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# $PhICl_2$ and Wet DMF: An Efficient System for Regioselective Chloroformyloxylation/$\alpha$-Chlorination of Alkenes/$\alpha,\beta$-Unsaturated Compounds

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Supporting Information

**ABSTRACT:** $PhICl_2$ in wet DMF was found to form an efficient system for realizing difunctionalization of various alkenes and olefinic derivatives possessing a wide range of functional groups. This novel methodology provides convenient access to either regioselective chloroformyloxylated products or $\alpha$-chlorinated olefinic products, depending on the type of structure of the original unsaturated starting material. The mechanism of the reaction is proposed and discussed.


Difunctionalization of alkene and unsaturated compounds represents a powerful methodology in organic synthesis since in such reactions two new $\sigma$ bonds and two stereogenic centers are generated in one step.[1] Among these methods, halofunctionalization,[2] also termed cohalogenation, has attracted much attention for a long time, for the vicinal halofunctionalized product can further be subjected to various organic transformations.[3] Taking advantage of the significant synthetic potential of such compounds in their capability to rapidly increase molecular complexity, many research groups have been devoted to developing regio- and stereoselective reaction systems in order to generate multifunctional alkane derivatives.[4] In 2013, Yeung[4a] disclosed a procedure involving $Ph_2Se$-catalyzed chloroamidation of olefinic substrates by using NCS as the chloro source (Scheme 1, eq 1). Lately, Tang[4b] reported the first highly enantioselective intermolecular bromoesterification of alkenes by using NBS as the bromo source in the presence of $(DHQD)_2PHAL$ and (+)-CSA (Scheme 1, eq 2). Dodd[4c] demonstrated that using $PhI(OAc)_2$ in conjunction with LiBr in ethanol allowed the regioselective ethoxybromination of various enamides (Scheme 1, eq 3). Herein, we disclose another approach for the regioselective chloroformyloxylation process of unsaturated compounds with $PhICl_2$ and wet DMF.

**Scheme 1. General Methods for Halofunctionalization Reactions of Olefinic Compounds**

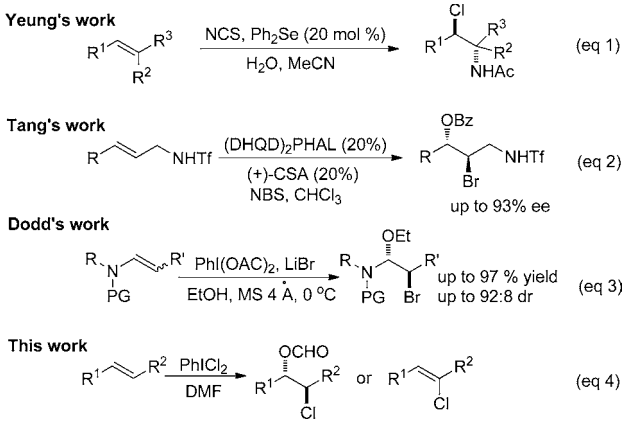
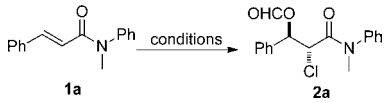



**Table 1. Optimization of the Reaction Conditions[a]**




| entry | oxidant (equiv) | solvent[b] | concn | additive (equiv) | time (h) | yield[c] (%) |
|---|---|---|---|---|---|---|
| 1[d] | $PhICl_2$ (1.0) | DMF | 0.1 | | 12 | 80 |
| 2[e] | $PhICl_2$ (1.3) | DMF | 0.1 | | 12 | 83 |
| 3 | $PhICl_2$ (1.5) | DMF | 0.1 | | 7 | 88 |
| 4 | $PhICl_2$ (1.5) | DCE | 0.1 | DMF (5) | 12 | trace |
| 5[f] | $PhICl_2$ (1.5) | DCE/DMF | 0.1 | | 9 | 75 |
| 6 | $PhICl_2$ (1.5) | HCOOH | 0.1 | | 5 | 30 |
| **7** | **$PhICl_2$ (1.5)** | **DMF** | **0.15** | | **2** | **91** |
| 8 | $PhICl_2$ (1.5) | DMF | 0.2 | | 2 | 84 |
| 9 | $PhICl_2$ (1.5) | DMF | 0.15 | $H_2O$ (1) | 1.5 | 87 |
| 10 | $PhICl_2$ (1.5) | DMF | 0.15 | $H_2O$ (2) | 1 | 82 |
| 11 | $PhICl_2$ (1.5) | DMF | 0.15 | $H_2O$ (5) | 1 | 75 |
| 12[g] | $PhICl_2$ (1.5) | dry DMF | 0.15 | | 12 | 0 |

[a]All reactions were carried out at room temperature with **1a** (0.4 mmol) under air. [b]Commercial DMF containing 0.3% $H_2O$ (v/v) unless otherwise noted. [c]Isolated yield. [d]Based on 70% conversion. [e]Based on 90% conversion. [f]The ratio of DCE and DMF was 1:1. [g]The reaction was carried out under $N_2$ atmosphere.

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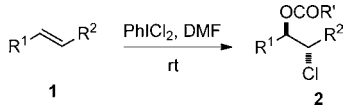
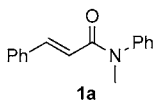
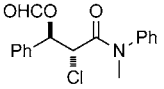
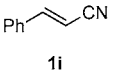
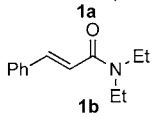
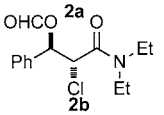
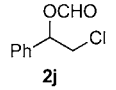
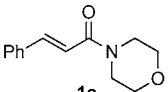
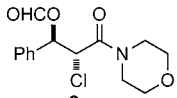
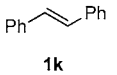
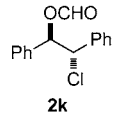
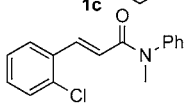
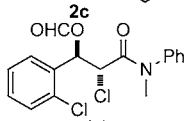
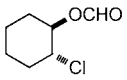
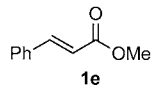
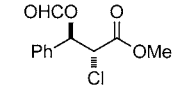
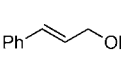
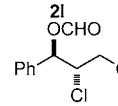
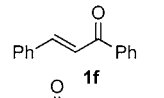
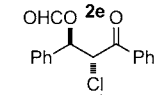
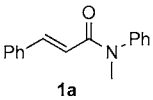
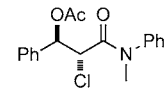
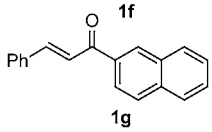
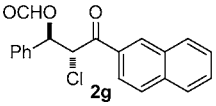
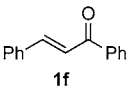
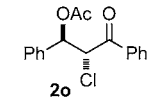
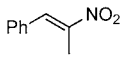
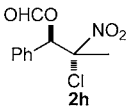
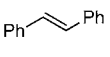
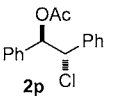
**Table 2. Regioselective Chloroformyloxylation of Alkenes and Unsaturated Compounds with $PhICl_2$[a]**




| entry | substrate | product | yield (%)[b] | dr[c] | entry | substrate | product | yield (%)[b] | dr[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  1a |  2a | 91 | 96:4 | 9[e] |  1i |  2i | 65 | 88:12 |
| 2 |  1b |  2b | 83 | 95:5 | 10 |  1j |  2j | 76 | 71:29[f] |
| 3 |  1c |  2c | 80 | 85:15 | 11 |  1k |  2k | 91 | 91:9 |
| 4 |  1d |  2d | 87 | 95:5 | 12 |  1l |  2l | 77 | 94:6 |
| 5 |  1e |  2e | 91 | 97:3 | 13[g] |  1m |  2m | 83 | 65:35 |
| 6 |  1f |  2f | 95 | 93:7 | 14[h] |  1a |  2n | 87 | 88:12 |
| 7 |  1g |  2g | 93 | 95:5 | 15[h] |  1f |  2o | 90 | 95:5 |
| 8[d] |  1h |  2h | 60 | 75:25 | 16[h] |  1k |  2p | 83 | 92:8 |

[a]All reactions were carried out by treating substrates **1** (0.4 mmol) and $PhICl_2$ (1.5 equiv) in wet DMF (2.7 mL, $c$ = 0.15 M) under air. [b]Isolated yields. [c]Determined by crude $^1H$ NMR analysis. [d]Based on 50% conversion. [e]2 equiv of $PhICl_2$ was applied, based on 50% conversion. [f]Ratio of regioselectivity. [g]The structure of **2m** was confirmed through X-ray crystallographic analysis. [h]DMA was adopted as the solvent, and 2 equiv of $PhICl_2$ was applied.

Although iodobenzene dichloride ($PhICl_2$), a common hypervalent organoiodine(III) reagent, has been widely used as an oxidant as well as halogen source in organic reactions for a long time, its involvement in chloroformyloxylation reactions has not yet been reported.[5] On the other hand, *N*,*N*-dimethylformamide (DMF), aside from being an effective polar solvent commonly employed in organic reactions, is a multipurpose reagent broadly used in chemistry including as a ligand in the preparation of metallic complexes,[6] as a dehydrating reagent[7] and even as a catalyst.[8] Furthermore, DMF can also act as a multifunctional building block for various subunits such as $-NMe_2$, $-CONMe_2$, $-CHO$, and $-OCHO$, etc. in many different types of reactions.[9] Based on these facts, we ventured out the investigations of treating an unsaturated compound with a combination of $PhICl_2$ and DMF in hopes of developing an alternative access to new difunctionalized product from an unsaturated compound.

We first studied the reaction of the readily available unsaturated amide, *N*-methyl-*N*-phenylcinnamamide **1a** and $PhICl_2$ in DMF. To our delight, an 80% yield of chloroformyloxylated product **2a** (which was confirmed by X-ray crystallographic analysis) based on 70% conversion of the starting material **1a** was obtained after 12 h (Table 1, entry 1). Increasing the dosage of the oxidant showed a positive result, with the starting material consumed completely and the yield improved to 88% (Table 1, entries 2 and 3). Considering that DMF acts as the nucleophile in this reaction, two other control experiments were set up. After switching the solvent to DCE and employing 5 equiv of DMF as the reactant, only a trace amount of the desired product was detected (Table 1, entry 4). On the other hand, when DMF and DCE were used as cosolvents in a ratio of 1:1, the reaction proceeded smoothly to give the chloroformyloxylated product in a moderate yield of 75% (Table 1, entry 5). Counterintuitively, when DMF was replaced by formic acid, which seemed a more direct source of the formyloxyl group in the product, and only 30% yield of **2a** was obtained (Table 1, entry 6). Concentration screening revealed that when the reaction was carried out at a concentration of 0.15 M, the reaction time could be shortened to 2 h and the yield increased to 91% (Table 1, entry 7). A higher concentration only resulted in a slightly decreased yield due to the formation of some unidentified byproducts (Table 1,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entry 8). Perceiving that the formyloxyl group installed to the double bond is derived from the hydrolysis of DMF, we subsequently evaluated the effect of $H_2O$ in the reaction system. With the increase of the amount of $H_2O$, the reaction rate was visibly accelerated. However, the yield continued to slightly decrease with the increase in $H_2O$, down to 75% when 5 equiv of $H_2O$ was present. This can possibly be attributed to the side reactions of hydrolysis of $PhICl_2$. Our further control experiments showed that when the reaction was run in well-dried DMF under nitrogen atomsphere, no desired product was detected. Based on all of the acquired test results, the optimized conditions to obtain the chloroformyloxylated product were concluded to be that of entry 7 in Table 1, namely, treatment of compound **1** with 1.5 equiv of $PhICl_2$ in slightly wet DMF (0.15 M).

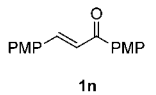
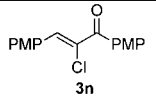
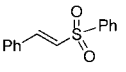
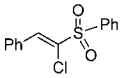
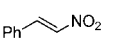
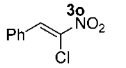
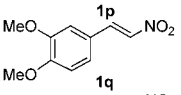
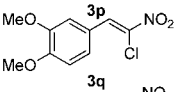
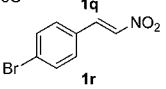
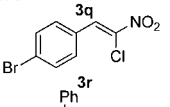
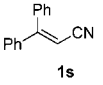
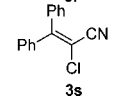
We continued to evaluate the scope and generality of the methodology at the optimized conditions. We were pleased to find that the chloroformyloxylation procedure was applicable across a broad range of unsaturated compounds and smoothly gave the *trans*-chloroformyloxylated products. Results show that variation of the amide by replacing the aniline moiety with diethylamine or morpholine had negligible influences on the course of the reaction (Table 2, entries 1−3). All of these substrates were transformed into the corresponding difunctionalized products in good to excellent yield with satisfactory diastereoselectivity. Moreover, switching $R^1$ from a phenyl group to an *o*-chloro-substituted phenyl group, which introduced the steric hindrance effect to the substrate, caused practically no effect on the reaction as the desired product was obtained in 87% yield with 90% de (Table 2, entry 4). Indeed, not only *α,β*-unsaturated amides but also *α,β*-unsaturated esters, ketones, nitro compound, and nitrile were tolerable under these reaction conditions, with the related chloroformyloxylated products all obtained in good to excellent yields within the range of parameters established in the method (Table 2, entries 5−9). To our delight, the procedure could also be applied to unactivated double bonds such as internal or terminal alkenes and afforded the difunctionalized product in moderate to good yields (Table 2, entries 10−13). When the solvent of the reaction was switched to DMA, the corresponding chloroacetyloxylated products were achieved in good yields and comparable selectivity (Table 2, entries 14−16).

Interestingly, when the phenyl groups in compound **1f** were replaced by *p*-methoxylphenyl groups, the corresponding substrate **1n** was converted to an *α*-chloro-substituted chalcone **3n** under the identical reaction conditions with no detection of the difunctionalized product (Table 3, entry 1). Indeed, further investigation revealed that this phenomenon was not the only exceptional case. When unsaturated sulfone **1o** was used, the *α*-chloro-substituted product **3o** was obtained in moderate 57% yield (Table 3, entry 2). Unsaturated nitro compounds **1p−r** were also transformed to the related *α*-chloro-substituted products, and unsaturated nitrile **1s** reacted in a similar manner and delivered the chloro-substituted product in 79% yield.

The extra step of elimination that takes place in this series of compounds can be attributed to the following two aspects. On the one hand, it is obvious that these strong electron-withdrawing groups, e.g., sulfonyl and nitro groups, increased the acidity of the *α* hydrogen which facilitated the elimination of formyloxyl group from the resulting chloroformyloxylated products. On the other hand, the elimination can be understood as the extra stability gained from the extended

**Table 3. *α*-Chlorination of Unsaturated Compounds**[a]


1 3

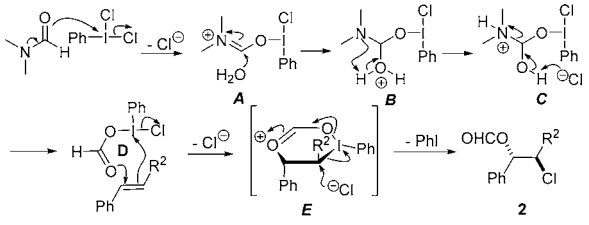
| entry | substrate | product | yield[b] |
|---|---|---|---|
| 1[c] |  1n |  3n | 74 |
| 2 |  1o |  3o | 57 |
| 3 |  1p |  3p | 65 |
| 4[d] |  1q |  3q | 80 |
| 5[e] |  1r |  3r | 57 |
| 6 |  1s |  3s | 79 |

[a]Reaction conditions: **1** (0.5 mmol), $PhICl_2$ (2 equiv) in wet DMF (3.3 mL) under air. [b]Isolated yields. [c]PMP = *p*-methoxylphenyl. [d]1.5 equiv of $PhICl_2$ was used. [e]Based on 50% conversion.

conjugation in these final products due to the push−pull feature of the compounds in most cases. For instance, in comparison to the compounds in Table 2, those in Table 3 carry either a more electron-donating group on one side, e.g., $R^1$ = PMP vs $R^1$ = phenyl, or a more electron-withdrawing group on the other side, e.g., E = $NO_2$ or $SO_2Ph$ vs $R^2$ being ketones and esters. The observation of highest yield from **1q** is consistent with this explanation as **1q** contains the most electron-donating $R^1$ group and also the most electron-withdrawing E group among all the compounds in Table 3, which yields the most pronounced push−pull effect. This explanation is, in addition, supported by the negative observation of only a trace amount of the desired product in the case where $R^1$ is a more electron-withdrawing *p*-chlorophenyl and E is the nitro group (not shown), where the push−pull feature is obviously much diminished. In comparison between **1i** and **1s**, even though the presence of the second phenyl group in the latter would not necessarily promote the push−pull feature, it nevertheless increases the amount of conjugation stability at the formation of the new double bond and consequently leads to the olefinic product **3s** as the more thermodynamically favored product.

On the basis of the above experimental results, a plausible mechanism has been proposed and is illustrated in Scheme 2.[10] First, DMF nucleophilicly attacks dichloroiodobenzene to give iminum salt **A**, which is converted to intermediate **B** through an indespensable hydrolysis step. After tautomerization, a

**Scheme 2. Plausible Mechanism**





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dimethylamine is eliminated to generate the new I(III) species **D**,[11] which is the key intermediate for the process. The nucleophilic attack of alkenes to **D** leads to intermediate **E**. The chloride ion nucleophilicly attacks intermediate **E** and along with the release of iodobenzene gives the product **2**.

In conclusion, we have discovered an efficient, metal-free system for a convenient regioselective chloroformyloxylation which can be applied to a wide range of $\alpha,\beta$-unsaturated compounds including but not limited to unsaturated ketone, amide, ester, and alkenes derivatives. For strong push−pull systems such as $\alpha,\beta$-unsaturated sulfone, aryl and nitro-compounds, and nitriles, $\alpha$-chloro substitution reaction takes place instead. In view of the mild reaction conditions and environmentally benign characteristics, the present method can be regarded as an useful alternative to the existing chloroformyloxylation reactions of unsaturated compounds.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, spectral data for all new compounds, crude NMR for dr ratio, and X-ray structural data of **2a** and **2m**. 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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(10) For an alternative mechanistic pathway, see the Supporting Information for details.

(11) Intermediate **D** has been detected by both crude $^1$H NMR and LCMS analysis when $PhICl_2$ was combined with DMF in the absence of an alkene.