

## Wittig Reagents as Metallocarbene Precursors: In Situ Generated Monocarbonyl Iodonium Ylides

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A proof of concept study was undertaken to determine the suitability of monocarbonyl iodonium ylides (MCIYs) as metallocarbene precursors. Exposing Wittig reagents to iodosylbenzene results in a pseudo-Wittig reaction that generates MCIYs in situ. These ylides are intercepted by transition-metal catalysts to generate metallocarbenes, which then

### Introduction

Transition-metal-catalyzed decomposition of diazo compounds to generate metallocarbenes allows entry into their diverse portfolio of associated transformations. Metallocarbenes readily undergo cyclopropanation, C-H insertion, and ylide formation, providing general methods for introducing molecular complexity.<sup>[1]</sup> One drawback of this methodology is that the initial diazo compounds are reported to be toxic/carcinogenic and explosive.<sup>[2]</sup> As such, their widespread use outside the academic laboratory is limited.<sup>[3]</sup> To circumvent the use of the diazo functional group, numerous reports of surrogates have appeared over the years. For  $\beta$ distabilized substrates, iodonium ylides have proven to be highly effective as diazo surrogates, and the efficacy of this method results from the acidity of the a-protons (Figure 1a). In this case, initially formed iodonium salt 2a is readily deprotonated to afford iodonium ylide 3, which acts as a metallocarbene precursor. A variety of electron-withdrawing groups (EWGs) are tolerated, and this methodology has now evolved into the one-pot generation and metalcatalyzed decomposition of iodonium ylides to afford products derived from cyclopropanation,[4] C-H-insertion,[4f] and oxonium ylides.<sup>[5]</sup>

In contrast to  $\beta$ -distabilized substrates, the generation of monocarbonyl iodonium ylides (MCIYs) for use as diazo surrogates has not been reported.<sup>[6]</sup> This is because of our inability to generate MCIYs by the typical onium (i.e., N, P, S, etc.) ion  $\alpha$ -proton abstraction.<sup>[7]</sup> The initially formed iodonium salt **2b** (Figure 1b) has no proton of sufficient

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undergo either dimerization or cyclopropanation reactions with a variety of alkenes. Additionally, the reaction between diazoester-derived metallocarbenes and Wittig reagents afforded cross-coupling products, illustrating a new type of olefination reaction for phosphonium ylides.



Figure 1. (a)  $\beta$ -Distabilized iodonium ylide synthesis and transmetalation. (b) Monostabilized iodonium ylide synthesis typically affords  $\alpha$ -functionalization products.

acidity for easy deprotonation, and given the high nucleofugality of the phenyliodonio group, it instead undergoes nucleophilic displacement to give  $\alpha$ -functionalized products **5**.

Although sulfonium<sup>[4g,8]</sup> and sulfoxonium<sup>[9]</sup> ylides serve as metallocarbene precursors in monostabilized substrates, these have not been adopted by the synthetic community. If they could be prepared, the potential of MCIYs as diazo surrogates could be determined. The only example of carbenoid reactivity resulting from a monostabilized iodonium ylide employed nitromethane as the substrate.<sup>[10]</sup> Hansen took advantage of its relatively acidic protons and developed one-pot processes for iodonium ylide generation and carbene transfer. This proved moderately effective in one-pot cyclopropanation and ring cleavage reactions (Scheme 1a). The only reported syntheses of MCIYs involve an acyl-transfer reaction to liberate the iodonium ylide from a preformed iodonium salt (Scheme 1b).<sup>[11]</sup>

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Scheme 1. (a) Monostabilized iodonium ylide from nitromethane. (b) An acyl transfer method for in situ generation of MCIYs. esp =  $\alpha, \alpha, \alpha', \alpha'$ -tetramethyl-1,3-benzenedipropionic acid.

#### **Results and Discussion**

As part of a program focusing on the use of hypervalent iodine reagents in synthesis, we proposed to develop a method for the generation and use of MCIYs as metallocarbene precursors. With all the potential variables that could be investigated [substrate, aryl iodide substitution, counterion (X) and base], we assume there is a combination that would prove successful for MCIY synthesis (Scheme 2a). Before delving too deeply into these studies, we wanted to first determine whether MCIYs were effective as metallocarbene precursors. The key to solving this lay in our ability to generate an MCIY under conditions that are compatible with the ylide being intercepted by a transitionmetal catalyst. Simplistically, we viewed the iodonium ylide arising from a combination of a substrate and a hypervalent iodine reagent that would react to form the MCIY. Aware of the oxophilicity of phosphorus, we proposed a pseudo-Wittig reaction between phosphonium ylide 10 and iodosylbenzene, which would generate MCIY 11 and triphenylphosphine oxide (Scheme 2b).<sup>[12]</sup> The following discussion concerns our results from this proof-of-concept study.



Scheme 2. Possible approaches to generating MCIYs: (a) substrate and reagent variations; (b) Wittig-type reaction with iodosylbenzene.

We investigated the cyclopropanation of styrene by Wittig reagent **10** as our model system, specifically because it is analogous to the cyclopropanation of styrene with ethyl diazoacetate (EDA, 12) and because catalyst influence on that transformation is well documented.<sup>[1]</sup> Reference samples of the cyclopropanation (i.e., 13) and carbene dimerization (i.e., 14) product isomers were prepared by heating 12, styrene, and Cu(OTf)<sub>2</sub> (Tf = trifluoromethanesulfonyl) in CHCl<sub>3</sub> at reflux (Scheme 3a). The related experiments using Wittig reagent 10, styrene, and Cu(OTf)<sub>2</sub> were monitored by GC analysis, which indicated the presence of dimers 14 but no cyclopropanation product 13 (Scheme 3b).



Scheme 3. (a) Cyclopropanation of styrene with EDA. (b) Attempted cyclopropanation of styrene by insitu generation of MCIY by ylide transfer between Wittig reagent and iodosylbenzene. Carbene dimerization product 14 results.

A series of experiments was carried out to differentiate between a carbenoid dimerization and an oxidative dimerization. Repeating the reaction without styrene at room temperature (Table 1, entry 1) and at reflux (Table 1, entry 2) showed an increase in the yield of 14 at elevated temperature. Conducting the reaction in the absence of a catalyst (Table 1, entry 3) gave no 14, though at reflux (Table 1, entry 4) 14 was observed, which suggests a possible background oxidative mechanism at elevated temperature. An increased iodosylbenzene concentration also failed to produce 14 (Table 1, entry 5). Conducting the reaction without oxidant afforded no 14, owing to the stability of phosphorus ylides, which are not suitable as direct precursors to metallocarbenes (Table 1, entries 6 and 7).<sup>[13]</sup> A variety of oxidants were tested (Table 1, entries 8-11), none of which produced 14. Various solvents (CHCl<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 1,2-dichloroethane, benzene, toluene, MeCN, xylenes, 1,2-dichlorobenzene) were also investigated, though no significant improvement in product formation (by GC) was observed. We concluded we were observing a pseudo-Wittig reaction between 10 and iodosylbenzene and that we were observing unprecedented reactivity between metallocarbenes and Wittig reagents.

As the cross-coupling of carbenes and Wittig reagents was, to the best of our knowledge, unknown, we carried out a series of experiments to support our proposal (Scheme 4). Cross-coupling between EDA (12) and Wittig reagent 15 was most effective with Cu(hfacac)<sub>2</sub> (hfacac = hexa-fluoroacetylacetonate), which gave product 16 in 41% yield upon isolation. An additional example was inspired by a

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Table 1. Control experiments to probe the dimerization reaction.

	Eto	oxidant Cu(OTf) <sub>2</sub> CHCl <sub>3</sub> , 7	O OEt OEt 0 14	
Entry	Oxidant (1.2 equiv.)	Cu(OTf) <sub>2</sub> [mol-%]	<i>Т</i> [°С]	Yield <sup>[a]</sup> [%]
1	PhIO	10	r.t.	8
2	PhIO	10	reflux	41
3	PhIO	_	r.t.	_
4	PhIO	_	reflux	17
5	PhIO (2.5 equiv.)	_	r.t.	_
6	-	10	r.t.	_
7	_	10	reflux	2
8	$PhI(OAc)_2$	10	r.t.	_
9	Oxone	10	r.t.	_
10	DMSO	10	r.t.	_
11	PhI(OH)OTs	10	r.t.	-

[a] The yields were determined by GC analysis of the crude reaction mixtures. Area-% values were compared to a concentration calibration curve prepared for maleate **14**.

report from the Davies laboratory, in which they cross-coupled diazoesters 17 and 12.<sup>[14]</sup> We carried out the analogous reaction between diazoester 17 and Wittig reagent 10 and recovered olefination product 18 in 53% yield.



Scheme 4. Cross-coupling reactions between Wittig reagents and diazoesters.

Having determined that we were observing carbenoid reactivity from transient iodonium ylides, we investigated the effect of catalyst on the transformation. A variety of catalysts commonly used for metallocarbene formation were tested, and in all cases product 14 was generated (Table 2). The  $Rh_2(tpa)_4$  (tpa = triphenylacetate) catalyst generated trace amounts of cyclopropanation product 13 (Table 2, entry 4), but when we used  $Cu(tfacac)_2$  (tfacac = trifluoroacetylacetonate) or Cu(hfacac)<sub>2</sub> as the catalyst, a significant increase in yield of cyclopropanation product 13 was observed (Table 2, entries 9 and 10). Copper catalysts have been observed to be less effective than rhodium catalysts in one-pot iodonium ylide transformations,<sup>[5,8b]</sup> but only these catalysts were found to intercept the transient MCIY and induce carbenoid reactivity (other than dimerization) to any reasonable extent. The GC yields indicate Cu(tfacac)<sub>2</sub> to be most effective, resulting in a 56% yield of metallocarbenederived products.

Table 2. Screening catalysts for efficacy in the MCIY-based cyclopropanation reaction.

	Eto PPh <sub>3</sub>	O (1.2 equiv.) ene (5 equiv.) catalyst CHCl <sub>3</sub> , r.t.	O OEt OEt O 14
Entry	Catalyst <sup>[a]</sup>	Yield [%] 13 <sup>[b]</sup>	<b>14</b> <sup>[c]</sup>
1 <sup>[d]</sup>	Cu(OTf) <sub>2</sub>	58	11
2	$Cu(OTf)_2$	_	8
3	$Rh_2(OAc)_4$	_	18
4	$Rh_2(tpa)_4$	3	8
5	$Rh_2(tfa)_4$	_	12
6	$Rh_2(piv)_4$	_	26
7	$Cu(BF_4)_2$	_	12
8	$Cu(acac)_2$	_	11
9 <sup>[e]</sup>	$Cu(tfacac)_2$	27	29
10	$Cu(hfacac)_2$	14	15

[a] Reactions were performed with 10 mol-% copper catalyst or 5 mol-% rhodium catalyst. tfa = trifluoroacetate, piv = pivalate, acac = acetylacetonate. [b] The yields were determined by GC analysis of the crude reaction mixtures. Area-% values were compared to a concentration calibration curve prepared for product 13. [c] The yields were determined by GC analysis of the crude reaction mixtures. Area-% values were compared to a concentration calibration curve prepared to a concentration calibration curve prepared for maleate 14. [d] Reaction was run with EDA (12) and styrene and its GC yield [%] values are included for comparative purposes. [e] Products were isolated as a mixture in 30% yield after purification.

To minimize the occurrence of carbene dimerization products, we added 10 by syringe pump over various times ranging from 0.5 to 18 h, but no significant increase in product formation was observed. Ochiai reported MCIYs to be unstable above  $-30 \,^{\circ}C$ ,<sup>[11d]</sup> so we repeated the reaction at lower temperatures to determine the effect. Reactions conducted at -60, -40, and 0 °C failed, and analysis of their reaction mixtures by <sup>31</sup>P NMR spectroscopy revealed mostly starting ylide 10, suggesting the reaction failed to initiate at lower temperature. We investigated whether iodosylbenzene could be depolymerized in solution,<sup>[15]</sup> with the goal of making the initial Wittig-type reaction more facile. Lewis acids (BF<sub>3</sub>·OEt<sub>2</sub>, ZnCl<sub>2</sub>, and MgBr<sub>2</sub>·OEt<sub>2</sub>) were added individually, but little improvement in reaction efficacy was observed. Finally, neither increasing the amount of PhIO used nor employing styrene as a reaction solvent resulted in any significant improvement in the generation of 13

To provide further evidence of carbenoid reactivity, we conducted the cyclopropanation reaction with cyclohexene (19), norbornene (20), and *trans*-stilbene (21).<sup>[16]</sup> For all reactions, an inseparable mixture of products 13a–c and 14 was isolated in moderate yield (Scheme 5). Though the yields are moderate, these examples provide clear evidence that MCIYs are suitable targets for continued investigation as metallocarbene precursors.





Scheme 5. Cyclopropanation of alkenes by using MCIY-derived metallocarbenes. Yield corresponds to the combined yields of isolated products **13** and **14**.

#### Conclusions

Few reports of MCIY reactivity exist owing to the inability to generate these ylides by traditional methods. Though MCIYs represent a potential surrogate for diazoketones and -esters, there existed no reports of MCIYs acting as metallocarbene precursors. By conceiving a means to generate these elusive intermediates from phosphonium ylides (through carbene transfer), we have successfully generated iodonium ylides in situ. We have shown how MCIYs can be intercepted by a variety of transition-metal catalysts and how they can serve as metallocarbene precursors. Both rhodium and copper catalysts induced carbenoid dimerization, and we showed a new crossed-olefination reaction between metallocarbenes and Wittig reagents. Finally, Cu- $(tfacac)_2$  and  $Cu(hfacac)_2$  were found to be effective catalysts for inducing cyclopropanation reactions on a variety of substrates. Though we were unable to improve this process to be synthetically viable, this study serves as proof of concept that MCIYs can serve as metallocarbene precursors. If a suitable method for MCIY synthesis were developed, their potential as diazo surrogates could be realized.

#### **Experimental Section**

General Procedure for in Situ Generation of MCIY-Derived Metallocarbenes: An oven-dried 10 mL round-bottomed flask was charged with iodosylbenzene (114 mg, 0.52 mmol, 1.2 equiv.), Cu(tfacac)<sub>2</sub> (16 mg, 10 mol-%), styrene (247  $\mu$ L, 2.15 mmol, 5.0 equiv.), and CHCl<sub>3</sub> (3.3 mL). A syringe was charged with a freshly prepared solution of Wittig reagent **10** (150 mg, 0.43 mmol, 1.0 equiv.) and CHCl<sub>3</sub> (1.0 mL). The solution was added by syringe pump over a period of 1 h, and the mixture was stirred for 30 min, by which time analysis of an aliquot by <sup>31</sup>P NMR spectroscopy indicated the consumption of **10**. At this time, the reaction was analyzed by GC for determination of product formation. The reaction was quenched by the addition of 10% aqueous K<sub>2</sub>CO<sub>3</sub> (5 mL) and EtOAc (10 mL). The aqueous layer was separated and extracted with EtOAc (2 × 10 mL). The combined organic fraction was washed with water (10 mL) and brine (20 mL) and dried with magnesium sulfate. It was filtered and concentrated by rotary evaporation (with added toluene to remove the excess amount of styrene), resulting in a crude oil. Purification by column chromatography (2, 5, 10 then 20% EtOAc in hexanes) afforded a mixture of products **13** and **14** (13 mg) in 30% yield.

**Supporting Information** (see footnote on the first page of this article): Experimental procedures and gas chromatograph traces for all experiments.

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