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Dichlorination of α-Diazo-β-dicarbonyls Using (Dichloroiodo)benzene

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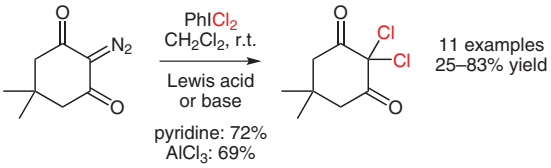

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Abstract α-Diazo-β-dicarbonyl compounds were chlorinated using (dichloro)iodobenzene and an activating catalyst. A broad range of reaction rates was observed, which paralleled the relative stability/nucleophilicity of the diazo compounds. Acyclic diazocarbonyls reacted faster than cyclics, and β-diketones were much faster to react than β-keto esters or β-diesters. Lewis acid activation was used for the first time, allowing us to overcome instances of poor chemoselectivity. Though the yields ranged from low to good, this chlorination reaction has again proven a mild and effective halogenation strategy.

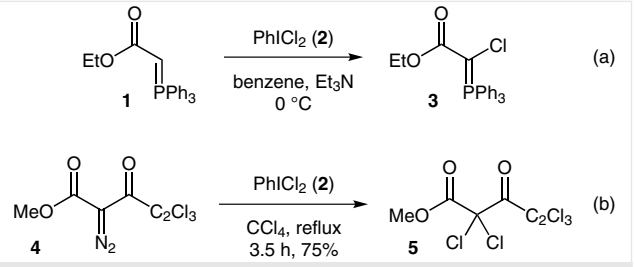
Key words diazo compounds, hypervalent iodine, halogenation, catalysis, ylides

Graham Murphy (right) received his undergraduate training at the University of Victoria, then joined the lab of F. G. West at the University of Alberta for his PhD, where he held an NSERC postgraduate award. He was a JSPS postdoctoral fellow with M. Hirama at Tohoku University, Japan, and an NSERC postdoctoral fellow at Colorado State University with J. L. Wood. After a year as a postdoctoral fellow with the Biorefining Conversions Network at the University of Alberta, he began his independent career in 2011 as an assistant professor at the University of Waterloo in Canada. His current research interests are based on the development of novel synthetic methodologies, specifically concerning applications of hypervalent iodine reagents.
Keith Coffey (left) was born in Ajax, Ontario. He achieved a BSc (Co-op) in biochemistry at the University of Waterloo, receiving his diploma in 2013. While pursuing his MSc in the Murphy lab, he worked on developing halogenation reactions and applying them to various biologically relevant skeletons.

Organoiodanes are a class of hypervalent I^{III} reagents that have maintained popularity since the 1880s[1] owing to their broad reactivity profile and their mild, environmentally benign reaction conditions.[2] Members of this class include iodosylbenzene,[3] Koser's[4] and Togni's[5] reagents, and (diacetoxyiodo)benzene and its derivatives.[6] A traditional reaction of the iodanes is the α-functionalization of carbonyl compounds, which is promoted by the reductive formation of iodobenzene. This is a highly versatile, mild, and metal-free strategy for α-carbonyl functionalization with halide, acetate, sulfonate, aryl, and alkyl groups, as either a racemic or asymmetric process.[7]

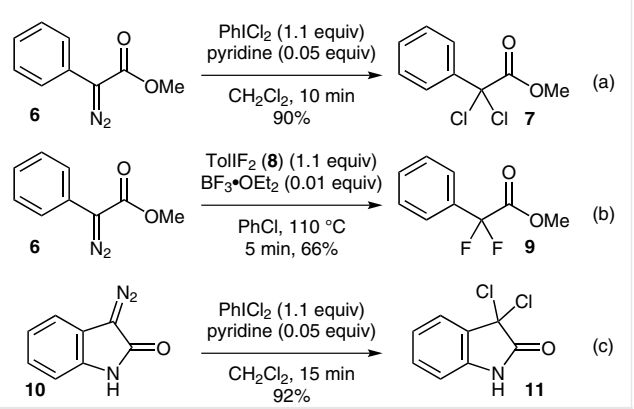
When $ArIX_2$-type iodanes are used in this chemistry, the ligand not incorporated into the substrate is discarded. In light of this, we set out to develop a reaction in which both ligands from such an iodane would be transferred to the α-carbonyl position in a single transformation. Successful development of this chemistry would increase the efficacy of the iodane, expand the reaction scope of hypervalent iodine reagents, and offer a chemoselective synthesis of the *gem*-dihalide unit. To accomplish this, our substrate would need to be nucleophilic at its α-carbonyl position and possess a potential leaving group on the same carbon. Our belief was this pre-existing leaving group may be displaced by the second ligand from the iodane during the α-functionalization reaction. Phosphonium ylides (e.g., **1**)

were our initial choice of substrate because of their structural diversity and availability, but these react with iodanes (e.g., (dichloroiodo)benzene, **2**) to give α-functionalized Wittig reagents (Scheme 1, a).[8] There was a single report of diazonium ylides reacting with iodane **2** to give *gem*-dichlorides in 24–75% yield (Scheme 1, b).[9] This result gave legitimacy to our hypothesis, and we have since developed this to be a mild, operationally facile reaction that might be applicable to the vast spectrum of differentially substituted iodanes.



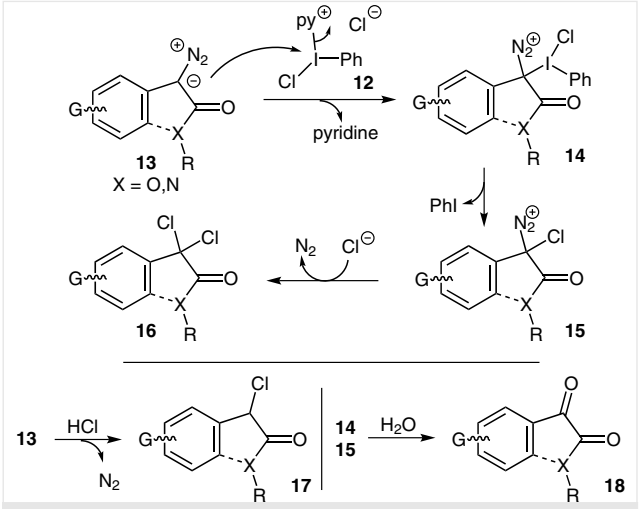
Scheme 1 Reactions of phosphonium and diazonium ylides with $PhICl_2$ (**2**)

To date, we have successfully chlorinated and fluorinated phenyldiazoacetate derivatives, using $PhICl_2$ (**2**) and $TolIF_2$ (**8**) respectively (Scheme 2, a and b).[10] A new route to the biologically relevant 3,3-dihalo-2-oxindole scaffold was devised through chlorination of the 2-oxindole skeleton (Scheme 2, c).[11] The chlorination reactions were generally complete in minutes, with good to excellent yields. These also exhibited exceptional functional-group compatibility, with halides, unsaturations (allyl, propargyl), ethers, esters, acetyls, acetamides, carbamates, and sulfonates being tolerated. Substitution of **6** or **10** with strongly electron-withdrawing groups, which resulted in lower yields, or substitution with strongly electron-donating groups, which occasionally resulted in over-chlorination at the arene,[12] were limitations observed to date for this reaction.



Scheme 2 *gem*-Dichlorination and *gem*-difluorination of diazocarbonyl compounds

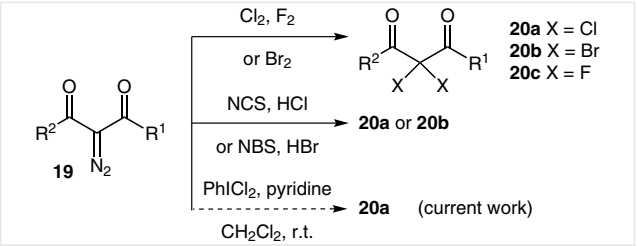
Key observations from these studies, such as the necessity of an activator, the minimal variation in reaction rate and the adverse effects of aryl substitution, have led to the following proposal for the reaction sequence (Scheme 3). It begins with Lewis base or Lewis acid activation of $PhICl_2$ (**2**) giving complex **12**. This activated species undergoes nucleophilic attack by diazonium ylide **13**, giving adduct **14** that possesses two excellent leaving groups. Its transit to the *gem*-dihalogenated products requires successive chlorination events, possibly by reductive elimination (**14** to **15**) or nucleophilic displacement by chloride (**15** to **16**). Monochloride (**17**) and glyoxylate/isatin (**18**) are two commonly encountered side products, whose formation we have been able to suppress by changing the Lewis acid/base and solvent. While two pathways for their formation are offered, we have not ruled out other possibilities.



Scheme 3 Proposed sequence of events for the *gem*-dichlorination reaction and possible origins of the side products

α-Diazo-β-dicarbonyls are among the most studied diazos, and were a natural choice for study in our α,α-dihalogenation reaction. The expected products, α,α-dihalo-β-dicarbonyls, can be made directly from the parent dicarbonyl, but these methods often lack chemoselectivity and generate monohalide side products.[13] Methods selective for the dihalide products combine elemental halogens (F_2, Cl_2, Br_2) or halosuccinimides/haloacids with α-diazo-β-dicarbonyl compounds,[14–16] however, these more aggressive reagents result in poor functional-group tolerance (Scheme 4). As $PhICl_2$ acts like Cl_2 in reactions with diazo compounds, our chlorination reaction offers a milder, more functional-group-tolerant means to prepare *gem*-dichlorides.

Modified $ArICl_2$-type reagents aim to facilitate removal of the iodoarene byproducts from chlorination reactions.[17] Designer reagents, such as polystyrene-supported[18] or biphenyl-[19] and triazine-derived[20] dichloroiodanes rely on the insolubility of the aryl iodide for easy recovery. Benzoic

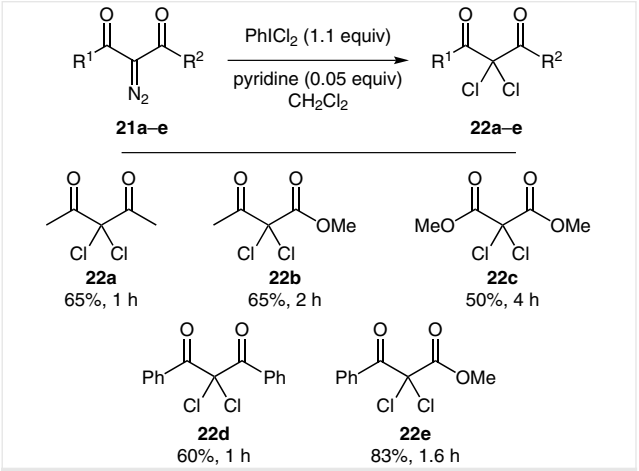


Scheme 4 Methods to generate α,α-dichloro-β-dicarbonyls from diazo compounds

acid,[19] and fluorous aryl- and alkyl-derived iodanes[21] have also been developed, where the aryl iodides are recovered in the reaction workup. Recovery of the iodide allows these reagents to be recycled through regeneration of the iodane. Another chlorination strategy used $PhICl_2$ generated in situ from iodosylbenzene and HCl.[22] Presumably, this reaction would be incompatible with diazo precursors, but it sets the stage for an atom-economical iodane-based chlorination, where a catalytic amount of aryl iodide is oxidized[23] and converted into $PhICl_2$ in situ, and reacts selectively with a substrate.

Though diazo compounds are often believed to be highly reactive species,[24] significant stabilization is gained by substitution with strongly electron-withdrawing groups. The α-diazo-β-dicarbonyls have increased thermal, photochemical, catalytic, and Lewis or Brønsted acid stability compared to simple diazocarbonyl compounds.[25] A study of diazo nucleophilicity has suggested these are weakly nucleophilic compared to monocarbonyl diazos, such as **6**.[26] We hoped to exploit the differences in nucleophilicity within the β-dicarbonyl class of diazo compounds, which decreases from β-diketones to β-diesters, and from acyclic to cyclic scaffolds.[25b,27] Given the broad stability range of the β-dicarbonyls, which is in stark contrast to the similarly reactive derivatives of **6** and **10**, we carried out this study aiming to glean additional mechanistic insight from the varying reaction rates. And, although we expected the diazos to be slower to react, we believed this chemistry would make this a valuable addition to existing strategies.

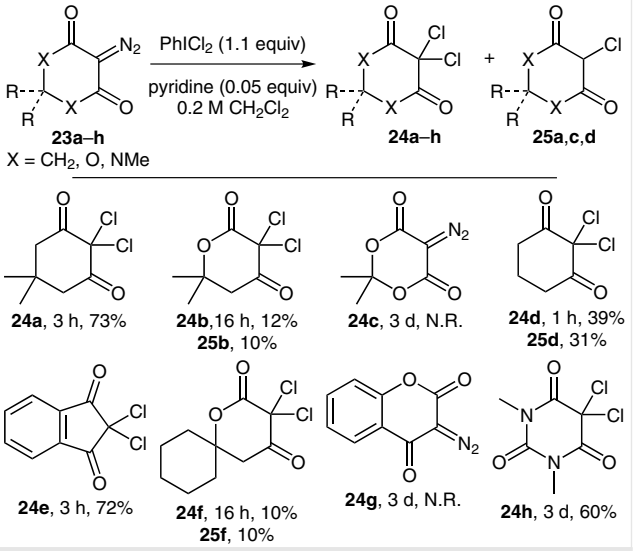
A series of acyclic α-diazo-β-dicarbonyl compounds were prepared to test our chlorination reaction and assess the relative reactivities of the different substrates. Compounds **21a**–**e** were synthesized by diazo transfer between *p*-ABSA and a commercially available dicarbonyl. We subjected **21a** to our standard chlorination conditions, and though the reaction was slow, the product **22a** was recovered in 65% yield (Scheme 5). We investigated the effect of solvent, Lewis base, and temperature, and we found our standard conditions were the most rapid and effective. The additional diazo stabilization associated with β-keto ester **21b** manifested itself as a longer reaction of identical yield. Even slower to react was β-diester **21c**, which took four hours to consume the starting material, and gave **22c** in 50% yield. Compounds **21d**,**e** were also chlorinated with ease, and again the β-keto ester **21e** reacted slower. Overall, the acyclic substrates underwent the Lewis base catalyzed chlorination in acceptable yield and, as anticipated, with reaction rates that closely correlated with the relative diazo stabilities.



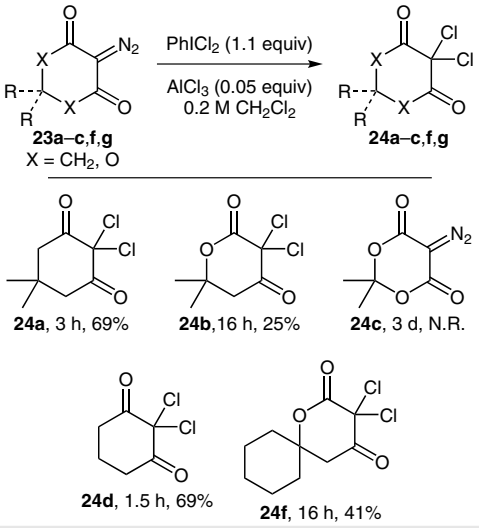
Scheme 5 Chlorination of acyclic diazo-β-dicarbonyl compounds with $PhICl_2$ (**2**)

We next investigated the chlorination of the inherently less reactive cyclic α-diazo-β-dicarbonyl compounds. While chlorination of **23a** provided **24a** in good yield over three hours, the β-keto ester analog **23b** gave **24b**/**25b** in 22% combined yield over 16 hours (Scheme 6). Diazo stabilization was even more pronounced for diazo Meldrum's acid (**23c**), which was completely unreactive in the chlorination reaction over three days.[28] While diketone **23d** underwent a poorly chemoselective chlorination, giving ca. 1:1 mixture of chlorination products, diketone **23e** chlorinated with ease, giving the product in 72% yield. Two additional β-ketolactones **23f**,**g** were tested, and where the former reacted poorly, the latter was unreactive over three days. Lastly, we investigated barbituric acid derivative **23h** and were pleased to recover **24h** in moderate yield over three days. These kinetic observations are again consistent with the relative nucleophilicities of the diazo compounds, with the cyclic derivatives reacting much more slowly than the acyclics.[27] The cyclic β-keto lactones and β-diesters behaved consistently, reacting poorly or not at all. On the other hand, the cyclic β-diketones displayed some unusual reactivity. Where **23a**,**e** reacted cleanly to give the respective dichlorides, **23d** gave a mixture of chlorination products, possibly suggesting a beneficial substitution effect.

We were puzzled why the chemoselectivity was eroded for **23b**,**d**,**f** to give ca. 1:1 mixtures of products. Control experiments between **23a** and **23d** were conducted using the same source of solvent, pyridine and iodane, but the product distribution remained unchanged. From these it was abundantly clear that acidic impurities were not responsi-



Scheme 6 Chlorination of cyclic diazo-β-dicarbonyl compounds with $PhICl_2$ (**2**)



Scheme 7 Chlorination of cyclic diazo β-dicarbonyl compounds under Lewis acid activation

ble for **25d** being generated. The chlorination of **23d** was also conducted without pyridine, and after 48 hours and minimal conversion, equal amounts of **24d** and **25d** were observed. From this experiment we reaffirm that pyridine activation is key to achieving timely chlorination reactions, and we conclude that competing chlorination pathways are operative, whether pyridine is present or not.

In our investigation of phenyl diazoacetate derivatives,[10] varying quantities (up to 15%) of monochloride byproducts were generated depending on the Lewis base activator used. Through systematic changes to the solvent and activator, we discovered conditions that shut down the pathway leading to the monochloride products. Surprisingly, in this investigation of β-dicarbonyls such changes had little effect on the poor chemoselectivity.[29] Based on our fluorination reactions, which provide exclusively the difluoride products (Scheme 2, b), we tried Lewis acid activation of iodane **2**. In analogy to the use of $BF_3{\cdot}OEt_2$ in the fluorination reactions, we tested BCl_3 as an activator in the chlorination of **23a**, as well as $AlCl_3$, a known activator for alkyl and acyl chlorides. Though BCl_3 activation failed, $AlCl_3$ activation gave exclusively **24a** in the same time and yield as under pyridine activation (Scheme 7). We then applied these conditions to **23b** and **23c**, and while **23b** reacted to give **24b** as the sole product in 25% yield, **23c** again remained completely unreactive. Lastly, substrates **23d** and **23f** were subjected to the $AlCl_3$-catalyzed reaction, and both reacted chemoselectively, giving only the desired products in equal or greater yield to the pyridine-catalyzed reactions.[30] Thus we found that Lewis acid activation of iodanes was effective in our chlorination reactions, and that such conditions could be used to improve poorly chemoselective reactions.[31]

Herein we present a mild and efficient Lewis base- and Lewis acid-catalyzed chlorination of α-diazo-β-dicarbonyl compounds. The study employed the bench-stable iodane (dichloroiodo)benzene, which is reproducibly prepared on multigram scale from inexpensive reagents,[32] and diazocarbonyl compounds prepared in one step by diazo transfer reactions. The acyclic β-dicarbonyl compounds were found to chlorinate chemoselectively, giving only the desired products in moderate to good yields over a few hours. The cyclic β-dicarbonyls were much slower to react overall, and while some reacted to give exclusively the dichlorides, others displayed poor chemoselectivity or failed to react at all. This study led to a greater understanding of the dichlorination reaction, proving that at least two different chlorination events are operative in our reaction and that our monochloride byproducts are not a result of acidic impurities. Employing $AlCl_3$ as the activator helped overcome the instances of poor chemoselectivity, presumably by enabling the dichlorination process over competing pathways, and proved as effective as pyridine catalysis. We were also able to draw parallels between the nucleophilicity of the diazo species and the rates of our dichlorination reaction, which has enabled us to suggest the association of diazo and activated iodane complex as the rate-limiting step in our mechanism. In conclusion, this reaction offers a mild, generally applicable, and attractive addition to the existing methods for the synthesis of α,α-halo-β-dicarbonyl compounds from β-diketones and β-keto esters. We are presently working to improve the reactivity of β-diesters (e.g., Meldrum's acid) and apply the fluorination reaction to β-dicarbonyls, and our results will be presented in due course.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380304.

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(24) **Caution:** Diazo compounds are reported to be toxic and potentially explosive. Appropriate safety measures should be observed when working with them.
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(29) For example, chlorination of **23d** using 5 mol% DMAP or 2,6-lutidine, or either 1 mol% or 10 mol% pyridine gave mixtures of **24d**/**25d**. The best improvement came from using 5 mol% pyridine in DCE, which gave **24d** in 51% yield. However, chlorinating **23a** in DCE gave **24a** in only 43% yield, so this effect was not pursued.
(30) Using DCE in the $AlCl_3$-catalyzed reactions gave lower yields than CH_2Cl_2: **24b**, 8%; **24d**, 49%.
(31) Another dramatic Lewis acid effect was found when chlorinating 10-diazoanthrone. In contrast to pyridine, which gave anthroquinone as the product, using $AlCl_3$ gave 10,10-dichloroanthrone as the sole product.
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