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Cyclopropanation of alkenes with metallocarbenes generated from monocarbonyl iodonium ylides*

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Reacting Wittig reagents and the hypervalent iodine reagent iodosotoluene, in the presence of 10 mol% Cu(tfacac)₂ and 5 equiv. of alkene, results in a novel cyclopropanation reaction. The reagent combination is believed to generate a transient monocarbonyl iodonium ylide (MCIY) *in situ*, which can be intercepted by the copper catalyst to give a metallocarbene. Both ester and ketone derived phosphoranes can be used, as can styrenyl and non-styrenyl alkenes, which provides cyclopropanes in yields up to 81%.

Iodonium ylides,¹ an important subset of hypervalent iodine (HVI) compounds, are amenable to many different types of reactions, including cycloaddition reactions² or as electrophiles in nucleophilic substitutions.³ Most commonly, iodonium ylides are employed as less hazardous surrogates for diazo compounds in metallocarbene chemistry,^{1,4} or more recently, in metal-free cyclopropanation reactions.⁵ In addition to the versatility offered by these reagents, key benefits of hypervalent iodine-mediated reactions include their mild and selective oxidizing ability and often their environmentally friendly reaction conditions.⁶

Iodonium ylides containing two stabilizing groups (Fig. 1, **A**) are predominately found in the literature, owing to their increased thermal stability,^{1,7} and their easy synthesis from active methylene compounds and PhI(OAc)₂ under basic conditions.⁸ The stability of **A** results from the delocalization of the anionic charge across the two electron-withdrawing groups attached to the ylidic carbon.⁹ Conversely, monocarbonyl iodonium ylides (MCIYs, **B**) are significantly less stable due to the lone electron-withdrawing group present,¹⁰ which makes them extremely rare. A consequence of only possessing one electron-withdrawing group is that the straightforward approach for generating other monocarbonylonium ylides fails (*e.g.* proton abstraction from the α -carbon of an onium ion).¹¹ This is due

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†Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra of new compounds. See DOI: 10.1039/c8ob02636j to the decreased relative acidity of this proton when only one electron-withdrawing group is present. Owing to the extremely high nucleofugality of the phenyliodonio group,¹² α -carbonyl functionalization typically occurs at the expense of ylide formation.¹³ This has resulted in long-standing problems for the isolation, characterization and systematic evaluation of MCIYs in synthesis.

Though their isolation has yet to be achieved, MCIYs have be generated in situ and characterized spectroscopically. This was first achieved by Ochiai and co-workers, who unmasked a MCIY at low-temperature through an acyl transfer reaction on a (2-acetoxyvinyl)iodonium salt (Scheme 1A, a).¹⁰ Ochiai subsequently demonstrated the utility of these MCIYs, reacting them with carbonyl compounds to give α,β -epoxy ketones,¹⁰ or with activated imines to give 2-acylaziridines (Scheme 1A, b and c).¹⁴ They also reported another example of this ionic reactivity, effecting an α-alkylation reaction with trialkylboranes (Scheme 1A, d).¹⁵ The precursors required to generate MCIYs in this fashion is a significant limitation, as only α -keto iodonium ylides appear to be accessible.¹⁶ Furthermore, the conditions used to generate these MCIYs (LiOEt at low temperature) would also be prohibitive for investigating them in metallocarbene reactivity.

A long-standing pursuit in our lab was to develop an *in situ* synthesis of these ylides, under conditions where the potential of these as metallocarbene precursors could be assessed. In a previous proof-of-concept paper, we reported a reaction between iodosobenzene (2a) and ester-derived Wittig reagent



Fig. 1 Structures of dicarbonyl iodonium ylides and monocarbonyl iodonium ylides (MCIYs).

A. Synthesis and ionic reactivity of MCIYs





Scheme 1 Synthesis and reactivity of MCIYs.

1a, carried out in the presence of a copper catalyst and styrene, which provided low yields (by %GC) of cyclopropane **4a** (Scheme 1B).¹⁷ This novel cyclopropanation reactivity was envi-

sioned to arise when phosphorane **1a** and iodane **2a** combined to give a transient MCIY which, upon being intercepted by the transition metal catalyst, undergoes transylidation to give a metallocarbene. Herein, we report the first systematic evaluation of this strategy for generating MCIYs, and employing these as metallocarbene precursors in cyclopropanation reactions. This new strategy provided access to both ester- and ketone-derived MCIYs, and was effective with a broad scope of alkenes.

We began this study by testing various iodosoarenes, iodoxvlarenes and other iodanes in the reaction. First, we focused on the *ortho*-stabilized, soluble iodane **2b** reported by Protasiewicz and co-workers.¹⁸ The polymeric nature common to iodosoarene compounds renders them insoluble in many organic solvents, and we believed that using a soluble variant, where the polymeric structure is disrupted by an ortho-sulfonyl moiety, might result in an improvement over the 17% yield realized with iodosobenzene 2a (Table 1, entry 1). Reacting 1a and 2b at room temperature in CHCl₃ without a catalyst gave a homogeneous mixture, but no cyclopropanation product was observed (Table 1, entry 2). A variety of copper- or rhodiumderived catalysts were tested, but again, none of the desired cyclopropane was recovered (Table 1, entries 3-7). Further variation of reaction parameters (e.g. time for syringe addition, temperature or iodane loading) were also fruitless (see ESI[†]). We also tested the partially-soluble ortho-tolyliodoso compound (2c), which again did not improve the reaction. Various other substituted iodanes were tested, and while para-anisyl derivative 2d failed, the para-tolyl (2e), para-nitrophenyl (2f)

Table 1 Optimization of the cyclopropanation reaction^a

		$EtO PPh_3 G I = O$ $1a 2$	5 equiv. styrene (3a) 10 mol% Cu(tfacac) ₂ solvent, rt, time	Ph CO ₂ Et		
Entry	Iodosoarene 2 (G=)	2 (equiv.)	Solvent	Time (h)	Catalyst (mol%)	Yield (%)
1	2a (H)	1.2	CHCl ₃	1.5	$Cu(tfacac)_2(10)$	17
2	$2\mathbf{b} (o-\mathrm{SO}_2^t \mathrm{Bu})$	1.0	$CHCl_3$	20	_	0
3	2b	1.2	$CHCl_3$	20	$Cu(acac)_2$ (10)	0
4	2b	1.2	$CHCl_3$	24	$Cu(tfacac)_2$ (10)	0
5	2b	1.2	$CHCl_3$	2	$Cu(hfacac)_2(10)$	0
6	2b	1.2	$CHCl_3$	2	$Rh_2(OAc)_4(5)$	0
7	2b	1.2	$CHCl_3$	5	$Rh_2(tpa)_4(5)$	0
8	2c (<i>o</i> -Me)	2	$CHCl_3$	1.5	$Cu(tfacac)_2$ (10)	0
9	2d (<i>p</i> -OMe)	2	$CHCl_3$	1.5	$Cu(tfacac)_2(10)$	0
10	2e (<i>p</i> -Me)	2	$CHCl_3$	1.5	$Cu(tfacac)_2(10)$	53
11	$2f(p-NO_2)$	2	$CHCl_3$	1.5	$Cu(tfacac)_2(10)$	48
12	$2\mathbf{g}(p^{-t}\mathbf{B}\mathbf{u})$	2	$CHCl_3$	1.5	$Cu(tfacac)_2(10)$	45
13	2e	1.2	$CHCl_3$	1.5	$Cu(tfacac)_2(10)$	34
14	2e	3	CHCl ₃	1	$Cu(tfacac)_2$ (10)	30
15	2e	4	$CHCl_3$	1.5	$Cu(tfacac)_2(10)$	0
16	2e	2	CH_2Cl_2	1.5	$Cu(tfacac)_2(10)$	43
17	2e	2	CH ₃ CN	1.5	$Cu(tfacac)_2$ (10)	0
18	2e	2	$CHCl_3$	1.5	$Rh_2(OAc)_4(5)$	0
19^b	2e	2	$CHCl_3$	1.5	$Cu(tfacac)_2(10)$	0

^{*a*} Reaction conditions: **1a** is added dropwise *via* syringe pump over one hour to a solution of **2**, catalyst and styrene (5 equiv.) in solvent (0.1 M) at room temperature. The reaction is further stirred until the indicated length of time is reached. Isolated yields of 2.3 : 1 *trans : cis* mixtures. ^{*b*} The tri-*n*-butyl variant of **1a** was used.

and *para-t*-butylphenyl (**2g**) derivatives all worked, giving the desired product **4a** in 45–53% yield (entries 10–12). Further trials, including using additives to break the polymeric iodosoarene structure,¹⁹ using other iodanes (*e.g.* PIDA) or iodoxylarene (ArIO₂) derivatives also failed to improve the reaction outcome (see ESI†). Contrary to expectation, the solubility of the iodosoarene did not prove critical to achieving good reactivity, and while iodosoarenes possessing strongly electrondonating substituents failed in the reaction (**2c**), electron-poor substrates (**2f**) were effective. Finally, steric hindrance between the *ortho*-substituent on the iodosoarene and the phosphorane appears to be important, as the *ortho*-tolyl derivative **2c** failed, whereas the *para*-tolyl derivative **2e** proved the most effective, with the increased yield (over **2a**) presumably arising from mild electronic stabilization by the methyl group.

Having identified **2e** as the most productive iodosoarene, we attempted to improve the reaction by testing the various reaction parameters. Changing the loading of the iodane was not beneficial, and we found that using more than 3 equiv. of **2e** resulted in a reaction mixture containing an overwhelming amount of insoluble material, which did not give any cyclopropane products (entry 15). Varying the solvent did not improve the yield of **4a** (entries 16 and 17), neither did using other copper or rhodium catalysts (*e.g.* $Rh_2(OAc)_4$, entry 18, also see ESI†). Out of curiosity, we also attempted the cyclopropanation reaction using the less bulky tri-*n*-butyl-phosphorane (entry 19), and while the starting material was consumed, no cyclopropanation product was formed.

After determining the optimal reactions conditions, we then expanded the reaction scope to discover what other types of cyclopropane motifs could be synthesized. First, the effect of various electron-poor, -neutral, and electron-rich functional groups on styrene were investigated. The para-chloro and parat-butyl derivatives gave the corresponding cyclopropanes 4b and 4c in moderate yield, but a significant increase was observed with the para-methoxy derivative, which gave 4d in 57% yield (Scheme 2). Further methoxy substitution on the styrene gave increasingly higher yields, with dimethoxy 4e and trimethoxy 4f being recovered in 68% and 74% yield, respectively. Both α -methyl and α -trimethylsiloxy substitution on styrene was tolerated, giving 4g and 4h in 63% and 56% yield. Styrene bearing a β -methyl group was also viable (4i, 59% yield), however, β -nitro substitution caused the reaction to fail (4j, 0% yield). The cis and trans isomers of the β-methoxy-substituted styrenes 3k and 3l were individually subjected to the reaction, which gave 4k and 4l in 60% and 61% yield. The highest yield was observed with a tetramethoxystyrene derivative, which resulted in a single diastereomer of cyclopropane 4m in 81% yield. These results are consistent with an electrophilic metallocarbene being generated in the reaction, which would react most effectively with an electronrich alkene.

The nature of the Wittig reagent was next investigated, and we found both the benzyl ester derivative (**1b**), as well as the acetyl derivative (**1c**) were effective at cyclopropanating styrene, giving **4n** and **4o** in 55% and 46% yield. The yield decreased significantly when benzoyl derivative **1d** was used (**4p**, 30% yield), but the reactivity was restored with increased methoxysubstitution on the alkene, giving **4q** in 54% yield and **4r** in 78% yield, both as single diastereomers.

Non-styrenyl alkenes were also investigated, and we found 1-phenyl-1,3-butadiene would undergo regioselective cyclopropanation at the terminal alkene, giving **4s** in 61% yield. We were pleased to find that allylbenzene could undergo cyclo-



Scheme 2 Synthesis of cyclopropanes from Wittig reagent precursors 1a-d. ^aThe alkene stereochemistry is indicated in the product drawn. ^bProducts typically recovered as $\sim 2-3:1$ mixtures of diastereomers, except 4k,m,q,r which were single diastereomers by ¹H NMR.



Fig. 2 Proposed reaction mechanism.

propanation, giving **4t** in 49% yield, as could dihydropyran and the TMS-enol ether of cyclohexanone, which gave **4u** and **4v** in 60% and 63% yield, respectively. Therefore, it appears that usable yields can also be obtained with non-styrenyl aliphatic alkenes and enol ethers, without observing products of competing C–H insertion, oxonium ylide formation or cycloaddition processes.²⁰

Finally, the viability of an intramolecular cyclopropanation reaction was also investigated (eqn (1)). The Wittig reagent 1c was allylated in 86% yield to give 1e,²¹ and when this was subjected to 2e and Cu(tfacac)₂, it underwent cyclopropanation to give 4w in 63% yield.

$$1c \xrightarrow{\begin{tabular}{c} Br \\ \begin{tabular}{c} & & Br \\ \hline & & BuLi, THF \\ \hline & & & PPh_3 \\ \hline & & & PPh_3 \\ \hline & & & 10 \mod \% \ Cu(tfacac)_2 \\ \hline & & & & HCl_3, \ rt, \ 3.5 \ h \\ \hline & & & 4w \ 63\% \end{array}$$

We propose that the cyclopropanation reactions occur by the sequence of reactions illustrated in Fig. 2. Upon combining Wittig reagent **1a** with iodosotoluene **2e**, a formal Wittig reaction could occur to generate the monocarbonyl iodonium ylide **C** and phosphine oxide. Attack by this ylide on the electrophilic copper catalyst leads to ylide decomposition with expulsion of iodotoluene, generating copper carbene **D**. Upon engaging with styrene, the cyclopropanation reaction occurs, regenerating the catalyst.

Conclusions

In conclusion, we report here the first systematic evaluation of *in situ* generated monocarbonyl iodonium ylides as metallocarbene precursors, and show for the first time their use as diazo surrogates in metallocarbene reactions. The combination of Wittig reagents and *para*-iodosotoluene leads to transient MCIYs, which readily undergo cyclopropanation reactions with alkenes. The optimized procedure was catalyzed by $Cu(tfacac)_2$, and yields up to 81% were achieved. The reaction was tolerant to both ketone- and ester-derived Wittig reagents, and the scope of alkenes was broad, with the highest yields being obtained with the most electron-rich olefins. We are continuing to investigate MCIYs in metallocarbene and metal-free reactivity, and we will disclose the results in due course.

Conflicts of interest

There are no conflicts to declare.

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