Photosensitized Nickel Catalysis Enabled Silyl Radical Mediated Direct Activation of Carbamoyl Chlorides to Access (Hetero)aryl Carbamides

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The transformation of a readily available molecule to a medicinally relevant functionality is the heart of organic synthesis which literally unfolds new direction in the field of drug discovery and development. Accordingly, synthetic chemistry fraternity is constantly striving to introduce a range of avant-garde techniques to construct an incredibly important fundamental entity like "amide bonds" which connect the amino acids in proteins and exist as a prevalent structural motif in biomolecules. In this context, we want to introduce the concept of cross-electrophile coupling by merging the photoredox and transition metal catalysis to construct carbamides from superabundant (hetero)aryl chlorides or bromides along with commercially feasible carbamoyl chlorides. However, there is barely any report on direct activation of carbamoyl chloride so far. To circumvent the challenge, we employ the intrinsic affinity of silyl radical species towards halogen atom to harness the carbamoyl radical directly from carbamoyl chlorides which is seemingly the first of its kind. The success of this protocol relies on the prior formation of 'aryl halides to Ni-catalyst' oxidative addition intermediate that assists in generation of the vital carbamoyl radical. The breadth of application of this technique is significantly demonstrated by the synthesis of a plethora of (hetero)aryl carbamides with diverse functionalities. As stated earlier, we outline the direct utility of this protocol by the late-stage amidation of halide containing drug molecules and pharmacophores.

The omnipresence of amide functional groups in natural products and synthetic organic molecules accentuates its indispensable character and enriches us with a vast array of dynamic and resourceful carboxamides. The C(O)–N linkages are existing enormosly in biomolecules like proteins, peptides, commercially available local anesthetics, various pharmacologically active scaffolds, and industrially relevant materials like polymers, surfactants, and agrochemicals[1-3]. Even a broad spectrum of benzamide and its derivatives have been recognized to manifest anticancer and antipsychotic activities[4,5]. Moreover, many naturally occurring plant-based amides impart medicinal benefits like antitumor, antibacterial, antifungal, and insecticidal properties.

Considering the ubiquitous applicability and importance of amides, efficient methods for their synthesis is highly enviable. In this regard, many name reactions and classical dehydrative condensation strategies have been dedicated to the synthesis of amides[6]. However, the conventional utilisation of stoichiometric amounts of expensive and toxic coupling reagents as well as incompatibility with sterically hindered amides make them unappealing. As a consequence, a gradual shift towards unconventional methods is now evident. Recent discoveries and upsurge of research in the domain of transition metal catalysis have started outweighing the dependence on orthodox cross coupling reaction conditions to construct amide bonds. Some advancements in catalytic carbonylative amidation have been materialized recently that include the involvement of group IV transition metals and more precisely Pd-catalyst in three-component coupling of an organohalide with carbon monoxide (CO) or its surrogates and amine[7-10]. However, the requirement of noxious CO gas, elevated temperature and high CO pressure impose the challenge toward the success of these transformations which restricts the ample substrate scope tolerance with insensitive functional groups (Fig 1a). The constant strive to bring about the state-of-the-art methodologies has invigorated scientists to dig deep into the field of photochemistry. One of the significant patrons to this discipline is photoredox catalysis[11-13]. This visible-light-induced activation approach has been found to catalyze an assortment of cross-coupling, hydrogen isotope exchange, and C-H activation reactions.

In quest of diverting tracks from traditional synthetic approaches to contemporary protocols, Polyzos and co-workers carried out carbonylative amidation by infusing photochemistry and flow chemistry principles together[14]. Such method unlocks the door to multiphoton excitation catalysis, and corroboration with continuous flow set-up drastically reduces reaction times. But the use of carbon monoxide is still an impediment and best if avoided. Expanding the horizon of light-mediated dual catalysis, Melchiorre and co-workers recently utilized a photoexcitable catalyst, nickel salt and brought them under the visible light to efficiently transform carbamides from their respective aryl or heteroaryl bromide counterparts (Fig 1a)[15]. The process involved bench-stable 4-carbamoyl-1,4-dihydropyridine derivatives as the carbamoyl radical source, giving promising results with a wide range of substrates. However, the synthesis of the carbamoyl precursor(s) renders the process rather lengthy, thereby could not foster the carbamoyl radical from the readily available source. These two methods are mostly suitable for aryl bromides. Although, among the commercially available aryl halides, aryl chlorides are more abundant (Fig 1b) and ubiquitous in natural products and pharmaceutically relevant molecules[16].

We aimed at synthesizing these biologically and industrially rich aryl carbamides from aryl chlorides and bromides in a single step by utilizing commercially feasible carbamoyl chlorides as our core reactant. To the best of our knowledge, there are hardly any exploration of direct activation of carbamoyl chloride[17]. Rather a prefunctionalized carbamoyl source or even *N*,*N*-dimethyl formamide have been utilised for the transition metal catalysed synthesis of amides from aryl halides[18-21]. Nevertheless, the limited substrate scope, harsh reaction condition constitute practical limitation to these approaches. Moreover, in the regime of photochemistry, the generation of carbamoyl radical *via* SET reduction of the corresponding chloride is impeded by their exceedingly high reduction potential (Fig 1c). Consequently, the available techniques to initiate carbamoyl radicals mostly rely on the HAT process from corresponding formamide or on SET activation of intentionally synthesized antecedents with suitable redox active groups[22-27]. To circumvent the challenges, we envisage to utilise the innate affinity of silicon towards halogen atom which lead us to choose a suitable halogen atom transfer (XAT)-agent precursor likely tris(trimethylsilyl)silane (TTMSS) in the new realm of Ni-photoredox dual catalysis for direct activation of carbamoyl chloride leading to the fruitful orchestration of amide bond (Fig 1c)[28,29]. Although, the silane mediated halogen atom abstraction is rarely explored at sp^2-carbon centre[30] and a possibility of facile oxidative addition of reactive acyl moiety to the low valent metal will be the impediments towards the favourable outcome[31,32]. Thus, the successful realization of our methodology requires the identification of an appropriate mechanism for direct generation of carbamoyl radical and the precise formation of oxidative addition of aryl halides to Ni-complex under mild conditions (Fig 2a). However, more challenges are awaiting in this regards since the cyclic voltammetry study revealed that the excited photoredox catalyst $*[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ could not reduce carbamoyl chloride to engender carbamoyl radical. Even the Stern–Volmer study reassured that there is no interaction between carbamoyl chloride and excited state of photocatalyst (For details, see SI). In contrast, the photoredox catalyst $*[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ ($E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +0.59 V vs Fc^+/Fc in CH_3CN) could oxidise tris(trimethylsilyl)silane (TTMSS) (E^{ox} [TTMSS/TTMSS$^{\bullet+}$] = +0.43 V vs Fc^+/Fc in CH_3CN) to generate the $(TMS)_3Si$ radical upon loss of a proton. Once again, the luminescence quenching studies disclosed that TTMSS could not decreases the fluorescence intensity of the photocatalyst which invalidated the single-electron transfer between these two. We eventually recognized that discretely synthesized Ni(II)-aryl bromide oxidative addition complex **B1** (E^{ox} [Ni^{II}/Ni^{III}] = +0.31 V vs Fc^+/Fc in CH_3CN) would rather quench the excited state of photocatalyst (Fig 2b & 2c). This outcome implied that a direct single-electron transfer is possible between the oxidative addition complex **B1** and the excited state of Ir-photocatalyst which would inturn generate a short lived Ni(III) upon oxidation. Revisiting the literature, we found that Nocera and Doyle groups individually reported the visible-light promoted elimination of chlorine radical from Ni(III) trichloride and Ni(III) aryl chloride species respectively[33,34]. In accordance with their reports, we perceived a similar photoelimination of bromine radical from Ni(III) species that participated in sequential HAT from TTMSS followed by an instant XAT by the silyl radical from carbamoyl chloride, rendering the cardinal carbamoyl radical intermediate (Fig 1c).

With these informations, a suitable mechanism for the silane-mediated carbamoylation of aryl or heteroaryl halides is recommended (Fig 2a). We proposed that facile oxidative addition of Ni(0) (**A**) into an aryl halide would produce Ni(II) aryl halide intermediate (**B**). Synchronously, the heteroleptic photoredox catalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (**C**) could easily absorb photon under visible light excitation to transform into strongly oxidizing long-lived triplet excited complex (**D**) $*Ir[dF(CF_3)ppy]_2(dtbbpy)+$ ($E_{1/2}^{red}$ [$*Ir^{III}/Ir^{II}$] = +0.59 V vs Fc^+/Fc in CH_3CN) which would be capable of oxidizing Ni(II) complex (**B**) (E^{ox} [Ni^{II}/Ni^{III}] = +0.31 V vs Fc^+/Fc in CH_3CN) to afford transient Ni(III) intermediate (**E**) (Fig 2b). Photolysis of this intermediate **E** would allow to generate a halogen radical and Ni(II) species (**F**). The resulting halogen radical could take part in hydrogen atom transfer with TTMSS (**G**) (H-Br BDE = 87 kcal mol^{-1}, H-Cl BDE = 102 kcal mol^{-1}, $(TMS)_3Si$-H BDE = 84 kcal mol^{-1})

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to yield the nucleophilic silyl radical (**H**). Subsequent chlorine-atom abstraction from the carbamoyl chloride (**2**) by this open-shell $(TMS)_3Si$ radical species (**H**) would fetch the key carbamoyl radical (**I**). Also, the isolated TTMSS-chloride from the reaction mixture authenticated our understanding. Rebound of this resulting carbamoyl radical (**I**) with Ni(II) would produce corresponding aryl–Ni^{III}–$CONMe_2$ complex (**J**). Subsequent reductive elimination then afforded the desired amide product and generate Ni^{I} species (**K**). Finally, a single electron-transfer (SET) reduction of the resulting Ni(I) intermediate (**K**) by highly reducing photocatalyst Ir^{II} (**L**) ($(E_{1/2}{}^{red}[Ir^{III}/Ir^{II}]$=-1.72 V vs Fc^{+}/Fc in CH_3CN) would simultaneously regenerate low-valent nickel catalyst (**A**) and ground-state photocatalyst (**C**), concluding both the catalytic cycles.

With this mechanistic postulation, we ideated a mild, convenient, and broadly applicable metallaphotoredox-catalyzed synthesis of a wide assortment of aryl and heteroaryl carbamides. The strategy is pertinent with aryl or heteroaryl bromides and most significantly with aryl chlorides also. This will greatly increases the relevancy and eminence of our protocol in opening up more chemical space in pharmaceutically relevant fragment based drug discovery.

We commenced our experimental studies with 4-bromo benzotrifluoride **1** as the substrate and *N*,*N*-dimethylcarbamoyl chloride **2** as the coupling partner (Fig 2d) (see Supplementary Information for further details). Indeed, $[Ir\{dF(CF_3)ppy\}_2(dtbbpy)]PF_6$ (1 mol%) was proved to be the photocatalyst of choice, providing us the highest yield. Among various electronically and sterically distinct silyl reagents, tris(trimethylsilyl)silane (2.5 equiv) was the optimum of all. Furthermore, $NiBr_2$.glyme (5 mol%) was found to be better catalyst along with the bidendate ligand 4,4'-di-tert-butyl-2,2'-bipyridine (6 mol%). Various organic and inorganic bases were put to test, however, only 1,1,3,3-tetramethylguanidine (TMG) bestowed satisfactory yield. Notably, TMG not only acted as a base in this reaction but also reduced the Ni(II)-precatalyst to Ni(0) which was substantiated by the react-UV-vis study (Fig 2e). Further, different polar aprotic solvents were studied, and acetonitrile remained our solvent of choice. We also carried out time optimization, and the 24-hour reaction window produced gratifying yield with exposure to a 34 W blue LED (440 nm) light source. Post optimization, we also demonstrated some control experiments in order to broadly understand the role of light and dependence of reaction on other parameters. From the results in our hand, we concluded that all the conditions as stated are vital for the reaction, and in absence of any of these, the reaction was almost silent (Fig 2d).

Subsequently, we wanted to assess the capability of the protocol and subsequently evaluated the scope with respect to diverse aryl halides (Fig 3a). In particular, substrates bearing electron-withdrawing groups, like trifluoromethyl, fluoro, ester, ketone, nitrile or sulfone, afforded the respective amides in high yields (entries **3**-**12**, Fig 3a) (74–85% yield). As depicted earlier, we were ecstatic that aryl chlorides were identically compatible to provide the desired products as well although the yields were slightly less than the aryl bromides. In accord with our optimized conditions, electron-rich and electron neutral haloarenes also performed well with a wide functional group tolerance furnishing the corresponding carbamides in moderate to good yield (entries **13**-**22**) (54-81% yield). We further checked the positional biasness on the arene moiety and to our delight, meta- and ortho-substituted aryl halides exhibited significant competency with this transformation (entries **23**-**27**) (59-81% yield). Additionally, polyaromaric halides such as naphthalene, tetraphene and pyrene successfully participated under the optimized reaction conditions (entries **28**-**31**) (62-72% yield). Inspired by compatibility and preponderance with versatile aryl halides, we desired to explore the potential for drugs and natural products bearing aryl bromides. Along that line, we had anchored natural products likely a monoterpenoid mint “menthol”, a steroid “estrone”, a type of lipid “cholesterol”, the most abundant monosachharide “β-D-glucose pentaacetate” and a nonsteroidal anti-inflammatory drug (NSAID) “naproxen” with suitable aryl bromides. The successful outcomes with these structurally diversified aryl halides truly demonstrated the versatility of the protocol (entries **32**-**36**, Fig 3b) (53-79% yield). We had also synthesized the bromo derivative of homoveratric acid methyl ester, a dopamine metabolite for the inhibition of brain mitochondrial respiration, that also afforded the desired carbamide **37** with acceptable yield.

After the favourable outcomes with a plethora of aryl halides, we turned our focus to the scope of heteroaryl halides (Fig 4a). At the outset, a diversely substituted halo pyridines were found to be suitable under the optimized conditions and afforded the respective pyridine carbamides in good yields. (entries **38**-**43**, Fig 4a) (66–79% yield). Next, the substituted chloro quinoline also afforded the desired product with good efficiency (entry **44**, 80% yield). It was noteworthy that multiple nitrogen containing heteroarenes, such as pyrimidine and indazole halides were readily converted into the corresponding carbamides in moderate yields (entries **45**-**47**). However, dehalogenation of these hereoarenes were the side products which actually curtailed the yield of the desired carbamides. In the same context, other five-membered halo heteroarenes likely 3-bromo thiophene (entry **48**) and 2-bromo thiazole (entry **49**), 3-bromo benzothiophene (entry **50**) were also found to be competent under the standard protocol. Similarly, other [5,6]-fused heterocycles having the halogen atom on the adjacent arene ring also participated in this reaction. In particular, carbamide derivatives of benzothiophene, benzofuran, benzo[1,3]-dioxole, carbazole, benzothiazole, indole and azaindole were obtained in good to high yields (entries **51**-**58**; 58–81% yield).

After the successful amplification of our methodology to a variety of aryl and heteroaryl halides, we also intended to explore the generality of this transformation on a range of carbamoyl chlorides (Fig 4b). We corroborated that a number of symmetrical as well as unsymmetrical carbamoyl chlorides were the appropriate antecedents for the metallaphotoredox catalysed amidation of aryl halides. These carbamoyl chlorides are either commercially available or can easily be synthesized from the corresponding amines by the treatment of triphosgene. Symmetrical carbamoyl chlorides likely dimethyl, diethyl and diisopropyl ones afforded the corresponding amides with 4-bromo benzotrifluoride in good yields (entries **3**, **59** and **60**). The inclusion of cyclic carbamoyl chloride containg a five membered pyrrolidine, six membered piperidine & morpholine and a seven membered azepine moieties also provided the corresponding amides in good yield (entries **61**-**64**) (71-78% yield). Besides, unsymmetrical carbamoyl chlorides having an aryl and alkyl group also got involved in this transformation. In this aspect, *N*,*N*- phenylmethyl, -phenylisopropyl carbamoyl chlorides successfully rendered the corresponding amides in good yield (entries **65** and **66**; 69% and 63% respectively). Moreover, substitution on the aryl ring was also tested and those carbamoyl chlorides having -CN and -OMe group on the aryl ring also furnished the desired amide in acceptable yield (entries **67** and **68**). Finally unsymmetrical dialkyl carbamoyl chloride was also compatible with this protocol, thereby allowing the access to valuable weinreb amide in moderate yield which can be utilised for further application (entry **69**).

Being conscious about the pharmaceutical and agrochemical congruity of the amide group, we finally sought to manifest the utility of our procedure in the late-stage amidation of halide containing drug molecules and medicinal agents (Fig 4c)[35-37]. We were overwhelmed that our protocol proved to be worthy as the carbamide-containing derivatives of nonsteroidal anti-inflammatory drug “indomethacin”, a topical anti-fungal agent “climbazole”, a selective COX-2 inhibitor “etoricoxib”, an oral medicine for the treatment of abnormal blood lipid levels “fenofibrate” and an antiemetic drug “dramanine” were synthesized in good to high yields from their corresponding aryl halide precursors (entries **70**-**74**) (65–75% yield). It is noteworthy that four out of these five drugs contain aryl chloride motif. Significantly, in “dramanine”, a selective carbamidation was eventuated particularly at aryl bromide over the aryl chloride functionality which enables a scope of further modification. These positive findings accentuate the possibility in expanding in the domain of drug discovery and may modulate the potency of the parent drugs[38,39].

As a conspectus, we have demonstrated a more general, operationally simple, widely applicable metallaphotoredox catalysed amidation of a broad range of aryl and heteroaryl halides in synchrony with a variety of cabamoyl chlorides. Besides the usual aryl bromides, this protocol is precisely efficacious for relatively less inspected aryl, heteroaryl chlorides and even with the chloro containing drug molecules. Simultaneously, this procedure utilises the silyl radical-mediated halogen abstraction mode that represents the first of its kind to access the carbamoyl radical directly from commercially available carbamoyl chloride. Additionally, the late stage drug diversification further emphasized the real-time utility of this metallaphotoredox catalysed crosscoupling reaction. Ensuing its distinct convenience and broad applicability to pharmaceutically relevant scaffolds, we expect this method will pave a new horizon within the realm of synthetic and medicinal chemistry research.

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METHODS SUMMARY

Ni/Ir-dual catalysed cross-electrophilic coupling between aryl halides and carbamoyl chlorides

To an oven-dried screw cap reaction tube equipped with a magnetic stir bar was added Ir photocatalyst (2 mg, 0.01 equiv.), $NiBr_2$.glyme (3 mg, 0.05 equiv.), dtbbpy (3.2 mg, 0.06 equiv.), 4-bromobenzotrifluoride (28 µL, 0.2 mmol, 1.0 equiv.), and *N*,*N*-dimethyl carbamoyl chloride (29 µL, 0.3 mmol, 1.5 equiv.) inside the Glove box. To this reaction vial was added TTMSS (169 µL, 2.5 equiv.), 1,1,3,3-tetramethylguanidine (75 µL, 0.6 mmol, 3.0 equiv.) followed by addition of 1.5 mL CH_3CN. The tube was sealed with a rubber fitted screw cap followed by sealing with Parafilm, taken out from the Glove box and irradiated with a 34 W Kessil PR-160L Blue LED from 3 cm away for 24 hours under the continuous flow of fan to maintain the temperature at 35-40 °C . The reaction was quenched by exposure to air, followed by water and subsequent extraction with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuum. The crude residue was purified by flash chromatography on silica gel (100-200 mesh size) to afford the desired product as yellow gummy liquid (35.5 mg, 82%).

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Author contributions

S.M., D.M. conceived the concept. S.M., S.R., P.G performed the reactions, analyzed the products, and carried out the mechanistic studies. D.M. supervised the experimental work. S.M., S.R., D.M. wrote the manuscript.

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Additional information

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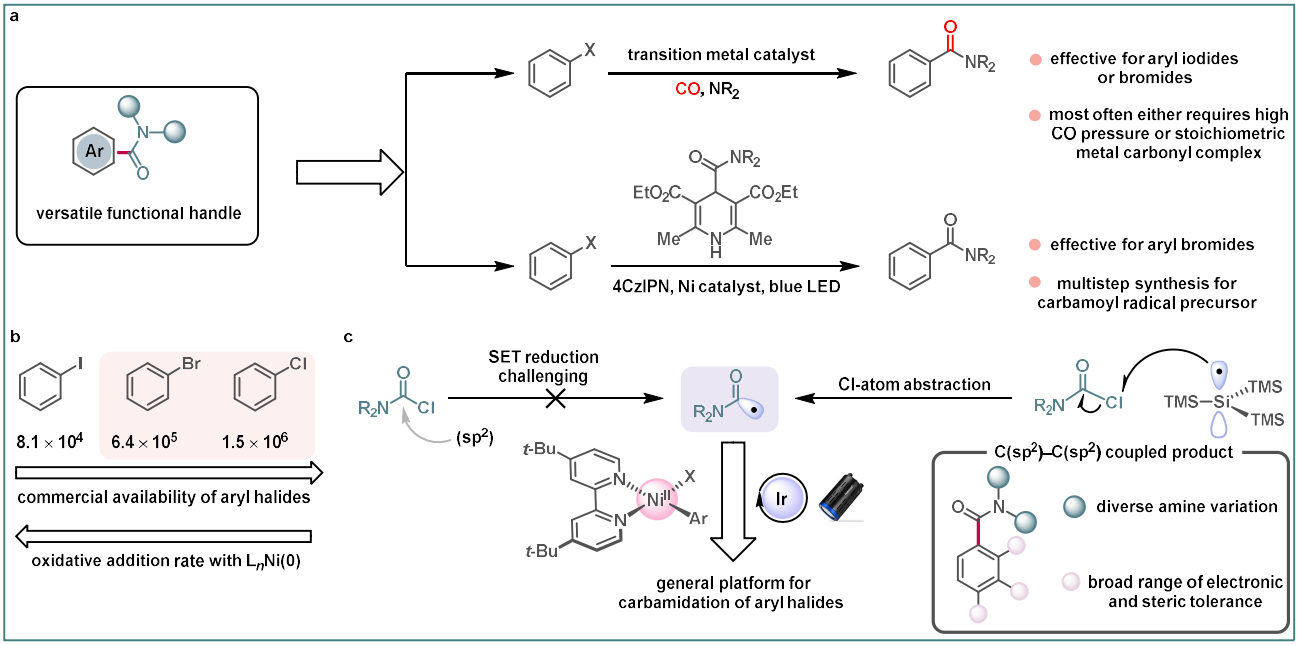

Fig. 1 | Overview of strategic development for cross-electrophilic coupling between aryl halides and carbamoyl chlorides. a, Established strategies for carbamide synthesis from aryl halides. b, Commercial abandance and reactivity of aryl halides. c, Strategic development for the direct activation of carbamoyl chloride to acess wide variety of carbamides.

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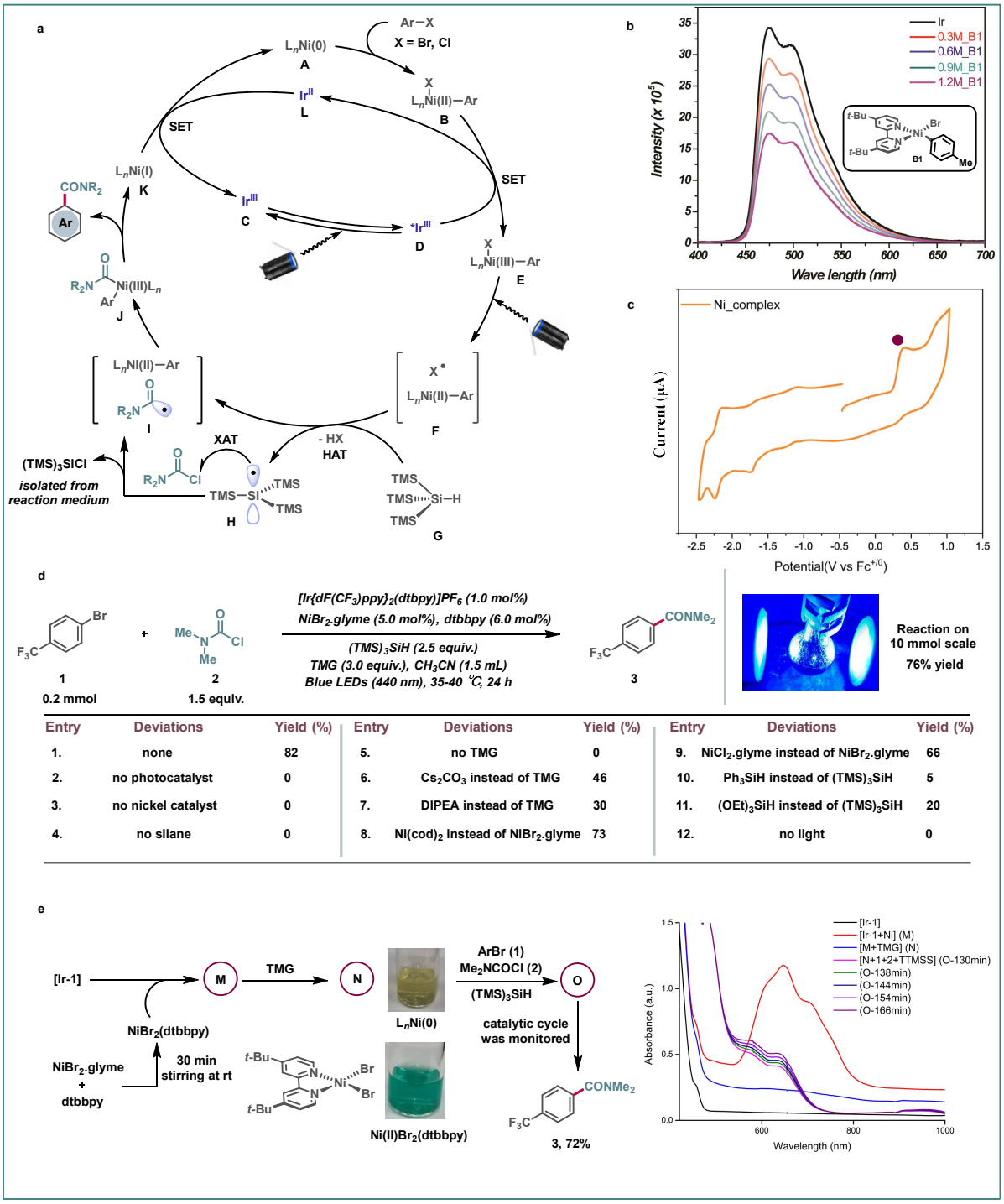

Entry	Deviations	Yield (%)	Entry	Deviations	Yield (%)	Entry	Deviations	Yield (%)
1.	none	82	5.	no TMG	0	9.	$NiCl_2$.glyme instead of $NiBr_2$.glyme	66
2.	no photocatalyst	0	6.	Cs_2CO_3 instead of TMG	46	10.	Ph_3SiH instead of $(TMS)_3SiH$	5
3.	no nickel catalyst	0	7.	DIPEA instead of TMG	30	11.	$(OEt)_3SiH$ instead of $(TMS)_3SiH$	20
4.	no silane	0	8.	$Ni(cod)_2$ instead of $NiBr_2$.glyme	73	12.	no light	0

Fig. 2 | Development of the Ni/Ir-dual catalysed cross-electrophilic coupling between aryl halides and carbamoyl chlorides. a, The proposed mechanism for the carbamidation reaction of aryl halides requires the merging of Ir-photocatalyst, Ni-catalyst and XAT reactivity of tris(trimethylsilyl)silane. **b**, Fluorescence quenching of Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ by electron transfer with (dtbbpy)Ni(II)(p-tolyl)Br (**B1**) in CH$_3$CN. **c,** Cyclic voltammogram of (dtbbpy)Ni(II)(p-tolyl)Br (**B1**) shows an irreversible first oxidation at E_p = 0.31 V versus Fc^+/Fc in CH$_3$CN which corresponds to the Ni^{II}/Ni^{III} redox couple. **d**, Optimization of the reaction condition between 4-bromo benzotrifluoride **1** and *N*,*N*-dimethyl carbamoylchloride **2** and relevant control reactions. **e**, UV–vis absorption spectroscopy studies support the individual steps in the catalytic cycle.

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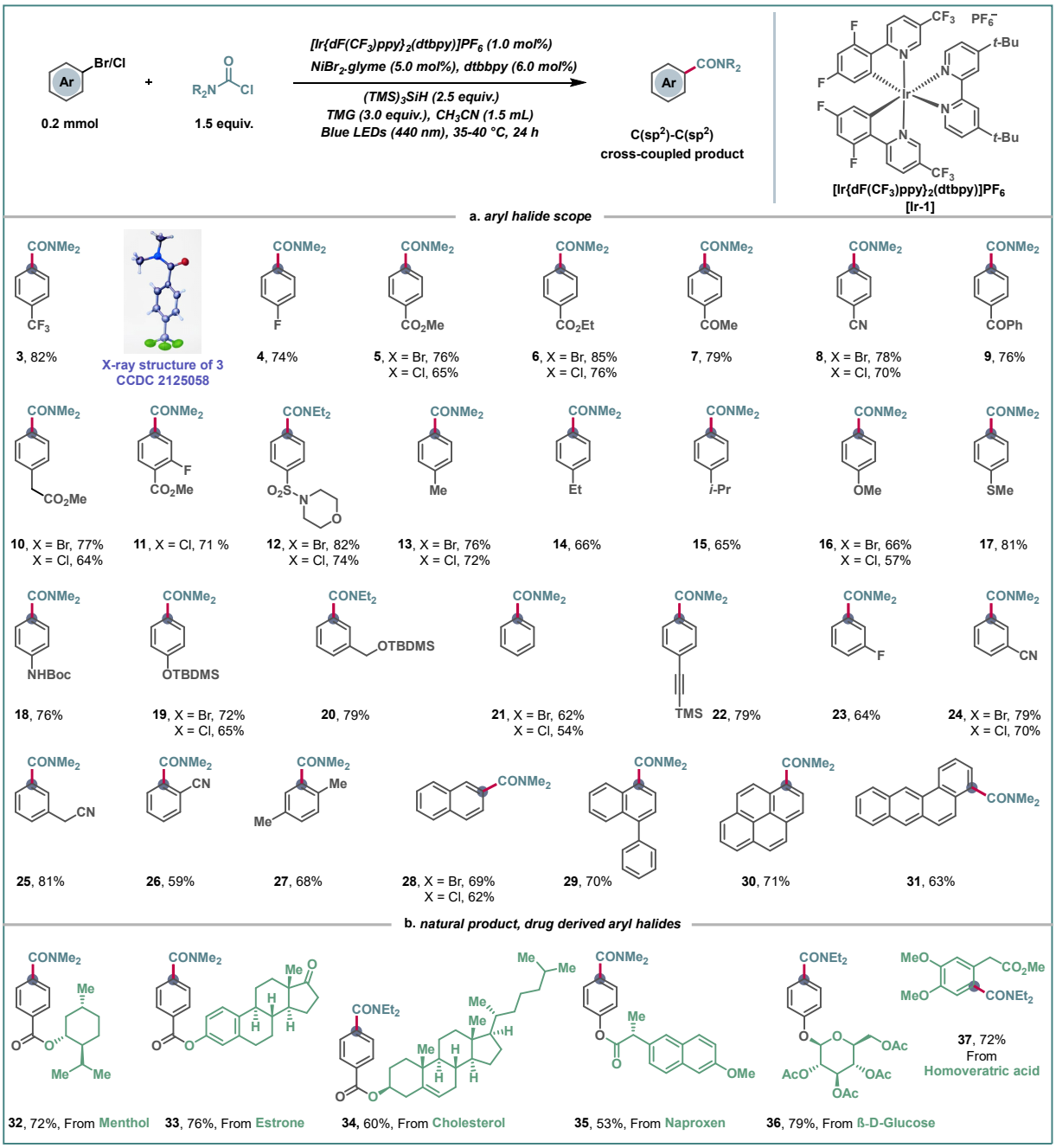

Fig. 3 | a, Scope of the aryl halide partners for the amidation reaction. b, Scope of natural product, drug derived aryl halide partners. Reaction condition: Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1.0 mol%), tris(trimethylsilyl)silane (TTMSS) (2.5 equiv.), NiBr$_2$.glyme (5.0 mol%), dtbbpy (6.0 mol%), aryl halide (1.0 equiv.), *N*, *N*-dialkyl carbamoyl chloride (1.5 equiv.), 1,1,3,3-tetramethylguanidine (TMG) (3.0 equiv.), CH$_3$CN (1.5 mL), Blue LEDs, 24 h. All substrates worked efficiently at 35-40 °C. All yields are isolated.

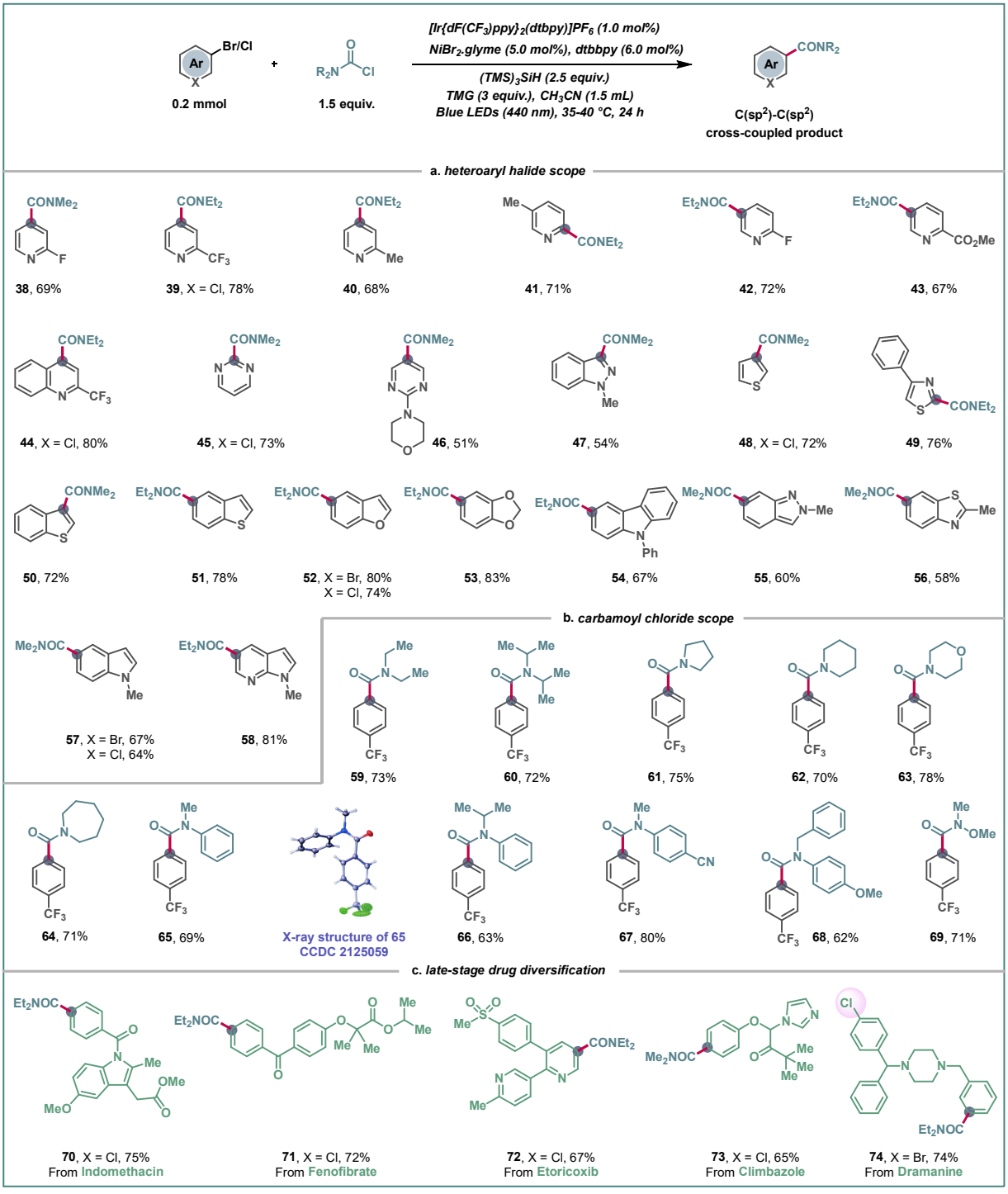

Fig. 4 | a, Scope of the heteroaryl halide partner for the amidation reaction. b, Scope of the carbamoyl chloride partner for the amidation reaction. c, Expanding the chemical space of amidation reaction by late-stage drug diversification. Reaction conditions: Ir[(dF(CF$_3$)ppy)$_2$(dtbbpy)]PF$_6$ (1.0 mol%), tris(trimethylsilyl)silane (TTMSS) (2.5 equiv.), NiBr$_2$.glyme (5.0 mol%), dtbbpy (6.0 mol%), aryl or heteroaryl halide (1.0 equiv.), *N*, *N*-dialkyl carbamoyl chloride (1.5 equiv.), 1,1,3,3-tetramethylguanidine (TMG) (3.0 equiv.), CH$_3$CN (1.5 mL), Blue LEDs, 24 h. All substrates worked efficiently at 35-40 °C. All yields are isolated.