Enantioselective, Catalytic Trichloromethylation through Visible-Light-Activated Photoredox Catalysis with a Chiral Iridium Complex

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ABSTRACT: An enantioselective, catalytic trichloromethylation of 2-acyl imidazoles and 2-acyl pyridines is reported. Several products are formed with enantiomeric excess of ≥99%. In this system, a chiral iridium complex serves a dual function, as a catalytically active chiral Lewis acid and simultaneously as a precursor for an *in situ* assembled visible-light-triggered photoredox catalyst.

Visible light constitutes an environmentally friendly and sustainable source of energy for activating chemical transformations, whereas asymmetric catalysis holds promise as one of the most economical strategies for the synthesis of non-racemic compounds. Interfacing asymmetric catalysis with visible light activation is therefore an area of high current interest.[1] Photosensitization provides the opportunity to induce single electron transfer (SET) processes under very mild conditions, thereby producing intermediate radical ions and radicals with useful reactivities.[2-4] However, at the same time, the high reactivities of such intermediates pose a significant challenge for interfacing them with asymmetric catalysis, indicated by the still limited number of mechanistically distinct visible-light-driven catalytic asymmetric reaction schemes.[5]

We recently introduced a simple chiral-at-metal iridium complex (Λ-**IrS**, Figure 1) as an effective asymmetric photoredox catalyst for the visible-light-induced enantioselective α-alkylation of 2-acyl imidazoles with electron deficient benzyl bromides and phenacyl bromides.[6] Despite its novelty, one can criticize that α-alkylations of carbonyl compounds with primary organobromides may be well executed under S_N2 conditions without the absolute need for involving redox chemistry.[7] Going beyond our previous proof-of-principle demonstration, we were therefore seeking an application in which redox catalysis is highly advantageous or even required. As a result, we here wish to report the first method for an enantioselective, catalytic trichloromethylation through visible light activated photoredox catalysis.

Trichloromethyl groups are present in natural products and contribute to their pharmacological properties.[8] However, methods for the stereoselective implementation of CCl_3 groups as part of stereogenic carbons are limited.[9,10] Notably, Zakarian and co-workers developed an elegant diastereoselective Ru-catalyzed redox-mediated radical addition to titanium enolates.[10]

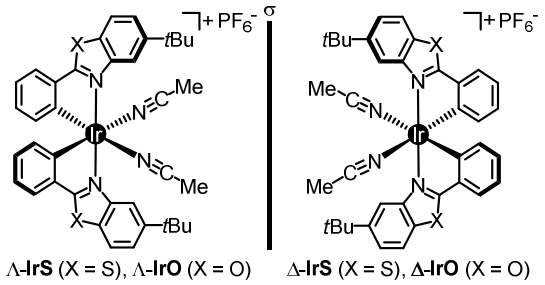
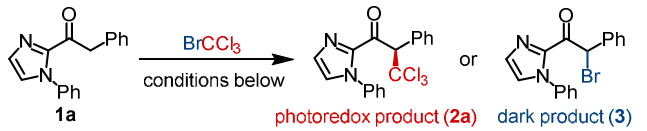


Figure 1. Chiral iridium complexes for merging visible-light-activated photoredox catalysis with Lewis acid catalysis.

We started our study by investigating the enantioselective α-trichloromethylation of 2-acyl imidazoles. Encouragingly, when we reacted 2-acyl imidazole **1a** with $BrCCl_3$ in the presence of iridium catalyst Λ-**IrS** and the base Na_2HPO_4 under visible light irradiation, we obtained the trichloromethylated product **2a** in 69% yield and with 94% ee (Table 1, entry 1). Using $NaHCO_3$ provided **2a** even in 77% yield and with outstanding 99.7% ee (entry 2). In the absence of any base, the yield and enantiomeric excess deteriorated (entry 3). More importantly, in the presence of air no trichloromethylation was observed, but instead a different product was obtained, namely the α-brominated 2-acyl imidazole **3** (entry 4). Compound **3** was also the only observed product in the dark (entry 5), while conversely under visible light irradiation no traces of **3** were generated (entry 2). Obviously, in this system, light induces a complete switch in the product formation and the reaction mechanism: Whereas the α-trichloromethylation (**2a**) can be rationalized with photoredox chemistry, the α-bromination (**3**) in the absence of light must rely on closed-shell S_N2 enolate chemistry with $BrCCl_3$ serving as an electrophilic brominating reagent.[11] Apparently, the reductive activation of $BrCCl_3$ is required for the observed α-trichloromethylation. In this respect it is worth noting that the closely related iridium complex Λ-**IrO** provides inferior results (entry 6), in line with our

recent experimental observation that this catalyst is more suitable for catalyzing oxidative chemistry.[12]

Table 1. Initial experiments for the catalytic enantioselective α-trichloromethylation activated by visible light[a]



entry	catalyst	hν[b]	additive	**2a** (%)[c]	**3** (%)[c]	ee (%)[d]
1	Λ-IrS	yes	Na_2HPO_4	69[e]	0	94
2	Λ-IrS	yes	$NaHCO_3$	77	0[f]	99.7
3	Λ-IrS	yes	none	18	0	87
4	Λ-IrS	yes	$NaHCO_3$, air	0	37	0
5	Λ-IrS	no	$NaHCO_3$	0	51	0
6	Λ-IrO	yes	$NaHCO_3$	13	0	93

[a] Reaction conditions: **1a** and $BrCCl_3$ (6 equiv) with catalyst (2 mol%) in MeOH/THF 4:1 at room temperature for 17-29 h, optional with base (1.1 equiv) and under light. [b] Light source 20 W compact fluorescence lamp (CFL). [c] Isolated yields. [d] Enantioselectivities of **2a** determined by HPLC on chiral stationary phase. [e] HCl elimination product was isolated in a yield of 11%. [f] See Supporting Information for NMR experiments which confirm that no detectable amounts of compound **3** are formed.

Next, we evaluated the scope of the visible light activated enantioselective trichloromethylation. Figure 2 shows the Λ-**IrS**-catalyzed α-trichloromethylation of twelve 2-acyl imidazoles, with the products (62-96% yield) featuring different substituents at the stereogenic carbon, such as phenyl groups with electron donating or electron accepting groups (**2a-f**), a naphthyl (**2g**) and thiophenyl (**2h**) moiety, an ether (**2i**), and aliphatic groups (**2j-l**). It is worth noting that ten of these products are formed with an enantiomeric excess of 99% or higher. For product **2c**, absolute no traces of the minor enantiomer can be detected (≥99.9% ee), demonstrating the high degree of stereocontrol that can be reached in this catalytic reaction.

Finally, we were wondering if we can replace the imidazole moiety with another coordinating group and we selected 2-acyl pyridines due to the prevalence of pyridines and piperidines in bioactive compounds (Figure 3).[13] Revealingly, with acetonitrile as a cosolvent and at a higher catalyst loading of 4 mol% for most examples to compensate for overall slower reaction rates, 2-acyl pyridines **4** were converted to their α-trichloromethylated products **5** in satisfactory to high yields (65-91%) and with high enantioselectivities (90-99.6% ee).

A plausible mechanism is shown in Figure 4, which can be classified as an electron-transfer-catalyzed nucleophilic substitution *via* $S_{RN}1$.[3,4,14] Accordingly, the catalytic cycle is initiated by bidentate coordinating of the 2-acyl imidazole or 2-acyl pyridine substrate to the iridium catalyst (intermediate **I**), followed by base-promoted deprotonation to an electron-rich iridium enolate (intermediate

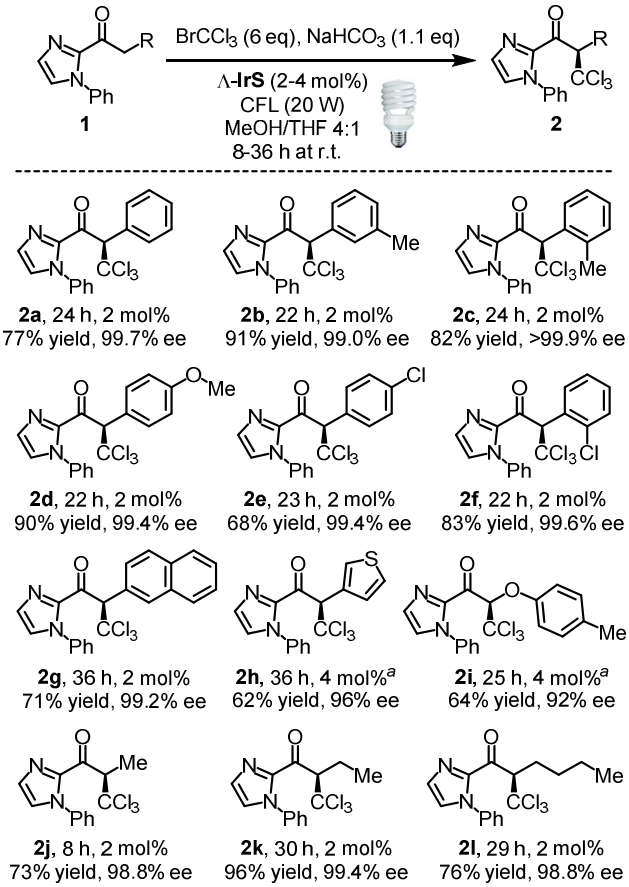


Figure 2. Substrate scope with 2-acyl imidazoles. [a] Higher catalyst loading to increase yield and enantioselectivity.

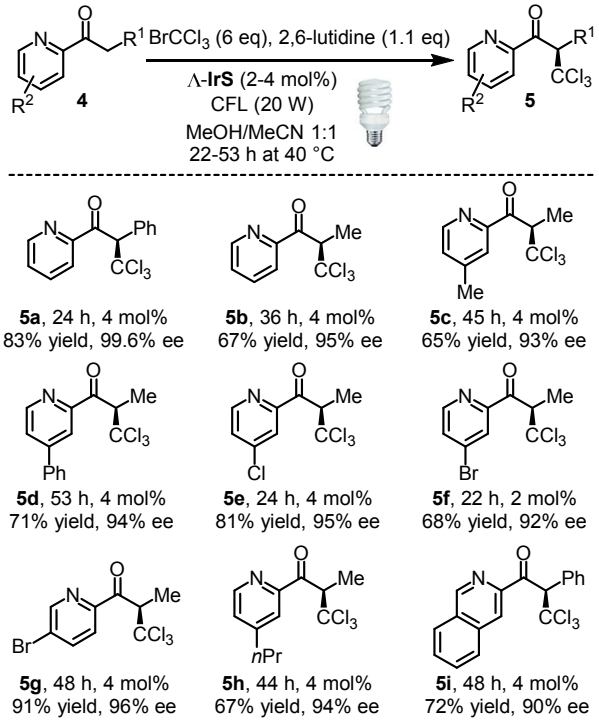


Figure 3. Substrate scope with 2-acyl pyridines.

II). The subsequent addition of a reductively generated electrophilic trichloromethyl radical to the nucleophilic double bond provides an iridium-coordinated ketyl radical (intermediate **III**), which is oxidized to an iridium-coordinated product (intermediate **IV**), followed by product release. In the case of the stronger coordinating 2-acyl pyridines,[15] the replacement of coordinated product with new substrate (**IV**→**I**) is probably mediated by an initial coordination of one or two acetonitriles, thus explaining the requirement for acetonitrile as a cosolvent.

The described catalytic cycle intertwines with a photoredox cycle that generates a trichloromethyl radical upon SET from the photoactivated photosensitizer to $BrCCl_3$ and subsequent release of bromide. A determined quantum yield of 5 indicates that the trichlorometh**y** radical is also formed by direct electron transfer from the strongly reducing ketyl radical intermediate **III** to BrCCl3, thereby leading to a chain propagation. The formation of transient trichloromethyl radicals could be verified by trapping with an electron-rich alkene (see Supporting Information). Importantly, previous mechanistic experiments[6] and a Stern-Volmer plot shown in Figure 5 strongly suggest that it is the neutral intermediate iridium enolate complex (**II**) which serves as the active photosensitizer, as its photoexcited state is quenched by $BrCCl_3$ significantly faster compared to the cationic complexes **I** and *rac*-**IrS**. Furthermore, the single-electron-oxidized complex **II** (corresponding to PS^+ in Figure 4) was trapped efficiently by TEMPO (see Supporting Information). Thus, chiral iridium enolate **II** is a key intermediate which provides the crucial asymmetric induction in the reaction with trichloromethyl radicals, in analogy to Zakarian's radical addition to metal enolates,[10] and simultaneously serves as the visible-light-activated photosensitizer for triggering electron transfer catalysis. It is also worth noting that enolate **II** is a common intermediate of both the light and dark reaction cycle, and the observed light-induced switch in product formation (Table 1) can be explained with an outcompetition of the electrophilic bromination by the fast radical addition step.[16]

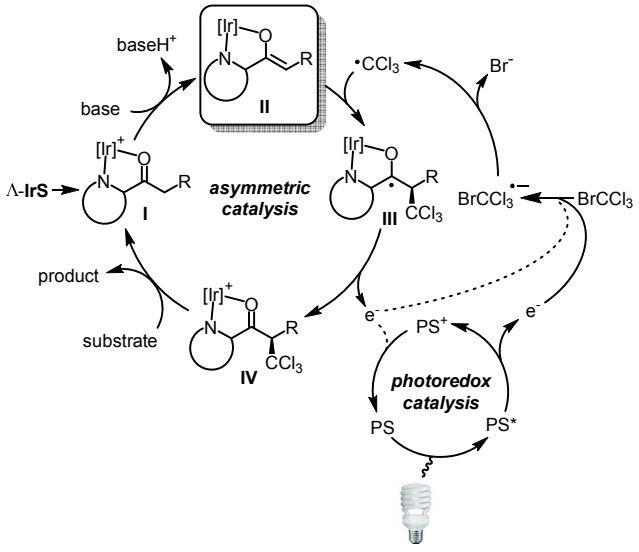


Figure 4. Putative mechanism for the visible light activated asymmetric catalysis. SET = single electron transfer, PS = photosensitizer in form of enolate intermediate **II**.

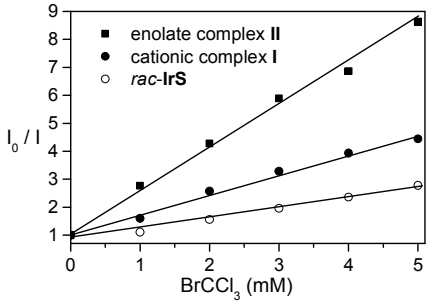


Figure 5. Luminescence quenching experiments. I_o and I = luminescence intensities in the absence and presence of the indicated concentrations of $BrCCl_3$, respectively. *N*-Methyl instead of *N*-phenyl imidazole derivatives were used for **I** and **II** due to higher stability of the enolate complex.

In conclusion, we here reported the first example of an enantioselective, catalytic trichloromethylation. Excellent enantioselectivities are observed with multiple reactions reaching 99% ee and even higher. The method is based on a chiral iridium complex which serves a dual function, as a catalytically active chiral Lewis acid and simultaneously as a precursor for an *in situ* assembled visible-light-triggered photoredox catalyst. The development of related enantioselective perfluoroalkylations is underway in our laboratory.

ASSOCIATED CONTENT

Supporting Information. Experimental details and chiral HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) See Supporting Information for a further mechanistic discussion regarding the competition between light and dark reaction.

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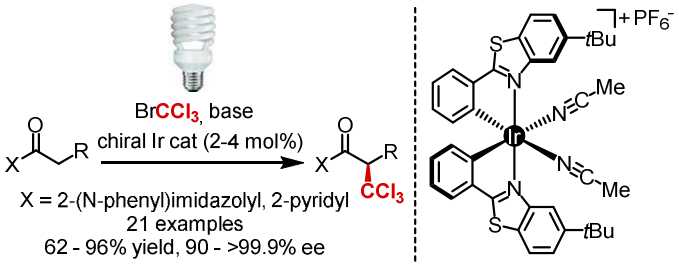
BrCCl3, base
chiral Ir cat (2-4 mol%)
X = 2-(N-phenyl)imidazolyl, 2-pyridyl
21 examples
62 - 96% yield, 90 - >99.9% ee
+ PF6-
tBu
Me
Ir
tBu