sunlight. [d] 2-Bromo-1-(4-chlorophenyl)-2,2-difluoroethanone (1.5 equiv).

Table 4: Scope with respect to other fluoroalkyl moieties.[a]



[a] Reaction conditions: hydrazone (0.2 mmol), $[Au_2(\mu\text{-dppm})_2](OTf)_2$ (**10**; 2 mol%), R_F–Br (2 equiv), imidazole (3 equiv), MeCN (0.6 mL), UVA light (315–400 nm), RT; yields of isolated products. [b] Fluoroalkyl bromide (3 equiv). [c] CF_3I (4 equiv), irradiated with sunlight.

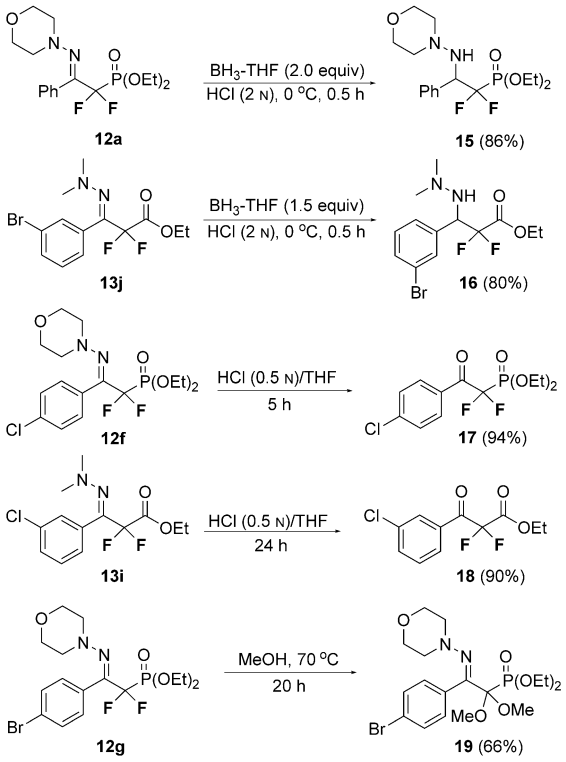
trifluoromethylating reagent. Even with strongly electron-donating groups on the arene, no perfluoroalkylation of the aromatic ring was observed (**14d**, **14f**, and **14h**).

As illustrated in Scheme 3, the C=N double bonds of the products could be selectively reduced with BH_3–THF under very mild reaction conditions to yield compounds **15** and **16**. Thus, this method constitutes a powerful route to *gem*-difluoromethylated β-amino phosphonic acids and β-amino acid derivatives. Furthermore, the difluoromethylated hydrazones can be hydrolyzed to the corresponding difluoromethyl ketones **17** and **18** by simple acid treatment. Direct heating of the difluoromethylated product in methanol at 70 °C enabled the substitution of two C–F bonds by methanol, producing dimethoxy ketal **19**.

The addition of radical trapping reagents (TEMPO, 1,1-diphenylethylene) or an electron-transfer scavenger (1,4-dinitrobenzene) significantly inhibited this transformation,[13] indicating that a single-electron-transfer radical process is operating. Moreover, the key radical intermediate was observed in an EPR spin-trapping experiment with 5,5-dimethyl-1-pyrroline *N*-oxide (Figure 1). A simulated spectrum matched the experimental data in terms of the line shape. A radical chain pathway could be ruled out by light on/off experiments as well as the reaction quantum yield ($\Phi = 1.44\,\%$).[13]

A possible mechanism is shown in Scheme 4. First, the irradiation of $[Au_2(\mu\text{-dppm})_2](OTf)_2$ (**10**) generates a high-energy, long-lived photoexcited state, $^*[Au_2(\mu\text{-dppm})_2]^{2+}$ (**24**), which is a strong one-electron donor [$E^0([Au_2]^{3+}/^*[Au_2]^{2+}) = -1.5$–$1.7$ V].[18] Next, a single electron transfer from the gold species **24** to **11a** delivers difluoromethyl phosphonate radical **25** and gold intermediate **21**.[19] The electrophilic radical **25** then attacks hydrazone **9a** to produce the three-electron π-bonding aminyl radical intermediate **26**. Owing to the lone pair on the adjacent nitrogen atom, **26** is much more stable than other aminyl radicals produced from imines and oximes.[20] Finally, oxidation of aminyl radical **26**[21] by gold species **21** followed by deprotonation affords the desired difluoromethylated product **12a**. DFT calculations showed that the products with the C=N bond in *E* configuration are lower in energy than those with *Z* configuration, and the isomerization activation energy usually amounts to more than 20 kcal mol^{-1}.[13] The gold photocatalyst favors the formation of the thermodynamic, *E*-configured product.

In conclusion, we have developed the first gold-catalyzed intermolecular photoredox C(sp^2)–H difluoroalkylation and



Scheme 3. Important transformations.

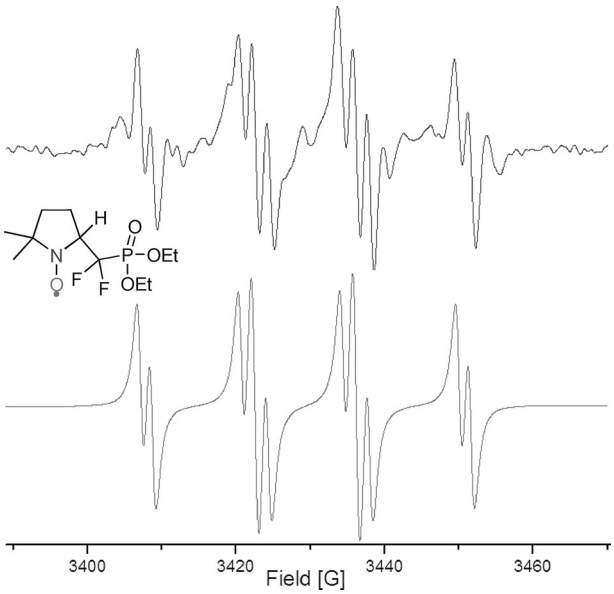
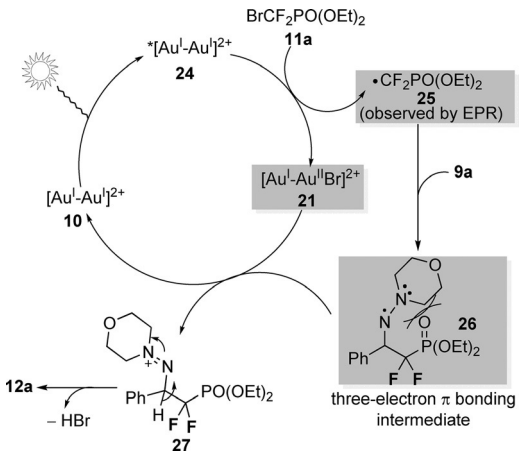


Figure 1. X-band EPR spectrum (298 K; top) of the radical derived from trapping $CF_2PO(OEt)_2$ with DMPO in the reaction depicted in Table 1. Simulated EPR spectrum (bottom) based on hyperfine coupling constants of $a_N = 12.7129$, $a_H = 14.6382$, and $a_F = 1.51504$ ($g = 2.00649$).

perfluoroalkylation of aromatic aldehyde hydrazones with commercially available fluoroalkyl bromides. Mild reaction conditions, a broad substrate scope, and excellent functional-group compatibility are attractive features of this method. The highly functionalized difluoroalkylated and perfluoroalkylated hydrazone products are excellent substrates for further transformations, for example, to *gem*-difluoromethylated β-amino phosphonic acids and β-amino acids. An EPR spin-trapping experiment indicated the involvement of a difluoroalkyl radical intermediate.



Scheme 4. Proposed mechanism.

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Keywords: C–H functionalization · fluorine · gold catalysis · photocatalysis

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[12] Visible-light-mediated difluoroalkylation reactions are still underdeveloped, and thus far, attention has mainly been focused on the radical difluoromethylation of electron-rich alkenes and arenes, see **7i** and **7l**–**7o**.

[13] See the Supporting Information for details.

[14] Although the direct electrophilic fluorination of β-keto esters with several equivalents of Selectfluor could give α,α-difluoro β-keto esters, the intrinsic limitations of this reagent, such as the poor functional-group compatibility, significantly restrict its widespread application.

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[16] CCDC 1047970 (**12r**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[17] a) A. Noble, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 11602 – 11605; b) K. Singh, S. J. Staig, J. D. Weaver, *J. Am. Chem. Soc.* **2014**, *136*, 5275 – 5278.

[18] The dimeric gold complex is easy to prepare from [(DMS)AuCl] and bis(diphenylphosphino)methane (dppm) at room temperature (its price is less than €100 for 250 mg). It absorbs light at about 300 nm to form a high-energy and long-lived photoexcited state; see: a) D. Li, C.-M. Che, H.-L. Kwong, V. W.-W. Yam, *J. Chem. Soc. Dalton Trans.* **1992**, 3325 – 3329; b) C.-M. Che, H.-L. Kwong, C.-K. Poon, V. W.-W. Yam, *J. Chem. Soc. Dalton Trans.* **1990**, 3215 – 3219. $[Ir(ppy)_3]$, however, is much more expensive than the dimeric gold photocatalyst (ca. €500 for 250 mg).

[19] Cyclic voltammetry of **11a** showed an irreversible reduction with a peak potential of −0.99 V vs. SCE in MeCN. Cyclic voltammetry of **9a** showed an irreversible oxidation with a peak potential of 1.03 V vs. SCE in MeCN. For cyclic voltammetry experimental details, see the Supporting Information.

[20] a) A. G. Fallis, I. M. Brinza, *Tetrahedron* **1997**, *53*, 17543 – 17594; b) G. K. Friestad, *Tetrahedron* **2001**, *57*, 5461 – 5496; c) S. Torrente, R. Alonso, *Org. Lett.* **2001**, *3*, 1985 – 1987; d) D. Hager, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2014**, *136*, 16986 – 16989.

[21] The calculated SOMO energy for **26** is −6.26 eV (DFT/UM062X/6-311++g(d,p)).

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