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β-C(sp^3)–H chlorination of amide derivatives *via* photoinduced copper charge transfer catalysis

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ABSTRACT

An atom economic β-C(sp^3)–H chlorination of amide derivatives has been developed. This mild protocol employs $CuCl_2$ instead of palladium catalysts with atom-economic HCl as chlorine sources and enables the late-stage functionalization of medicine derivatives. Mechanism studies suggest a plausible visible light triggered ligand-to-metal charge transfer (LMCT)/1,4-hydrogen atom transfer (HAT) cascade.

Amide moieties are ubiquitous structural motif in various natural products, pharmaceuticals, and fine chemicals [1–3]. In particular, β-halogenated amides are key building blocks in many pharmaceuticals, agrochemicals as well as synthetic precursors (Scheme 1a) [4–9]. Owing to its atom- and step-economy, Pd catalyzed β-C–H halogenation was developed as one of the most powerful synthetic methods for β-haloamides (Scheme 1b) [10–19]. Yu and coworkers employed $PhI(OAc)_2$ and I_2 as halogen sources to achieve Pd-catalyzed β-diiodination of carboxylic acid derivative [20,21]. Sahoo [22], Rao [23], Besset [24] and Yu [25] disclosed Pd-catalyzed β-halogenation of aliphatic amides, using *N*-halosuccimide or *N*-halophthalimide as halogen sources. In these cases, acid additive or special ligand were required. Despite these advances, palladium catalysts were required and large amount of by-products would be produced from these halogen sources. Therefore, a distinct protocol using less-expensive catalysts with atom economic halogen sources would be environmental benign and highly demanding.

HCl is a sustainable halogen sources as hydrogen atom would go into its by-product compared with *N*-halosuccimide or *N*-halophthalimide. Lu's group disclosed the only case for both β-chlorination and β-bromination of pivalic acid, using NaCl or KBr as halogen sources with extra oxidants [26,27]. However, utilization of halogens in HCl would be more challenging, as the activation of H–Cl bond is energy costing.

Visible-light-mediated ligand-metal charge transfer (LMCT) processes emerged as a powerful strategy for efficient organic synthesis [28–50]. Several photo-induced LMCT systems were developed to generate halogen radicals [28–37]. In these works, previous expensive catalysts were replaced by earth-abundant Ni [29], Ce [43], Cu [28,30] or Fe [33,35,37] salts, which upon irradiation would undergo LMCT with readily available halogen sources to generate halogen radicals. In 2021, Wan's group disclosed chlorine radical generation from the combination of $CuCl_2$ and HCl [28]. Inspired by Wan's work and recent visible light enabled copper catalysis [51–55], we envisioned that chlorine radical generated from copper charge transfer catalysis would form amide radical **A**, which might trigger 1,4-HAT [56–59] to produce β-halogenated amides (Scheme 1c). Along our efforts on remote site-selective C–H functionalization [60–63], we herein report photoinduced copper catalyzed β-C(sp^3)–H chlorination of amides derivatives (Scheme 1c). Combination of LMCT and 1,4-HAT processes allowed the utilization of atom economic HCl as halogenation sources with less expensive $CuCl_2$ catalysts. Furthermore, this mild halogenation approach enabled the late-stage functionalization of complex medicinal derivatives.

At the outset, the study was initiated by exposing *N*-phenyl pivalamide (**1a**) to $CuCl_2$ as catalysts and *N*-chlorosuccinimide (NCS) as halogen sources, providing the β-chlorinated product **2a** in 25% yield with aromatic chlorination products (Scheme 2). To avoid halogenation of arenes, we chose electron-deficient aniline derivative *N*-(2,5-dichlorophenyl)pivalamide (**1b**) as model substrate and HCl as halogen sources, affording monochlorinated **2b** and dichlorinated **2b'** in 70% and <5% yield respesctively (Table 1,

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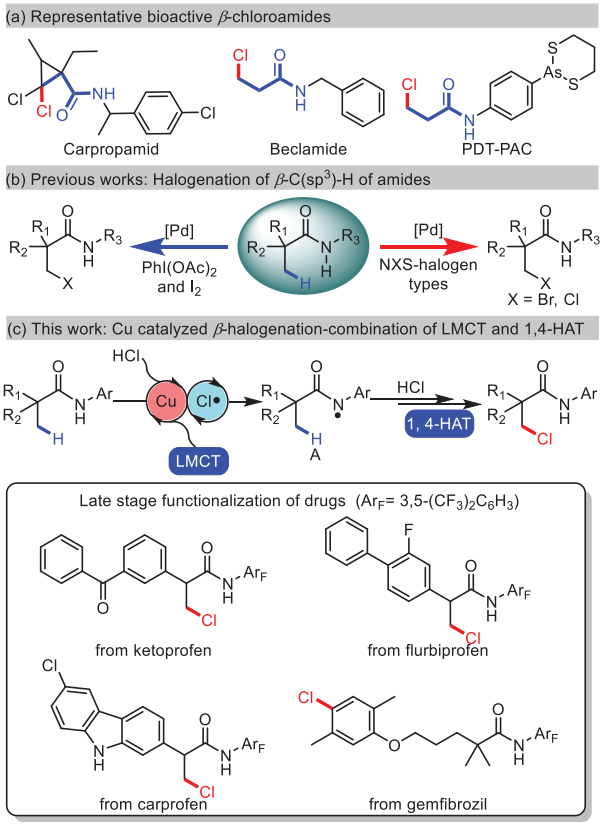
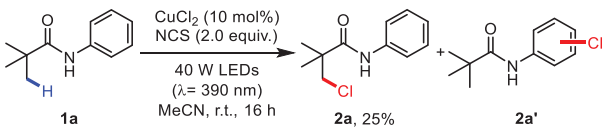
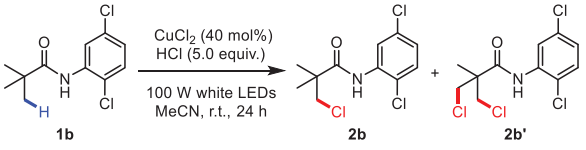


Scheme 1. Challenges of β-C(sp^3)–H halogenation and the current work.



Scheme 2. Preliminary study on the chlorination of amide derivatives.

Table 1
Optimization of the reaction conditions.[a]



Entry	Deviation from the standard conditions	Yield (%)[b]
1	–	70 (<5[c])
2	CuCl, $FeCl_3$, $NiCl_2$, $CeCl_3$ instead of $CuCl_2$	45, 62, 50, 39
3	TBACl, LiCl, NCS instead of HCl	20, 35,58
4[d]	Standard conditions of Ref. [32]	9
5[e]	Standard conditions of Ref. [30]	24
6	Without $CuCl_2$ or light	<5, 0
7	DCE, CH_2Cl_2, TFA, AcOH instead of MeCN	28, 38, 47, 30
8	36 W CFL instead of 100 W white LED	35
9	50 °C instead of r.t.	58
10	Under oxygen	72
11	Under argon	21

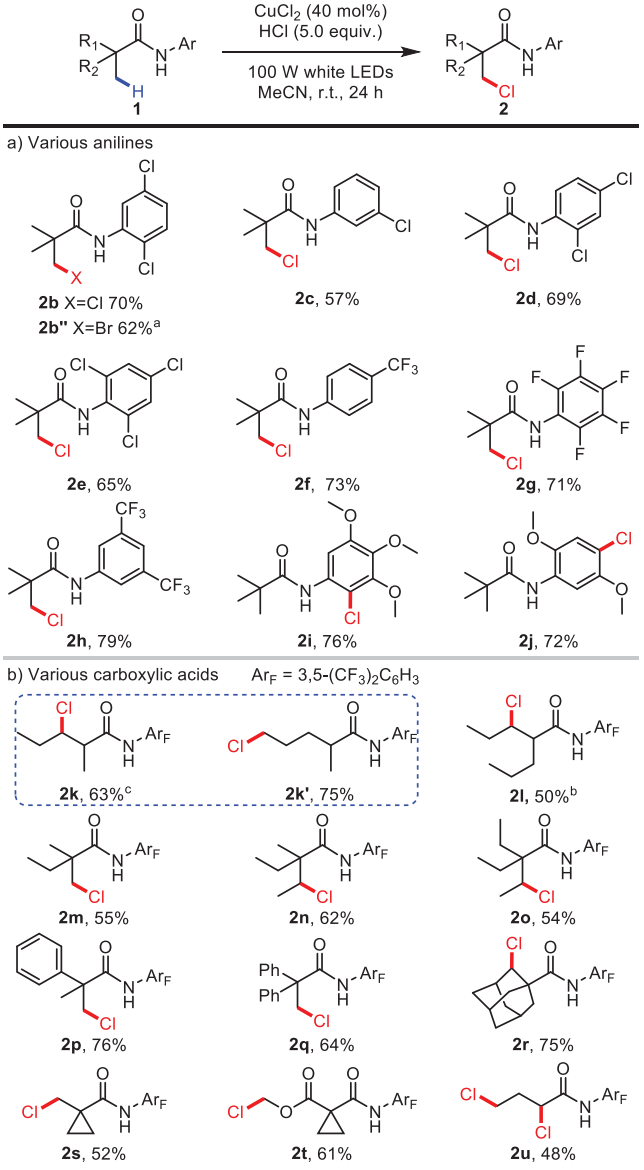
[a] Standard conditions: **1b** (0.1 mmol), HCl (5.0 equiv.), $CuCl_2$ (40 mol%), in MeCN (0.5 mL) under air, irradiated with 100 W white LEDs at r.t. for 24 h.
[b] Isolated yields.
[c] Yield of **2b'**.
[d] **1b** (0.3 mmol), $FeCl_3$ (25 mol%) in MeCN (1.0 mL) for 36 h [32].
[e] **1b** (0.3 mmol), $CuCl_2$ (20 mol%), LiCl (50 mol%) in MeCN (1.0 mL) at 60 °C for 36 h [30]. TBACl = tetrabutylammonium chloride. DCE = 1,2-dichloroethane. TFA = trifluoroacetic acid.

entry 1). Diverse metal catalysts, which were reported to undergo LMCT processes [28–30,33,35,37,43], provided inferior yields (entry 2). Replacement of HCl with other halogen sources and readily available halogen salts used in LMCT processes significantly reduced the reaction efficiency (entry 3), probably attributing to good synergistic effect between $CuCl_2$ and HCl. In addition, we tested previously established LMCT conditions by other groups (entries 4 and 5) [30,32]. In absence of either light or $CuCl_2$, the halogenation processes hardly vanished, indicating that the catalyst and light are critical for this reaction (entry 6). Further investigation of solvent, light sources and temperature confirmed the optimal conditions as: HCl (0.5 mmol, 5.0 equiv., 37% in water), $CuCl_2$ (40 mol%), in MeCN (0.5 mL) under air, irradiated with 100 W white light LEDs at r.t. for 24 h (entries 7–9). Notably, the reaction afforded slightly higher yield under oxygen and the yield of **2b** significantly decreased under argon (entries 10 and 11). Given the results of control experiments and previous reports [28], oxygen together with HCl oxidizes Cu(I) species to regenerate Cu(II) catalysts.

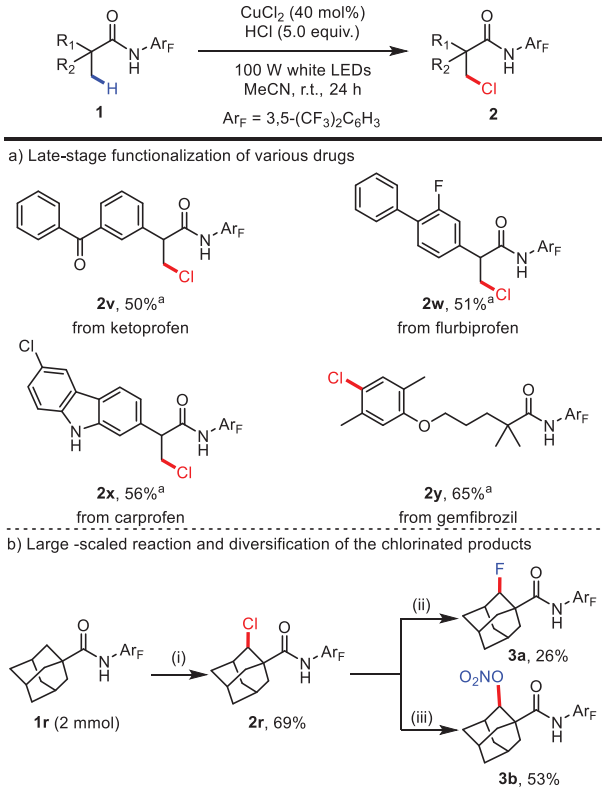
Having identified the optimized conditions, we set out to explore the scope for various anilides (Scheme 3a). Diverse chlorinated aniline derived amides exhibited good reactivity under optimal conditions (**2b**-**2e**). Notably, anilides with trifluoromethyl groups afforded better yields (**2f**, **2h**). However, chlorination only occurred on aromatic rings for anilides with electron-donating groups (**2i**, **2j**), which could be attributed to electron-rich nature of these arenes. Next, we turned our attention to the scope of 3,5-bis(trifluoromethyl)anilides (**2k**-**2u**) deriving from various carboxylic acids (Scheme 3b). Various secondary and tertiary carboxylic amides were successfully chlorinated (**2k**-**2r**) under optimal conditions. Interestingly, β-chlorination of 2-methylvaleric acid-derived amides under mildly acidic condition provided β-chloroamide **2k** and δ-chloroamide **2k'**. β-Halogenation selectively occurred on tertiary carboxylic amides bearing the aromatic rings without substitution on arenes (**2p**, **2q**). Given the importance of the bridged 1-adamantanecarboxylic acid in drug discovery, its derivative was selectively chlorinated at the beta position to provide **2r** in 75% yield. For the three-membered ring-containing anilides, the chlorination did not occur on the cyclopropyl ring (**2s**, **2t**), possibly owing to the steric constraint of the reaction. Notably, the unsubstituted cyclopropanecarboxylic acid derivative afforded the ring-opening dichloride product **2u**.

Encouraging by these results, this protocol was applied for the late-stage structural modification of drugs (Scheme 4a). Ketoprofen, flurbiprofen, and carprofen derivative, nonsteroidal anti-inflammatory drugs could be readily converted to their chlorinated derivatives (**2v**-**2x**) with recovery of starting materials. As expected, the electron-rich aryl moiety of gemfibrozil underwent an electrophilic chlorination reaction to provide the product **2y**. A large-scaled reaction by reacting 0.783 g of **1r** (2 mmol) with HCl afforded **2r** (0.588 g) in 69% yield. Furthermore, **2r** could be successfully transformed into **3a** and **3b** through nucleophilic substitution (Scheme 4b) [25,64].

We next sought to interrogate the mechanism of this reaction. Addition of TEMPO inhibited the reaction, and addition of 1,1-diphenylethylene successfully captured chlorine radical, affording the radical adduct **4** (Schemes 5a and b). To probe the generation of chlorine radical, a series of UV–vis spectra were carried out. UV–vis spectroscopy of $CuCl_2/CH_3CN$ and $CuCl_2/HCl/CH_3CN$ solution exhibited typical peaks of $[(MeCN)_2CuCl_2]$ and $[(MeCN)CuCl_3]^-$, respectively (Fig. 1a) [65], indicating $[(MeCN)_2CuCl_2]$ would react with HCl to form $[(MeCN)CuCl_3]^-$. According to literature [30], $[(MeCN)CuCl_3]^-$ would readily undergo LMCT to generate chlorine radicals. This was further confirmed by the irradiation of $CuCl_2/HCl/CH_3CN$ solutions, UV–vis spectroscopy of which showed $[(MeCN)CuCl_3]^-$ vanished (Fig. 1a). To further confirm the change



Scheme 3. Reaction scope. Standard conditions: **1** (0.1 mmol), HCl (5.0 equiv.), $CuCl_2$ (40 mol%), in MeCN (0.5 mL) under air, irradiated with 100 W white LEDs at r.t. for 24 h. [a] HBr (5.0 equiv.), $CuBr_2$ (40 mol%). [b] For 2 h.



Scheme 4. Standard conditions: **1** (0.1 mmol), HCl (5.0 equiv.), $CuCl_2$ (40 mol%), in MeCN (0.5 mL) under air, irradiated with 100 W white LEDs at r.t. for 24 h. [a] For 72 h. (i) Standard conditions; (ii) **2r** (0.1 mmol, 1.0 equiv.), AgF (4.2 equiv.), dry cyclohexane (1.6 mL), 120 °C, 38 h; (iii) **2r** (0.1 mmol, 1.0 equiv.), $AgNO_3$ (2.0 equiv.), EtOAc (2.0 mL), 120 °C, 80 h.

of cupric oxidation state in the catalytic cycle, the X-ray photoelectron spectroscopy (XPS) measurement of the reaction mixture using the $CuCl_2$/HCl system was carried out (Fig. 1b). Fig. 1b shows the high resolution XPS scans over Cu $2p_{3/2}$ peak. The peak at 932.5 eV was known as the characteristic of Cu^+ [66], while the peak at 934.3 eV together with shake-up satellite peaks on the higher binding energy side, 942.4, and 944.6 eV, indicated the presence of an unfilled Cu 3d shell and thus confirmed the existence of Cu^{2+} [67,68]. The results of UV–vis spectroscopy and XPS suggest that the β-chlorination reaction may proceed through a Cu(I)–Cu(II) involving LMCT mechanism. To investigate the possibility of 1,4-HAT processes, we subjected substrate **5** to the standard conditions (Scheme 5c). Notably, β-halogenated product **6** was not de-

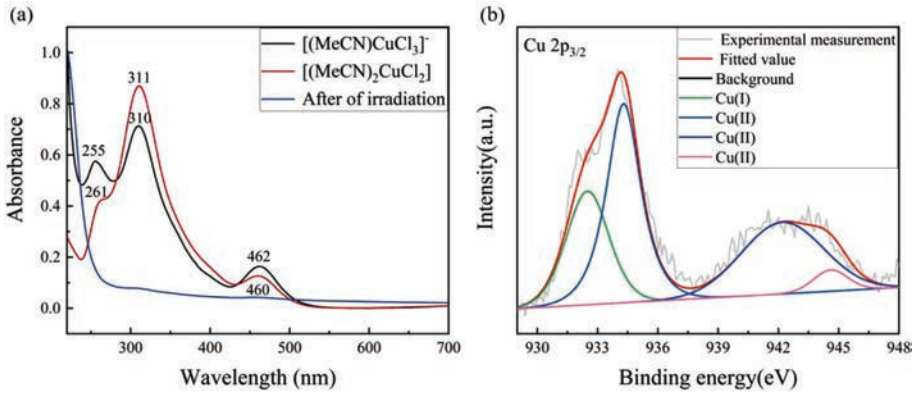
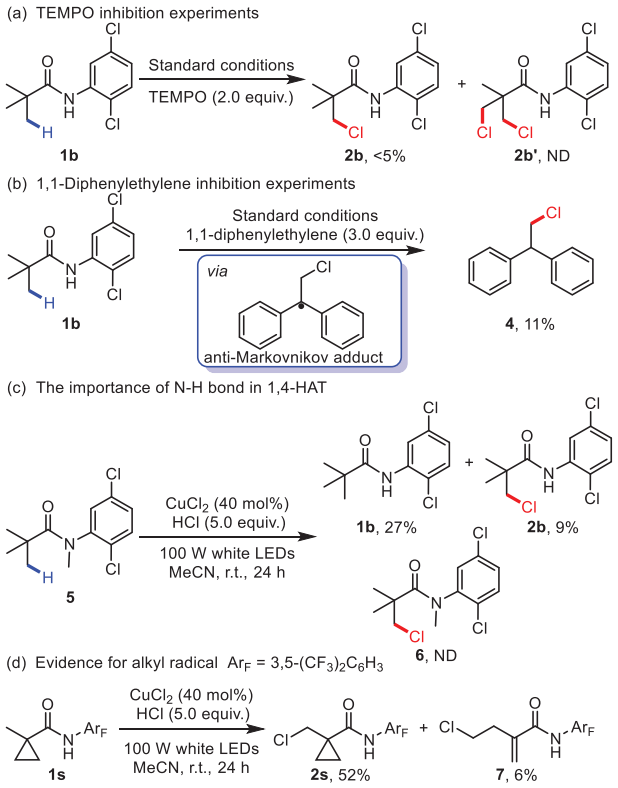
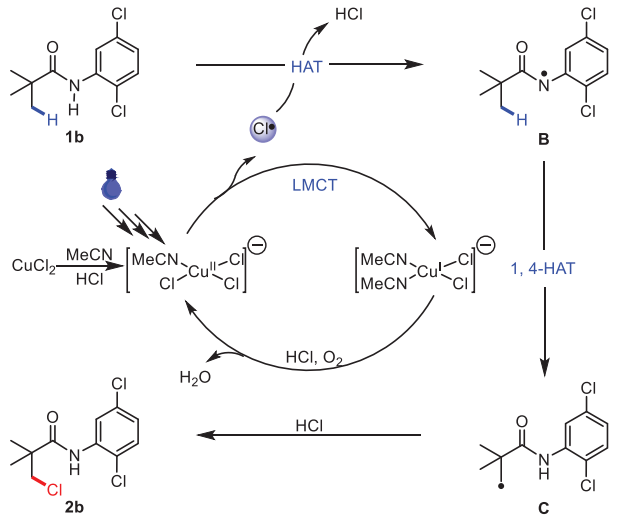


Fig. 1. (a) UV–vis characterization of the reaction. (b) The X-ray photoelectron spectroscopy (XPS) data of the reaction mixture.



Scheme 5. Mechanism experiment.



Scheme 6. Proposed mechanism.

tected, but 27% of product **1b** and 9% of product **2b** were obtained. It would be attributed to the lack of N-H bond in **5**, which is essential to trigger 1,4-HAT for β-halogenation by converting N-H bond into N−Cl bond with chlorine radical from LMCT. Under the standard condition, **1s** provided **2s** with 6% of ring-opening product **7**, a typical radical clock product (Scheme 5d) Quantum yield and light on/off experiments suggest that the transformation needed continuous irradiation of visible light and is not a radical chain processes (see Supporting information).

Based on our mechanistic experiments and previous studies [28,30], we proposed the plausible mechanism (Scheme 6). $CuCl_2$ is coordinated with the acetonitrile to produce Cu(II) complex $[(MeCN)_2CuCl_2]$, which is further converted to photoactive Cu(II) species $[(MeCN)CuCl_3]^-$ by reacting with HCl. Upon irradiation, $[(MeCN)CuCl_3]^-$ undergoes LMCT to generate chlorine radical, which abstracts N-H hydrogen of **1b** to afford **B** and HCl. **B** provides alkyl radicals **C** *via* 1,4-HAT, which reacts with HCl to generate **2b**. Finally, according to Wang's report [28], oxygen together with HCl oxidizes Cu(I) complex $[(MeCN)_2CuCl_2]^-$ to regenerate Cu(II) catalysts $[(MeCN)CuCl_3]^-$.

In summary, we have achieved additive-free β-C(sp^3)–H chlorination of amides *via* combination of photoinduced LMCT and 1,4-HAT. $CuCl_2$ instead of Pd catalysts has been developed as catalysts with atom-economic HCl as chlorine sources. Furthermore, the reaction enables the late-stage functionalization of medicinal related compounds. In addition, a feasible mechanism is proposed on the basis of several control experiments.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108546.

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