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Ketone-catalyzed photochemical C(sp^3)–H chlorination

Lei Han, Ji-Bao Xia, Lin You, Chuo Chen*

Department of Biochemistry, UT Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9038, USA

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ABSTRACT

Photoexcited arylketones catalyze the direct chlorination of C(sp^3)–H groups by *N*- chlorosuccinimide. Acetophenone is the most effective catalyst for functionalization of unactivated C–H groups while benzophenone provides better yields for benzylic C–H functionalization. Activation of both acetophenone and benzophenone can be achieved by irradiation with a household compact fluorescent lamp. This light-dependent reaction provides a better control of the reaction as compared to the traditional chlorination methods that proceed through a free radical chain propagation mechanism.

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1. Introduction

Halogenation is a common strategy to enhance the potency or alter the physical properties of small molecule drugs.[1–3] Naturally occurring halogenated molecules also often display medicinally useful activities.[4,5] Catalysts that promote C–H halogenation are thus highly valuable. We report herein a catalytic, light-dependent method for C(sp^3)–H chlorination (Fig. 1).

Whereas a variety of C–H fluorination methods[6–18] have been reported, free radical chain reactions remain to be the most frequently used method for C–H chlorination. In contrast, biological C–H chlorination is catalyzed by α-ketoglutarate (αKG)-dependent non-heme iron (Fe_{NH}) halogenases.[19–22] A good example is the sequential chlorination of the BarA-loaded L-leucine by BarB2 and BarB1 in the biosynthesis of barbamide (**1**) (Fig. 2).[23,24] Mechanistically, this halogenase-catalyzed C–H chlorination reaction is similar to C–H hydroxylation reactions catalyzed by the corresponding oxygenases.[25–27]

The reaction of **2** has inspired Que and co-workers to develop biomimetic chlorinating complexes.[28] They showed that [Fe(TPA)Cl_2](ClO_4) (**8**) promotes C(sp^3)–H chlorination upon activation with *tert*-butyl hydroperoxide (Fig. 3) (TPA = tri-(2-pyridylmethyl) amine). However, mechanistic studies indicated that the Fenton-type free radical chain reaction is also operative and there is little or no turnover of the catalyst.[29,30] Later, Groves and co-workers found that Mn(TMP)Cl (**9**) catalyzes C(sp^3)–H chlorination by bleach in the presence of a catalytic amount of tetra-*n*-butylammonium chloride (TMP = tetraphenylporphyrin).[31,32] However, heme mimetics could also promote aromatic C(sp^2)–H oxidation leading to low selectivity for aromatic substrates. For example, Fuji and co-workers found that Fe(TPFP)(NO_3) (**10**) catalyzed chlorination of electron-rich arenes by ozone and tetra-*n*-butylammonium chloride upon activation by a catalytic amount of trifluoroacetic acid (TPFP = tetrakis(pentafluorophenyl)porphyrin).[33]

A variety of directing groups have been developed to better control the regioselectivity of C–H chlorination. For example, Sanford and co-workers showed that a pyridine group can direct and facilitate catalytic halogenation of benzylic C(sp^3)–H groups by palladium.[34,35] Yu and co-workers also demonstrated that an oxazoline group facilitates palladium-catalyzed C(sp^3)–H halogenation,[36,37] and 2-nitrobenzenesulfonamide is an excellent directing group for copper-catalyzed C(sp^3)–H bromination.[38] Additional directing groups for palladium-catalyzed C(sp^3)–H halogenation include 2-pyridylsulfoximine,[39] amide,[40] and 8-aminoquinoline.[41] However, C(sp^3)–H halogenation without over-oxidation is still challenging. Notably, C(sp^2)–H chlorination can be achieved more easily by using, for example, chlorobis(methoxycarbonyl)guanidine (CBMG)[42] developed by Baran and co-workers as chlorinated arenes are less electron-rich and thus less reactive than their precursors toward aromatic substitution.

Baran and co-workers have demonstrated that site-selective halogenation can be realized by trifluoroethyl *N*-halocarbamate-

* Corresponding author.
E-mail address: Chuo.Chen@UTSouthwestern.edu (C. Chen).

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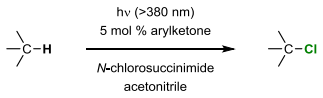


Fig. 1. A catalytic, light-dependent method for C–H chlorination.

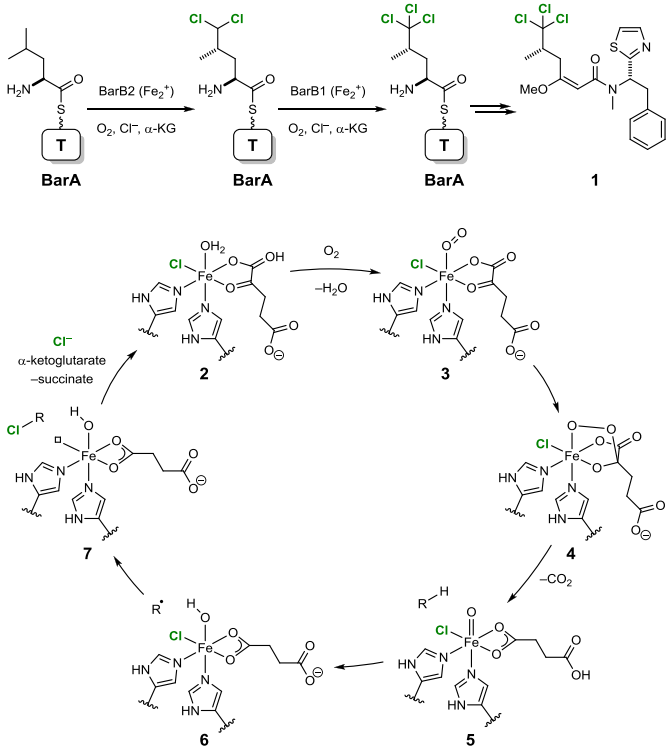


Fig. 2. C–H chlorination in the biosynthesis of barbamide (**1**) and the mechanism of C–H chlorination catalyzed by Fe_{NH}-αKG halogenase.

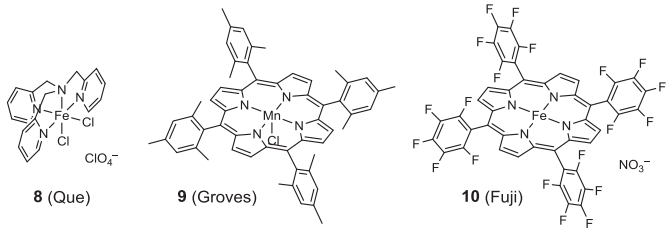


Fig. 3. Examples of reported C–H chlorination complexes.

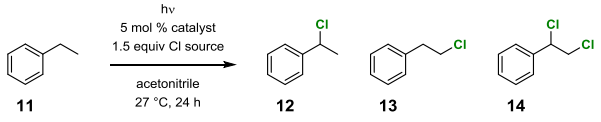
mediated Hofmann–Löffler–Freytag reaction.[43] Unlike the *N*-chloramine-mediated method, the *N*-cyclization product is not formed with the carbamate group. Ball and co-workers also showed that a peroxide group can be used as an internal oxidant to achieve copper-catalyzed regioselective C(sp^3)–H chlorination without over-oxidation.[44] Intermolecular oxidative radical halogenation has also been achieved by Alexanian, Vanderwal, and co-workers by *N*-haloamides.[45,46] They showed that *N*-chloro-*N*-(*tert*-butyl)-3,5-bis(trifluoromethyl)benzamide chlorinates sclareolide selectively and effectively. Addition of cesium carbonate helped suppress dichlorination. Thus, a large excess of substrates is not needed to prevent over-oxidation. However, one potential safety concern for performing large-scale free radical chain reactions is that the chain propagation process may lead to a runaway reaction. To date, the most practical method for introducing a chlorine atom onto an aliphic chain is arguably the silver-catalyzed decarboxylative chlorination reaction developed by Li and co-workers, although pre-installation of a carboxylic acid group is required.[47]

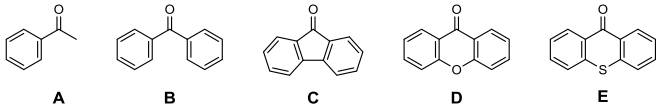
Walling discovered serendipitously in 1965 that photoreduction of triplet benzophenone by cyclohexane in the presence of internal standard Freon 112 ($CFCl_2CFCl_2$) led to the formation of cyclohexyl chloride.[48] He subsequently found that carbon tetrachloride is a better chlorine atom donor. UV-irradiation of a mixture of cyclohexane and benzophenone in carbon tetrachloride gave cyclohexyl chloride and benzpinacol in good yields. However, there is no report of the development of a catalytic system for this C–H chlorination reaction. We have demonstrated that triplet arylketones are functionally similar to the metal-oxo species **5** and can catalyze C(sp^3)–H fluorination.[6,7] We now show that catalytic C(sp^3)–H chlorination can also be achieved through this photochemical reaction.

2. Results and discussion

Our work started with optimization of the catalyst system for benzylic chlorination using ethylbenzene (**11**) as the standard substrate (Table 1). Because benzophenone ketyl radical is rather stable and susceptible to deactivation by dimerization, we first tested if acetophenone could offer a better catalyst turnover number. However, irradiation of **11** with UV light in carbon tetrachloride in the presence of 5 mol % of acetophenone gave only 12% yield of benzylic chloride **12** along with 7% of the homobenzylic chloride **13** (entry 1). Whereas there was nearly no reaction when irradiated with violet light for 24 h (entry 2), switching the chlorine atom donor to *N*-chlorosuccinimide (NCS) led to a quick reaction and **11** was consumed completely to give **12** together with **13** and the dichlorination product **14** (entry 3). The reaction proceeded well but slower when a household compact fluorescence lamp (CFL) was used as the light source (entry 4). Nonetheless, acetophenone, benzophenone, 9-fluorenone, xanthone, and thioxanthone can all catalyst C–H chlorination by NCS upon activation by CFL-irradiation (entries 4–8). Among these arylketones, benzophenone and 9-fluorenone provide the best reaction rates and selectivity (entries 5 and 6). We have also examined the

Table 1
Effects of the catalyst, chlorine donor, and light source on the benzylic chlorination of **11**.





Entry	Catalyst	Cl source	Light source	11	12	13	14
1	**A**	CCl_4[a]	350 nm[b]	81%	12%	7%	–
2	**A**	CCl_4[a]	419 nm[c]	>95%	–	–	–
3	**A**	NCS	419 nm[c]	0%	68%	12%	20%
4	**A**	NCS	CFL[d]	15%	70%	13%	2%
5	**B**	NCS	CFL[d]	0%	74%	7%	19%
6	**C**	NCS	CFL[d]	0%	72%	7%	21%
7	**D**	NCS	CFL[d]	6%	70%	15%	8%
8	**E**	NCS	CFL[d]	21%	67%	10%	2%

[a] No acetonitrile, carbon tetrachloride is used as the solvent.
[b] 16 × RPR-3500 Å lamps (24 W, 300–420 nm).
[c] 16 × RPR-4190 Å lamps (24 W, 375–465 nm).
[d] 1 × compact fluorescence lamp (19 W).

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