COMMUNICATION

A Modular Dual-catalytic Aryl-chlorination of Alkenes

Bo Li[1], Ala Bunescu[1], Daniel Drazen[1], Katherine Rolph[1], Jean Michalland[1,2,3] and Matthew J. Gaunt[1,2]*

[1] Yusuf Hamied Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge, United Kingdom, CB2 1EW
[2] Innovation Centre in Digital Molecular Technologies
Yusuf Hamied Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge, United Kingdom, CB2 1EW
[3] Compound Synthesis & Management, Discovery Sciences, Biopharmaceuticals R&D,
The Discovery Centre, AstraZeneca
Biomedical Campus
1 Francis Crick Avenue, Cambridge, United Kingdom. CB2 0AA

mjg32@cam.ac.uk

Supporting information for this article is given via a link at the end of the document.

Abstract: Alkyl chlorides are a class of versatile building blocks widely used to generate C(sp^3)-rich scaffolds through transformation such as nucleophilic substitution, radical addition reactions and metal-catalyzed cross-coupling processes. Despite their utility in the synthesis of high-value functional molecules, distinct methods for the preparation of alkyl chlorides are underrepresented. Here, we report a visible-light-mediated dual catalysis strategy for the modular synthesis of highly functionalized and structurally diverse arylated chloroalkanes *via* the coupling of diaryliodonium salts, alkenes and potassium chloride. A distinctive aspect of this transformation is a ligand-design-driven approach for the development of a copper(II)-based atom-transfer catalyst that enables the aryl-chlorination of electron-poor alkenes, complementing its iron(III)-based counterpart that accommodates non-activated aliphatic alkenes and styrene derivatives. The complementarity of the two dual catalytic systems allows the efficient aryl-chlorination of alkenes bearing different stereo-electronic properties and a broad range of functional groups, maximizing the structural diversity of the β-aryl ethyl chloride products.

The multi-faceted reactivity of alkyl chlorides makes them important building blocks for the assembly of architecturally complex C(sp^3)-rich molecules.[1] Despite their well-recognized utilities[2], methods to access alkyl chlorides directly from readily available reagents remain rare[3] beyond classical synthetic strategies such as Markovnikov additions to alkenes[4] and substitution reactions of alcohols.[5] One area that has resulted in the evolution of new technologies for the synthesis of complex alkyl chlorides has been transformations based on the difunctionalization of alkenes. Although seminal discoveries of high-valent Pd(IV)-mediated hydro- or aryl-chlorination of alkenes have underpinned the synthesis of many C(sp^3)-enriched alkyl chlorides[6], the use of highly oxidative chlorination reagents and toxic aryl transfer reagents, such as aryl tin or aryl mercury, can sometimes limit the utility of these methods.[7] We reasoned that the development of a mechanistically distinct modular, catalytic and, importantly, practical method for the synthesis of alkyl chlorides would be a valuable addition to the synthetic toolbox and of interest to chemists in academic and industrial environments.

Recently, we described the development of a dual catalytic platform for the aryl functionalization of alkenes based on a photocatalytic reduction of diaryliodonium salts, to generate an aryl radical, that adds to an alkene and was linked to a separate transition metal catalyzed group transfer cycle that orchestrated capture of the incipient homobenzylic radical with an anionic nucleophile. This platform resulted in new methods for the azido-arylation of alkenes[8] and the aryl-chlorination of vinyl boronic esters[9] (Figure 1A). We found that the modularity of this dual catalysis system enabled the combination of $[Cu(dpp)_2](PF_6)$ photocatalyst (dpp = 2,9-diphenyl-1,10-phenanthroline) and BQA•$Cu(OTf)_2$ (BQA = *N-tert*-butyl-1-(quinolin-2-yl)methanimine) based atom-transfer catalyst to be a highly effective system for the azido-arylation of a broad range of alkenes[8], while the aryl-chlorination of vinyl boronic esters was more efficiently facilitated by pairing the $[Ru(bpy)_3](PF_6)_2$ (bpy = 2,2'-bipyridine) photocatalyst and $[(bpmen)FeCl_2]$ (bpmen = *N,N*-dimethyl-*N,N*-bis (pyridin-2-ylmethyl) ethane-1,2-diamine) atom-transfer precatalyst.[9] Aryl radical-mediated alkene azido-arylation[10] and aryl-bromination[11] reactions based on our reactivity concept have been subsequently reported by others, who used arylthianthrenium salts or aryl dibenzothiophenium salts as aryl radical precursors.

We questioned whether the catalyst modularity of our distinct dual catalysis strategy could be engineered to accommodate a range of electronically diverse alkenes as part of a broadly applicable aryl-chlorination reaction (Figure 1B). In accommodating a range of alkenes in this aryl-chlorination, a critical question arises surrounding the needs of the catalyst-controlled chlorine group transfer step; use of different polarized alkenes will give rise to electronically distinct homo-benzylic radical intermediates that may have significantly different

reactivities that must be aligned to the reactivity of the group-transfer catalyst.

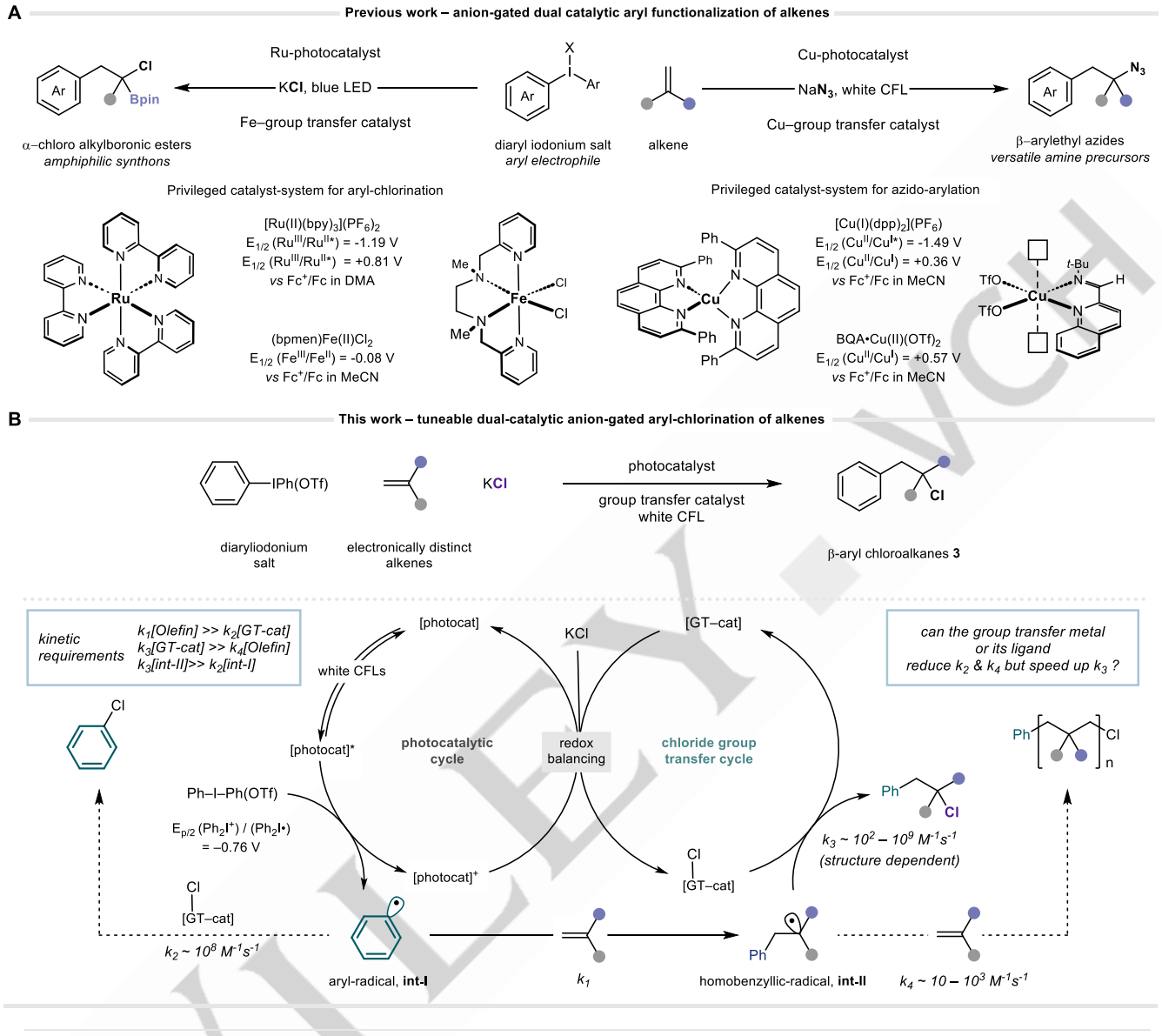
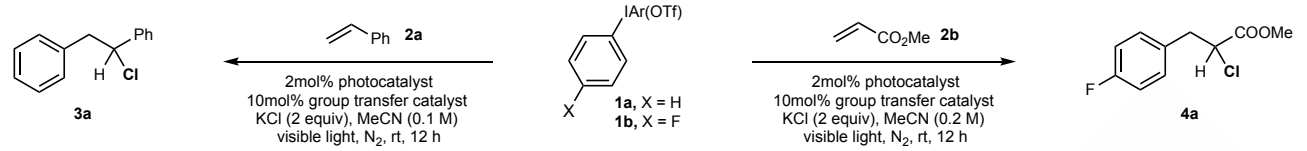


Figure 1. Towards a new dual catalyzed strategy for the modular synthesis of β-aryl ethyl chlorides.

We reasoned that the modularity of our dual-catalysis method would be ideally suited to interchanging metal salts and ligands for the group transfer step, potentially allowing reaction manifolds that could accommodate different types of substituted alkene. More specifically, the reactivity of the group transfer catalyst can be influenced by the nature of the metal center and the electronic and steric proprieties of its supporting ligand. Based on our previous studies, two side reactions required careful optimization: atom transfer from the metal-chloride complex to the photocatalytically-generated aryl radical **Int-I** (Sandmeyer reaction, k_2, ~10^8 $M^{-1}s^{-1}$, where k is the rate constant) and the iterative addition of β-aryl ethyl radical **Int-II** to the alkene (k_4, ~$10 – 10^3$ $M^{-1}s^{-1}$) that results in the formation of a mixture of oligomers (Figure 1B).[12] To enable productive aryl chlorination of alkenes, the addition of an aryl radical to the alkene must be faster than Sandmeyer-type chlorination; and the radical oligomerization should be slower than the chlorine atom transfer from the metal-chloride to the β-aryl ethyl radical **Int-II**. The rate of the chlorine atom transfer to aryl (k_2) and alkyl radical (k_4) can be modified by the nature of the metal center and the supporting ligand of the group transfer catalyst.

Here we report the identification of two different catalytic systems that enable multicomponent synthesis of β-aryl chloroethanes from electronically distinct alkenes. For styrene derivatives and non-activated alkenes, the dual catalytic system relies on the action of a copper-based photocatalyst and an iron-

based chlorine-transfer catalyst. However, for electron deficient alkenes, a copper-based photocatalyst and pyridylimine-ligated copper chlorine-transfer catalyst was required. In this case, such modular ligands present a versatile bidentate N(sp^2)-hybridized backbone, the modification of which allows the tailoring of the electronic and steric properties of the Cu(II)-group-transfer catalyst.



entry	alkene	photocatalyst	group transfer catalyst	**3a** or **4a** (%)	ArCl	oligomers
1	**2a**	$[Ru(bpy)_3](PF_6)_2$	$[(bpmen)FeCl_2]$	58	–	–
2	**2a**	$[Cu(dpp)_2](PF_6)$	$[(bpmen)FeCl_2]$	**89**	–	–
3	**2b**	$[Cu(dpp)_2](PF_6)$	$[(bpmen)FeCl_2]$	29	trace	>60
4	**2b**	$[Cu(dpp)_2](PF_6)$	$Cu(OTf)_2$ + BQA[a]	70	8	>10
5	**2b**	$[Cu(dpp)_2](PF_6)$	$Cu(OTf)_2$ + PPA[a]	70	20	<5
6	**2b**	$[Cu(dpp)_2](PF_6)$	$Cu(OTf)_2$ + BPA[a]	83	10	<5
7	**2b**	$[Cu(dpp)_2](PF_6)$	$[Cu(MeCN)_4](PF_6)$ + BPA[b]	**96**	trace	trace
8	**2b**	$[Cu(dpp)_2](PF_6)$	$Cu(OTf)_2$ + Bpy[a]	60	6	>15

N(sp²)-bidentate ligands for Cu-based transfer catalyst

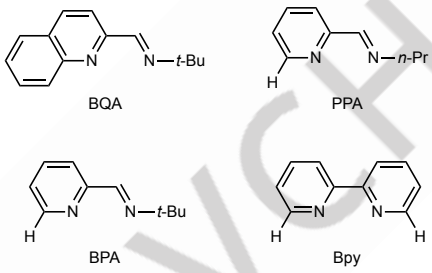


Figure 2. Evaluation of reaction conditions for the synthesis of a 1-aryl-2-chloroalkanes. Reactions were performed under following conditions unless stated otherwise: 0.1 mmol scale of diaryliodonium salt **1a** or **1b** (1.0 equiv), alkenes **2a** or **2b** (4.0 equiv), KCl, (2.0 equiv), group-transfer catalyst (10mol%), photocatalyst (2.0mol%), CH_3CN (0.1 or 0.2 M), room temperature, N_2, 40 W blue LED or 30 W CFL, 16 hours. Yields were determined by ^1H and ^{19}F NMR spectroscopy with CH_3NO_2 and $PhCF_3$ as an internal standard, respectively. [a] CD_3CN (0.1 M) was used instead of CH_3CN. [b] 2mol% of $[Cu(MeCN)_4](PF_6)$: BPA (1:1) was used and the reaction was performed in CH_3CN (0.2 M).

At the outset of our studies, we explored the aryl-chlorination reaction using styrene (**2a**) and methyl acrylate (**2b**) as representative examples of distinctly polarized alkenes. Selected data from our optimization studies are shown in Figure 2. Our initial reactions assessed styrene **2a** (4.0 equiv) in combination with diphenyliodonium triflate **1a** (1.0 equiv) as the aryl radical precursor and KCl (2.0 equiv) in the presence of 2.0mol% photocatalyst, $[Ru(II)(bpy)_3](PF_6)_2$, and 10mol% chlorine atom-transfer pre-catalyst, $[(bpmen)Fe(II)Cl_2]$, with acetonitrile as solvent and under irradiation with a 40 W blue LED lamp.[12] This initial reaction delivered the desired β-aryl ethyl chloride **3a** in 58% yield, determined by ^1H NMR spectrometry (Figure 2, entry 1). Following extensive evaluation among a range of photocatalyst (see Supporting Information section II.1.1), we were pleased to observe that **3a** was obtained in almost quantitative assay yield in the presence of $[Cu(I)(dpp)_2](PF_6)$ as photocatalyst and $[(bpmen)Fe(II)Cl_2]$ as group-transfer catalyst (entry 2). Cu(II)-based group-transfer catalysts bearing different bidentate N(sp^2)-enriched ligands were also assessed for their efficiency in facilitating the aryl-chlorination of **2a** in the presence of photocatalyst $[Cu(I)(dpp)_2](PF_6)$. Although these Cu(II)-catalysts were also found effective for group-transfer in the styrene system, the product **3a** was obtained in lower yield compared to the use of Fe(II)-catalyst (see Supporting Information, section II.2.2 and II.2.3).

Retaining the Cu(I)-photocatalyst and Fe(II)-group transfer catalyst conditions (entry 2), we next explored the aryl-chlorination of methyl acrylate (**2b**). After initial experiments using diphenyliodonium salt **1a** it was clear that formation of chlorobenzene (Sandmeyer reaction) and oligomeric material was being formed in considerable amounts. To enable us to track these side products, we switched the source of aryl radical to di(4-fluorophenyl)iodonium salt **1b** to allow the aryl-chlorination of **2b** to be quantitatively profiled using ^{19}F NMR spectroscopy, which would provide important information for the understanding the relative rates of the operational reaction pathways. Accordingly, aryl-chlorination of methyl acrylate with photocatalyst $[Cu(I)(dpp)_2](PF_6)$ and $[(bpmen)Fe(II)Cl_2]$ as group-transfer catalyst led to a low yield of the desired product **4a** (29%) and a significant amount of oligomerization (~60%, entry 3) indicating a much slower rate of the Fe(III)-mediated chlorine-transfer to the homobenzylic-radical relative to further radical addition to methyl acrylate. When switching the group-transfer catalyst to a *t*-butyl quinaldimine (BQA)-ligated Cu(II)-salt (entry 4), which had proven to be an excellent azido-transfer catalyst with a range of electron-deficient alkenes in our previous studies[8], a significant improvement to the yield of **4a** (to 70%) was observed and the formation of 4-fluoro-chlorobenzene and oligomers were suppressed. Despite the effectiveness of the BQA•Cu(II)-complex in facilitating chlorine atom-transfer, we reasoned that further ligand tuning to meet the different steric requirements of chlorine transfer, compared to the azide-transfer for which it was developed, might still improve the reaction. During copper-mediated group-transfer processes, the incipient radical will approach the distal nitrogen atom of the ligated azide[13], which moves the reaction center two more atoms away from the copper. The metal and radical centers in the chlorine atom-transfer process are only separated by a single chlorine atom, enhancing

the steric repulsion between the ligand and the substituents around the radical. Therefore, we postulated that reducing the steric impact of the BQA-ligand backbone could lead to a more kinetically favored Cu(II)-mediated chlorine atom-transfer to electron-deficient homobenzylic radical relative to the competing Sandmeyer chlorination and oligomerization pathways.

Removal of the steric hindrance in both the imine motif and the heterocyclic fragment led to the design of *N*-*n*-propyl-2-pyridinecarboxaldimine (PPA) and its deployment in the aryl-chlorination of **2b** produced the desired product **4a** in approximately the same yield as BQA-ligated copper catalyst (70%, entry 5). Notably, oligomerization was suppressed (<5%) but an increasing amount of Sandmeyer product was observed (20%), which suggested a less hindered catalyst increased the rate of the Sandmeyer pathway. Reintroducing steric bulk in the imine portion of the ligand (*n*-propyl to *t*-butyl) on a less hindered pyridyl scaffold led a *N*-*t*-butyl-2-pyridinecarboxaldimine (BPA)-ligated copper catalyst, which was found substantially improve the yield of **4a** to 83% (entry 6) by reducing the competing pathways (Sandmeyer product ~10%; oligomers <5%).[12b] Further optimization revealed that *in situ* generation of a BPA•Cu(I) pre-catalyst afforded **4a** in 96% yield with much lower catalyst loading (2.0mol%, entry 7). Bipyridine (bpy) was also evaluated (entry 8), which resulted in only a moderate yield of **4a** (60%) with an increased amount of oligomerization product (>15%), further reinforcing the impact of the pyridyl-imine derived ligands. Other combination of catalysts (see section II.1.3, II.2.1 and II.2.2 in the Supporting Information) and solvents (see section II.1.2 in the Supporting Information) were also evaluated but returned inferior results to the Cu/Fe and Cu/Cu dual catalyst systems described in Figure 2.

Taken together, these optimization studies reveal a clear catalyst modularity in this system, which dictated the product distribution across different types of alkenes. However, more importantly, tailoring the steric effects of the *N*-heterocyclic fragment of pyridylimine ligands is the key to the reactivity of the group-transfer step and could be critical for the development of reactions employing different anion nucleophiles in the aryl-functionalization of alkenes. In summary, optimization revealed two sets of reaction conditions that were identified for aryl-chlorination of styrenes (*condition A*) and electron-deficient alkenes (*condition B*), respectively. Exposure of an anhydrous acetonitrile solution of diaryliodonium salts (1.0 equiv), alkenes (4.0 equiv) and potassium chloride (2.0 equiv) to compact fluorescent lamp (30 W, CFL) irradiation in the presence of 2.0mol% $[Cu(I)(dpp)_2](PF_6)$ and the appropriate chlorine atom transfer precatalyst: 10mol% $[(bpmen)Fe(II)Cl_2]$ is efficient to facilitate the chlorination process when styrenes are used (*condition A*); and 2mol% of a pre-catalyst generated *in situ* from $[Cu(I)(MeCN)_4](PF_6)$ and BPA was optimal for reaction with electron-deficient alkenes (*condition B*).

With optimal reaction conditions in hand, the scope of this new transformation was evaluated using a selection of styrenes (Figure 3A). When using the catalyst combination of $[Cu(I)(dpp)_2](PF_6)$ and $[(bpmen)Fe(II)Cl_2]$ (condition A), a range of electronically and sterically diverse substituted styrenes (**3a-j**) were found to work well. Notable examples include the accommodation of readily electron rich, halogenated and electron deficient styrenes, where the substituents are distributed across a variety of positions. The tolerance of the reaction conditions to reducible bromine (**3d**) and nitro (**3i**) substituents represents an important feature for downstream modification of the products. Styrenes containing Lewis-basic heteroatoms, such as 2-vinyl pyridine showed good compatibility to the aryl-chlorination producing the desired product in 50% yield (**3k**). Given the electron deficient nature of this styrene derivative, we also tested the conditions tailored specifically to this type of alkene. In line with our optimization studies, the vinyl-pyridine performed well using condition B (66% yield), reflecting the impact of the heteroarene motif on the alkene reactivity. In contrast, the aryl-chlorination product derived from 2-vinyl thiophene was susceptible to facile elimination (see Supporting Information, Scheme S2). Non-activated alkenes are sometimes compatible with aryl-radical mediated difunctionalization, but the slower aryl radical addition step usually limits the yield and reactions often require very high equivalents of the alkene. step.[11, 14] In our reaction system, we found that a range of simple non-activated alkenes performed moderately well even with only 4 equivalents of the alkene, providing comparable and sometimes improved yields to related transformations[11, 14]. Pleasingly, a reaction with the Cu(I)-photocatalyst and Fe(II)-group-transfer catalyst gave the desired aryl-chlorination product in reactions with a several non-activated alkenes. For example, but-3-en-1-ylbenzene reacted to give the aryl-chlorination product **3n** in 40% yield. Interestingly, the dual catalysis reaction represented by conditions B (Cu(I)-photocatalyst and Cu-group-transfer catalyst) gave a modest conversion to **3n** in 27% yield. The superior compatibility of iron-based transfer catalyst in the aryl-chlorination of non-activated alkenes may attribute to a much slower Sandmeyer chlorination, meaning that aryl-addition to the alkene is competitive and forms the desired product. Further examples of non-activated alkenes include the reactions of methylenecyclobutane and *N*-Cbz-methylenepiperidine (to produce β-aryl-chloroalkanes bearing quaternary α-center (**3l**, **3m**) in synthetically useful yields. The reaction with remotely functionalized linear alkenes (**3n**-**3r**), including hydroxyl, halide and ester motifs, also provided the desired products in modest yields. Among the non-activated alkenes evaluated, those bearing remote ester functionalities noticeably led to higher yields of the desired aryl-chlorination adducts (**3r**, **3t**), which could be explained by a directing effect on the Fe group transfer catalyst.[15]

As anticipated from the optimization studies, the use of the BPA•Cu(I) salt as a pre-catalyst alongside $[Cu(I)(dpp)_2](PF_6)$ as photocatalyst (conditions B) proved to be excellent reaction conditions for the successful transformation of electron-deficient alkenes (**3u**-**3ah**, Figure 3B). In several cases, 1-aryl,2-chloroalkanes containing three orthogonal functionalities on the same carbon atom could be formed from this modular process, which would be challenging to obtain through established methods but useful for programmable downstream bond forming processes (**3aa**, **3ae**-**ag**). Methyl acrylate and acrolein, substrates that are often subject to radical-mediated polymerization, effectively produced β-aryl, α-chloro ester **3v** (72%) and aldehyde derivative **3y** (76%); hydroxyl and halide motifs were also

tolerated well, leading to **3aa** and **3ab** in 51% and 76% yield, respectively. Electron-deficient alkenes bearing a remote pyridyl group also gave rise to the desired aryl-chlorination adduct **3ae** in 60% yield, advocating the compatibility of the Cu-Cu catalyst system with Lewis basic functionality. Other alkenes displaying anilides and phthalimides were accommodated by the reaction and led to formation of **3af** and **3ag** in synthetically useful yields. In particular, **3ag** represents a highly functionalized β-amino acid scaffold. The successful aryl-chlorination of isoalantalactone (**2ah**), a natural product bearing two distinct alkenes, demonstrated that the (Cu/Cu)-catalyst system is chemoselective for the electron-deficient alkene, as expected from our previous studies on aryl azidation[7].

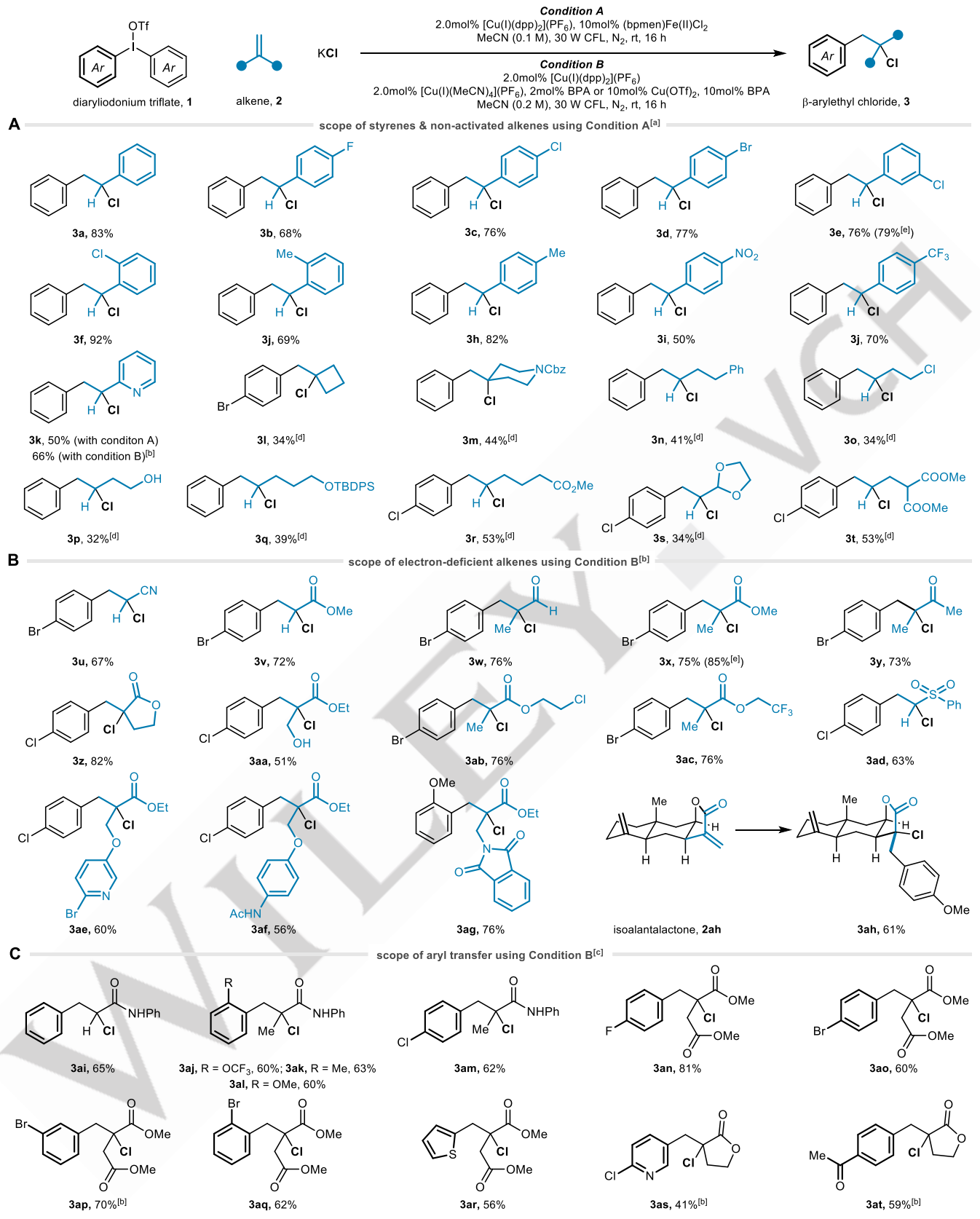


Figure 3. Scope of alkenes and aryl components in dual catalyzed aryl-chlorination of alkenes. [a] isolated yield with condition A; [b] isolated yield with condition B using $[Cu(MeCN)_4](PF_6)$ (2.0mol%)+BPA(2mol%) as group transfer pre-catalyst; [c] isolated yield with condition B using $Cu(OTf)_2$ (10mol%)+BPA(10mol%) as group transfer pre-catalyst [d] reaction performed at 0.2 M. [e] isolated yield using 1 mmol limiting reagent.

The scope of the aryl component was also assessed under the scheme of (Cu/Cu)-catalyst system (condition B) with several α,β-unsaturated amides and esters, which showcased that a range of diaryliodonium salts could be successfully employed (Figure 3C **3ai-3at**).[9,16] Substituents on the aryl group could be incorporated at the *ortho*, *meta* and *para* positions with halogens, alkyl groups and electron-donating groups (**3ak-3aq**). Aryl groups bearing electron-withdrawing substituents also worked satisfactorily (**3aj, 3at**). Transfer of thienyl and pyridyl units from the corresponding symmetrical diaryliodonium salts was also proved viable, albeit in a slightly diminished yield (**3ar, 3as**). Aryl group transfer from unsymmetrical iodonium salts was not evaluated since radical-mediated aryl transfer displays modest selectivity amidst differentially substituted arenes.[9] The synthesis of **3e** (using condition A) and **3x** (using condition B) on a 1 mmol scale with respect to the diaryliodonium triflate gave 79% and 85% yield of the corresponding products.

Following evaluation of the scope of the reaction, mechanistic studies provided experimental evidence for the presence of key intermediates and the turnover pathways for both the photocatalyst and the group-transfer catalyst (detailed in section V in the Supporting Information).[7,8] These studies suggest that under the optimal conditions (A-Cu/Fe and B-Cu/Cu), the transformation is proposed to start with visible-light excitation of the Cu(I) photocatalyst, which is then oxidatively quenched by the diaryliodonium triflate **1a** to form the aryl-radical **int-I** and an oxidized $[Cu(II)(dpp)_2]^{2+}$ species. The aryl radical can undergo addition to C–C double bond to form the homobenzylic radical **int-II** or **int-III**, depending on the alkene used.

In line with our previous work, [8,9] extensive mechanistic studies revealed subtle differences between the two dual catalysis systems in the manner through which the photocatalyst is turned over to close the catalytic cycle. In both dual-catalysis regimes photocatalyst turnover is enabled by interaction with the precursor to the active group-transfer complex, leading to concurrent formation of the active Fe(III) (Figure 4A) or Cu(II) (Figure 4B) chlorine atom-transfer species. In the Cu-Fe catalyst system (conditions A), the potentials of the oxidized photocatalyst $[Cu(II)(dpp)_2]^{2+}$ and group-transfer pre-catalyst $[(bpmen)Fe(II)Cl_2]$ (Figure 1A) are clearly capable of balancing the catalytic cycles through a thermodynamic intermolecular single electron transfer (SET) pathway (Figure 4A). Interestingly, however, we also found that the presence of excess chloride anion improved the turnover event. This can be explained by the parallel operation of an inner-sphere electron transfer (ISET) pathway to turnover the catalytic cycles, which we have observed in our previous studies (see Supporting Information for an extended discussion).[9] While the operation of these two pathways cannot be distinguished, it is clear that the anion-gated ISET pathway plays a substantial role. In the Cu/Cu system (conditions B and Figure 4B), the oxidation potentials of the respective species (Figure 1A) suggest that thermodynamic intermolecular SET between the oxidized photocatalyst $[Cu(II)(dpp)_2]^{2+}$ and the group-transfer pre-catalyst $[Cu(I)(BPA)]^{+}$ is not sufficient to mediate photocatalyst turnover alone. The presence of chloride anion was essential to photocatalyst turnover and highlights a synergy with the group-transfer pre-catalyst, wherein inner-sphere electron transfer (ISET) via bridging μ_2-Cl ligand occurs between the BPA•Cu(I) species and oxidized photocatalyst $[Cu(II)(dpp)_2]^{2+}$.[8] In each reaction platform (A or B), the metal–chlorine complex (Fe or Cu) reacts with to the homobenzylic radical **int-II** or **int-III** to furnish the desired aryl-chlorination product.

The remaining distinguishing feature of this transformation is the alignment of the electron properties of the alkenes with the type of chlorine group transfer catalyst. Styrenes display optimal reactivity with the Cu/Fe dual catalysis system (conditions A), whereas electron-deficient alkenes are better suited to the Cu/Cu catalyst pair (conditions B). This divergence appears to arise from the nature of the radical adduct. The benzylic radical derived from aryl-radical addition to styrene favors group transfer with a ligated Fe(III)–Cl complex, whereas a radical adjacent to a carbonyl or other electron withdrawing group that arising from addition to an acrylate (or similar) prefers group transfer with a Cu(II)–Cl species. Interestingly, electron deficient styrenes (**3k**) work well under both sets of reaction conditions, which suggests that a more subtle electronic effect may be operational in this platform rather that simply being influenced by the type of radical (**int-II/III**) formed from the corresponding alkene. At this stage, it is not clear what features of a particular metal and alkene substrate combination factors determine these preferences, but it is clear the modularity of the catalyst system can be tailored to suit different classes of substituted alkene substrate.

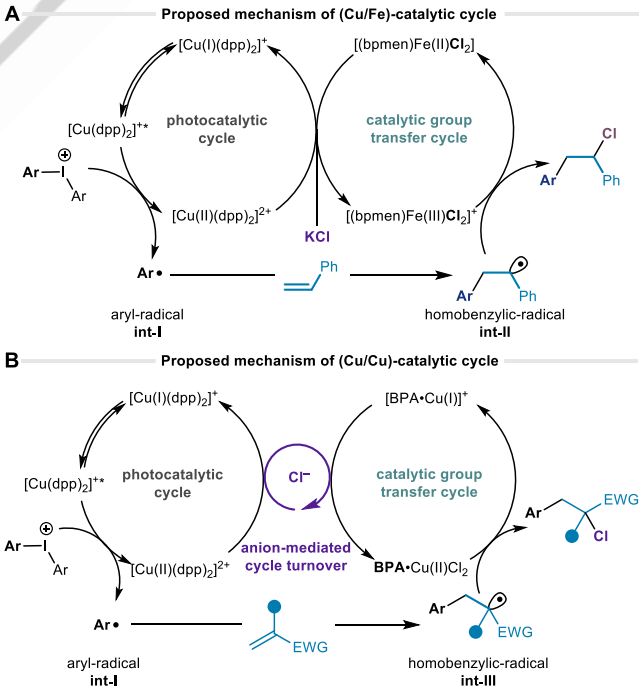


Figure 4. Proposed mechanism of the dual catalyzed aryl-chlorination of alkenes: (A) proposed mechanism for the (Cu/Fe)-catalyst system; (B) proposed mechanism for the (Cu/Cu)-catalyst system.

In summary, we have developed a multicomponent synthesis of versatile 1-aryl,2-chloroalkanes *via* dual catalyzed aryl-chlorination of alkenes. Functionalized chloro-alkane products of this type have been shown to display multi-faceted reactivity properties and are, as such, versatile building blocks that can be exploited in a wide range of synthetic transformations.[2] The transformation exploits aryl radical generation *via* photocatalytic reduction of readily available diaryliodium species and transition metal-catalyzed C–Cl bond formation, allowing sterically and electronically varied aryl moieties to be unbiasedly transferred to both activated and non-activated alkenes. The complementarity of the two dual catalytic systems allows the efficient aryl-chlorination of alkenes bearing different stereo-electronic properties and a broad range of functional groups, maximizing the structural diversity of the β-aryl ethyl chloride products. One of the unique features of this work was development of BPA-ligated Cu(II)-catalyst, driven by the rational design of a series of bidentate N(sp^2)-hybridized ligands, to facilitate chlorine atom-transfer to incipient electrophilic radicals, which were less effective with Fe-based chlorine atom-transfer catalysts. Moreover, tailoring the N-heterocyclic fragment of pyridylimine ligands could be critical for the development of reactions employing different anion nucleophiles in the wider development of this dual catalysis strategy for the aryl-functionalization of alkenes.

Supporting Information

All experimental procedures, extended mechanistic discussion, crystallographic data, and compound characterization (including ^{1}H ^{13}C ^{19}F NMR spectra, HRMS, and X-ray data) are available in the documents (PDFs). The authors have cited additional references within the Supporting Information.[16]

Acknowledgements

We are grateful to the Herchel Smith Fund at the University of Cambridge for a postdoctoral fellowship (A.B.) and EPSRC (EP/X015262/1).

Keywords: dual catalysis • ligand design • modular synthesis • product versatility

[1] a) L.-J. Cheng, N. P. Mankad, *Chem. Soc. Rev.* **2020**, *49*, 8036-8064; b) C.-L. Ji, X. Zhai, Q.-Y. Fang, C. Zhu, J. Han, J. Xie, *Chem. Soc. Rev.* **2023**, *52*, 6120-6138; c) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117-2188; d) A. Rudolph, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 2656-2670.

[2] a) Y. Liang, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 5520-5524; b) H. Cho, H. Suematsu, P. H. Oyala, J. C. Peters, G. C. Fu, *J. Am. Chem. Soc.* **2022**, *144*, 4550-4558; c) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265; d) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088-15089; e) S. Li, X.-Y. Chen, H. Sheng, C. von Essen, K. Rissanen, D. Enders, *Synthesis* **2018**, *50*, 1047-1052; f) K. E. Ozboya, T. Rovis, *Chem. Sci.* **2011**, *2*, 1835-1838; g) N. T. Kadunce, S. E. Reisman, *J. Am. Chem. Soc.* **2015**, *137*, 10480-10483; h) K. E. Poremba, N. T. Kadunce, N. Suzuki, A. H. Cherney, S. E. Reisman, *J. Am. Chem. Soc.* **2017**, *139*, 5684-5687; i) S. Xu, H. M. Holst, S. B. McGuire, N. J. Race, *J. Am. Chem. Soc.* **2020**, *142*, 8090-8096; j) W. T. Somerville, P. E. Spoerri, *J. Am. Chem. Soc.* **1952**, *74*, 3803-3807; k) P. M. Wood, L. W. L. Woo, M. P. Thomas, M. F. Mahon, A. Purohit, B. V. L. Potter, *ChemMedChem* **2011**, *6*, 1423-1438.

[3] a) A. Fawcett, M. J. Keller, Z. Herrera, J. F. Hartwig, *Angew. Chem. Int. Ed.* **2021**, *60*, 8276-8283; b) N. Fu, G. S. Sauer, S. Lin, *J. Am. Chem. Soc.* **2017**, *139*, 15548-15553; c) R. K. Quinn, Z. A. Könst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal, E. J. Alexanian, *J. Am. Chem. Soc.* **2016**, *138*, 696-702; d) Q. Qin, S. Yu, *Org. Lett.* **2015**, *17*, 1894-1897; e) D. J. Wilger, J.-M. M. Grandjean, T. R. Lammert, D. A. Nicewicz, *Nature Chemistry* **2014**, *6*, 720-726; f) J. Kim, X. Sun, B. A. van der Worp, T. Ritter, *Nature Catalysis* **2023**, *6*, 196-203.

[4] a) Wagner, *Justus Liebigs Annalen der Chemie* **1875**, *179*, 304; b) Mokijewski, *Chemiker-Zeitung, Chemische Apparatur* **1895**, *19*, 2254.

[5] Henry, *Recl. Trav. Chim. Pays-Bas* **1906**, *25*, 147.

[6] a) D. A. Petrone, J. Ye, M. Lautens, *Chem. Rev.* **2016**, *116*, 8003-8104; b) R. F. Heck, *J. Am. Chem. Soc.* **1968**, *90*, 5538-5542; c) D. Kalyani, A. D. Satterfield, M. S. Sanford, *J. Am. Chem. Soc.* **2010**, *132*, 8419-8427.

[7] a) M. Hempel, Y. K. Chau, B. J. Dutka, R. McInnis, K. K. Kwan, D. Liu, *Analyst* **1995**, *120*, 721-724; b) L. W. Chang, *The Journal of Toxicological Sciences* **1990**, *15*, 125-151.

[8] A. Bunescu, Y. Abdelhamid, M. J. Gaunt, *Nature* **2021**, *598*, 597-603.

[9] B. Li, A. Bunescu, M. J. Gaunt, *Chem* **2023**, *9*, 216-226.

[10] a) Y. Cai, S. Chatterjee, T. Ritter, *J. Am. Chem. Soc.* **2023**, *145*, 13542-13548; b) W. Zhang, T. Liu, H. T. Ang, P. Luo, Z. Lei, X. Luo, M. J. Koh, J. Wu, *Angew. Chem. Int. Ed.* **2023**, *62*, e202310978.

[11] Y. Cai, T. Ritter, *Angew. Chem. Int. Ed.* **2022**, *61*, e202209882.

[12] a) J. Qiu, K. Matyjaszewski, L. Thouin, C. Amatore, *Macromolecular Chemistry and Physics* **2000**, *201*, 1625-1631; b) W. Tang, Y. Kwak, W. Braunecker, N. V. Tsarevsky, M. L. Coote, K. Matyjaszewski, *J. Am. Chem. Soc.* **2008**, *130*, 10702-10713.

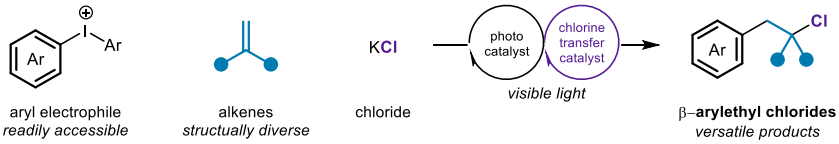
[13] L. Wu, Z. Zhang, D. Wu, F. Wang, P. Chen, Z. Lin, G. Liu, *Angew. Chem. Int. Ed.* **2021**, *60*, 6997-7001.

[14] P. M. Gorbovoi, G. N. Tulaidan, B. D. Grishchuk, *Russ. J. Gen. Chem.* **2008**, *78*, 133-135.

[15] H. Guan, S. Sun, Y. Mao, L. Chen, R. Lu, J. Huang, L. Liu, *Angew. Chem. Int. Ed.* **2018**, *57*, 11413-11417.

[16] a) M. Bielawski, D. Aili, B. Olofsson, *J. Org. Chem* **2008**, *73*, 4602-4607; b) M. Bielawski, M. Zhu, B. Olofsson, *Adv. Synth. Catal.* **2007**, *349*, 2610-2618; c) M. Kuriyama, N. Hamaguchi, O. Onomura, *Chemistry – A European Journal* **2012**, *18*, 1591-1594; d) R. Beaud, R. J. Phipps, M. J. Gaunt, *J. Am. Chem. Soc.* **2016**, *138*, 13183-13186.

Entry for the Table of Contents



We report a visible-light-mediated dual catalysis strategy for the modular synthesis of highly functionalized and structurally diverse β-aryl-alkyl chlorides *via* the coupling of diaryliodonium salts, alkenes, and potassium chloride.

Institute and/or researcher Twitter usernames: Gaunt_Group