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Dihaloiodoarenes: α,α-Dihalogenation of Phenylacetate Derivatives

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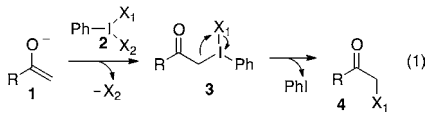
Supporting Information

ABSTRACT: A hypervalent iodine reagent-based α-carbonyl dihalogenation reaction is reported. Treating diazoacetate derivatives with either iodobenzene dichloride or iodotoluene difluoride results in *gem*-dichlorination or *gem*-difluorination products, respectively. The reaction is catalyzed by either Lewis acid or Lewis base activation of the aryl-λ^3-iodane ($ArIX_2$) species and proceeds rapidly and chemoselectively to the desired *gem*-difunctionalized products in good to excellent yield.

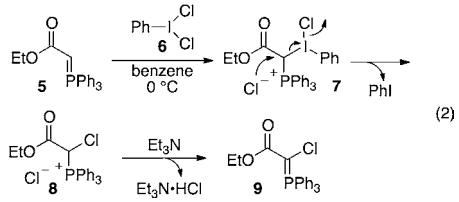
Hypervalent iodine derivatives were first disclosed by Willgerodt in the 1880s.[1] The modern resurgence in interest in iodine(V) (e.g., IBX[2] or DMP[3]) and iodine(III) reagents (e.g., PhIO[4] or $PhI(OAc)_2$[5]) has led to significant discoveries which have been documented in detail by Zhdankin and Stang.[6] The widespread use of hypervalent iodine reagents is due to their broad reactivity, coupled with the mild and environmentally benign conditions associated with their reactions.[6c] In analogy to the chemistry associated with organic transition metal complexes, terms such as ligand exchange and reductive elimination are often used to describe the transformations associated with hypervalent iodine reagents. We are investigating the potential for new, high-value transformations to occur within the ligand sphere of aryl-λ^3-iodane ($ArIX_2$) compounds.[7] In this regard, we have discovered a Lewis acid or Lewis base catalyzed transformation that enables transfer of both ligands from iodane to substrate, affording *gem*-disubstituted products, and setting the precedent for using aryl-λ^3-iodanes as a metal-free method α-carbonyl difunctionalization.

One of many transformations involving hypervalent iodine reagents is α-carbonyl functionalization. While the α-acetoxylation of ketones was originally reported by Mizukami,[8] significant contributions were made by Moriarty[9] and Koser,[10] investigating the α-hydroxylation and α-tosyloxylation reactions, respectively. The electrophilic/nucleophilic reactivity profile for iodane **2** enables C−C or C−heteroatom bond formation under mild, metal-free conditions (eq 1).[8,9b,c,10,11]

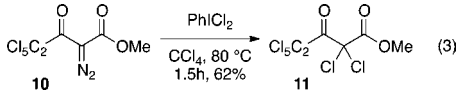


This versatile transformation occurs via the intermediacy of phenyliodonium adduct **3**, whose strong nucleofugality enables a variety of nucleophiles (such as acetate, azide, halide, sulfonate, phosphonate, and alkoxide, as well as enol ethers, alkenes, and aromatics) to displace iodobenzene by either reductive elimination (shown) or nucleophilic displacement (not shown).

Our intent was to develop a chemo- and regioselective, one-pot method for transferring both ligands from iodane to the α-position of carbonyl-containing substrates. Given the diversity of heteroatom-substituted iodanes (e.g., $PhICl_2$ (**6**), $PhIF_2$, $PhI(N_3)_2$, PhI(OH)OTs, etc.) and iodonium salts[12] (e.g., Ar_2IOTf, ArI(alkyl)OTf, etc.), such a reaction could be a versatile and generally applicable means of α-carbonyl difunctionalization. The key to the success of this reaction relies on the substrate already possessing a suitable leaving group in the α-position. Inspiration came from the work of Moriarty,[13] and others,[14] who have found that combining phosphorus ylides and iodanes results in the α-functionalization of Wittig reagents (eq 2). Association of ylide **5** and iodobenzene dichloride (**6**) gives adduct **7**, which undergoes nucleophilic attack to lose PhI and give salt **8**. This sequence terminates with the deprotonation of **8** to give chlorinated Wittig reagent **9**.



We envisioned a scenario where a substituent with increased leaving group ability (e.g., replace the triphenylphosphonium of **8** with diazonium) is displaced by the second chloride anion to give an α,α-dichloro functionalized product.[15] The sole report of such reactivity involved doubly stabilized β-dicarbonyl substrates (e.g., **10**) being chlorinated at elevated temperature in moderate yield (eq 3).[16] Here we report our efforts to



convert the diazo functional group of simple, monostabilized diazoesters into *gem*-dihalides by treating diazoacetate derivatives with dichloroiodo- or difluoroiodoarenes. In situ activation of the iodanes was the key to enabling a rapid conversion to the dihalogenated products in good to excellent isolated yield.

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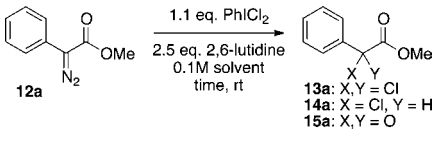
We began by testing the chlorination of α-diazo methyl phenylacetate **12a** with iodobenzene dichloride **6**, which is prepared by treating iodobenzene with bleach and HCl. Concerned with the possibility of residual acidic impurities in **6**, we combined the reagents at room temperature with an excess of 2,6-lutidine, and a mixture of dichloride **13a**, monochloride **14a**, and glyoxylate **15a** were recovered in near-quantitative yield (Table 1). A variety of common organic

Table 1. Solvent Effect on *Geminal*-Dichlorination Reaction

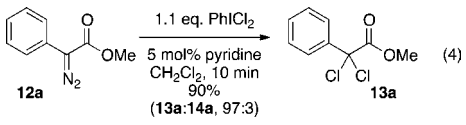


solvent	time	yield[a]	13a:14a
CH_2Cl_2	1 h	98%	5.1:1
DCE	1 h	94%	5.3:1
DME	5 h	58%	7.1:1
THF	16 h	23%	1:0
hexanes	16 h	81%	20:1
toluene	2 d	96%	5.4:1
CH_3CN	5 min	74%	7.2:1
CH_2Cl_2 (0.2 M)	20 min	96%	6.8:1

[a]Product **15a** was also isolated from these reactions in 2–40% yield.

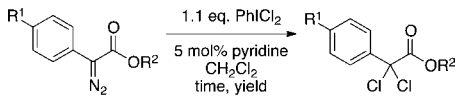
solvents was screened, and CH_2Cl_2 or DCE gave **13a**:**14a** in a 5:1 ratio in 96% yield in 1 h. Ethereal and nonpolar solvents were also selective for product **13a**, though yields were variable and reaction times lengthy. A 6-fold rate increase was observed in acetonitrile, at the expense of product yield (74%). Lastly, increased concentration in CH_2Cl_2 gave a 3-fold decrease in reaction time and proved more selective for **13a**.

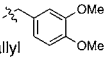
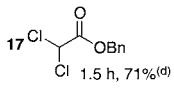
Additional organic (Et_3N, TMP, DIPEA, DBU) and inorganic (K_2CO_3, Cs_2CO_3) bases were surveyed, and while most were unsuitable, both pyridine (89% yield, 50 min) and DMAP (87% yield, 10 min) were effective at 1 mol% loading in 0.2 M CH_2Cl_2. Increasing the pyridine loading to 5 mol% was optimal, giving a 97:3 mixture of products **13a**:**14a** in 90% isolated yield in 10 min (eq 4). The minimal amount of base being used suggests residual acidic impurities from **6** are not a concern. But, because the reaction fails in the absence of base, we believe it is acting as a catalyst, activating iodane **6**.[17] This catalytic effect is crucial to our transformation, enabling the reaction to proceed rapidly at room temperature, and providing the desired product in high isolated yield.



The effect of diazoacetate substitution was tested, and variation of the ester substituent was well tolerated (Table 2). Both alkyl (**12a,b**) and benzyl (**12c,d**) substrates underwent rapid dichlorination in excellent yield, as did allyl ester (**12e**). The effect of aryl substitution was also tested, with halogen (**12f**), electron donating (**12g,i**), or electron withdrawing (**12h,j**) substrates undergoing chlorination in good to excellent yield. Benzyl diazoacetate (**16**) was also dichlorinated in 71% yield.[18] These results indicate the transfer of chloride ligands

Table 2. Diazoacetate Derivatives Used in the Dichlorination Reaction



12a	R^1=H	R^2=Me	**13a**, 10 min, 90%[b]
12b	R^1=H	R^2=*i*-Pr	**13b**, 10 min, 88%
12c	R^1=H	R^2=Bn	**13c**, 10 min, 95%
12d	R^1=H	R^2= 	**13d**, 15 min, 96%
12e	R^1=H	R^2=allyl	**13e**, 10 min, 89%
12f	R^1=Br	R^2=Me	**13f**,10 min, 87%
12g	R^1=OMe	R^2=Me	**13g**, 20 min, 79%
12h	R^1=OTs	R^2=Me	**13h**, 2h, 89%
12i	R^1=NHAc	R^2=Me	**13i**, 5 min, 78%
12j	R^1=NO_2	R^2=Me	**13j**, 5 min, 67%[c]
16			**17**  1.5 h, 71%[d]

[a]Isolated yields. Unless otherwise noted, both monochlorination (**14**) and glyoxylate (**15**) products were <2% by GC analysis. [b]The reaction could be conducted on a 1g scale without incident. [c]DMAP (1 mol %) was used as catalyst. [d]Monochlorination product was obtained in 10% yield.

from iodane to diazoester is mild, highly efficient, and tolerant to a variety of functional groups.

Given our success with the chlorination reaction, we decided to extend this methodology to include the fluorination of diazoesters. There is widespread interest in the synthesis of fluorinated compounds mainly because of fluorine's use as a metabolically stable bioisostere for hydrogen.[19] The synthesis of difluorophenylacetic acid derivatives has been accomplished by (1) fluorination of the glyoxylates;[20] (2) fluorination of the phenylacetates (or acid chloride);[21] and (3) radical-[22] or metal-mediated cross-coupling of arenes and halo-[23] or silyl-difluoroacetates.[24]

Subjecting **12a** to $TolIF_2$ (**18**) under the optimized chlorination reaction conditions produced difluoride **19a** in 29% yield. Believing the low yield to be a result of poor activation of $TolIF_2$ by pyridine (or DMAP), we searched for a suitable replacement.[25] The electrophilic iodane salt PhI-$(F)^+BF_4^-$ can be generated by treating $PhIF_2$ with BF_3·OEt_2,[26] so the effect of BF_3·OEt_2 on $TolIF_2$ was investigated as part of a solvent and temperature screen. From this study, the following optimal conditions were determined: 1 mol % of BF_3·OEt_2 added to **12a** and **18** in PhCl at 110 °C (eq 5).[27,28]

Knowing diazoesters can undergo thermal decomposition at elevated temperature, the intermediacy of carbenes in the fluorination mechanism was considered a possibility. However, addition of either $Rh_2(OAc)_4$ or $Cu(OTf)_2$ to **12a** and **18** in PhCl at 110 °C resulted in diazo decomposition, but failed to produce any difluorination product **19a**. This result suggests carbenes are not intermediates in the reaction and reinforces our proposed role for BF_3·OEt_2 in iodane activation.

We then fluorinated a series of diazoacetate substrates, with alkyl and benzyl ester derivatives undergoing ligand transfer in

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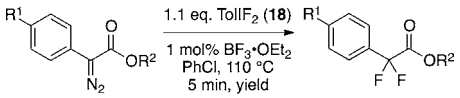
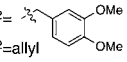
good yield (Table 3). The derivatives with electron withdrawing or halogen-substituted arenes also gave products **19** in good yield. Substrates with labile functional groups (Ar−OMe or −NHAc) on the arene either proceeded poorly (**19g**) or failed to afford the desired products (**19d,i**). These substrates were found to decompose (without significant evolution of N_2 gas) when heated in PhCl and treated with $BF_3{\cdot}OEt_2$. Decreasing the temperature or changing to the milder Lewis acid $B(OMe)_3$ failed to improve substrate stability. Lastly, diazoacetate **16** underwent thermal decomposition (with loss of N_2) at 110 °C and gave monofluoride **20** in 19% yield.

Table 3. Diazoacetate Derivatives Used in the Difluorination Reaction



12,16 (19,20), Yield

12a	R^1=H	R^2=Me	**19a**, 66%[a]
12b	R^1=H	R^2=*i*-Pr	**19b**, 75%[a]
12c	R^1=H	R^2=Bn	**19c**, 79%[a]
12d	R^1=H	R^2= 	**19d**, -
12e	R^1=H	R^2=allyl	**19e**, 17%
12f	R^1=Br	R^2=Me	**19f**, 66%[a]
12g	R^1=OMe	R^2=Me	**19g**, 26%
12h	R^1=OTs	R^2=Me	**19h**, 74%[a]
12i	R^1=NHAc	R^2=Me	**19i**, -
12j	R^1=NO_2	R^2=Me	**19j**, 79%[a]

16  **20**  19%

[a]Glyoxylates **15** were recovered in 15−20% yield.

We offer the following mechanism, illustrated for the chlorination reaction (Figure 1): (1) activation of the iodane to give electrophilic salt **21**;[17] (2) attack of activated iodane by diazoester **12a**; (3 and 4) sequential chlorination of intermediates **22** and **23** with expulsion of PhI and N_2, affording **13a**.[29] Product **14a** could result from trace quantities of HCl reacting with **12a**, and glyoxylate **15a** could result from intercepting intermediate **22** (or **23**) with water.

In conclusion, we disclose a novel transformation in which a (dihaloiodo)arene can deliver both ligands to a substrate in a *geminal* relationship. The iodanes investigated are easily prepared on multigram scale using inexpensive and readily available reagents (commodity chemicals HCl and HF). Development of the chlorination reaction enabled us to prove the feasibility of the proposed transformation and revealed to us the necessity of a catalytic iodane activator. Once initiated, the reaction proceeds in a rapid and chemoselective manner to provide the *gem*-dichlorinated products in good to excellent yield. In contrast to sequential dichlorination strategies, the products are recovered without contamination by monochlorinated byproducts. The iodane-based fluorination reaction was also highly effective, though it was found to require stronger activation, which was accomplished with $BF_3{\cdot}OEt_2$. This reaction offers a very attractive, metal-free alternative to existing methods for the exclusive synthesis of α-carbonyl difluorides. As a result, we anticipate this fluorination reaction being adopted as a general method for α-carbonyl functionalization. Investigations into the mechanism of the reaction, as well as the scope of suitable substrates and iodane reagents, are currently underway. Results from these synthetic investigations will be reported in due course.

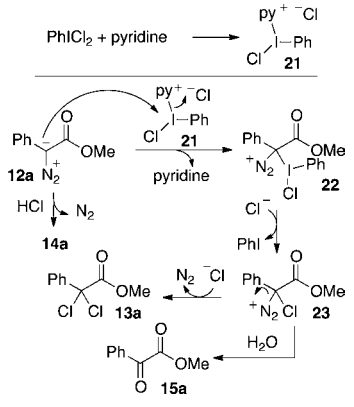


Figure 1. Proposed reaction mechanism.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and characterization data of new compounds. 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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(25) Conducting the reaction at 110 °C without a catalyst gave **19a** in 40% yield after 2 h.
(26) Zefirov, N. S.; Samsoniya, N. S.; Kutateladze, T. G.; Zhdankin, V. V. *Zh. Org. Khim.* **1991**, *27*, 220.
(27) Monofluorination products were not isolated and were only ever observed (by GC-MS) when conducting the reaction at lower temperatures.
(28) Caution: Diazo compounds are reported to be toxic and potentially explosive. Appropriate safety measures should be observed when working with them.
(29) We thank the Reviewers for their suggestion that reductive elimination, nucleophilic substitution, and expulsion of N_2/PhI by anchimeric assistance could all be operative in the conversion of **22** to **13a**.