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Enantioselective Intramolecular CH-Insertions upon Cu-Catalyzed Decomposition of Phenylidonium Ylides

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Abstract. The Cu-catalyzed intramolecular CH insertion of phenylidonium ylide **5b** has been investigated at 0 °C in the presence of several chiral ligands. Enantioselectivities vary in the range of 38–72 %, and are higher than those resulting from reaction of the diazo compound **5c** at 65 °C. The results are consistent with a carbenoid mechanism for Cu-catalyzed decomposition of phenylidonium ylides.

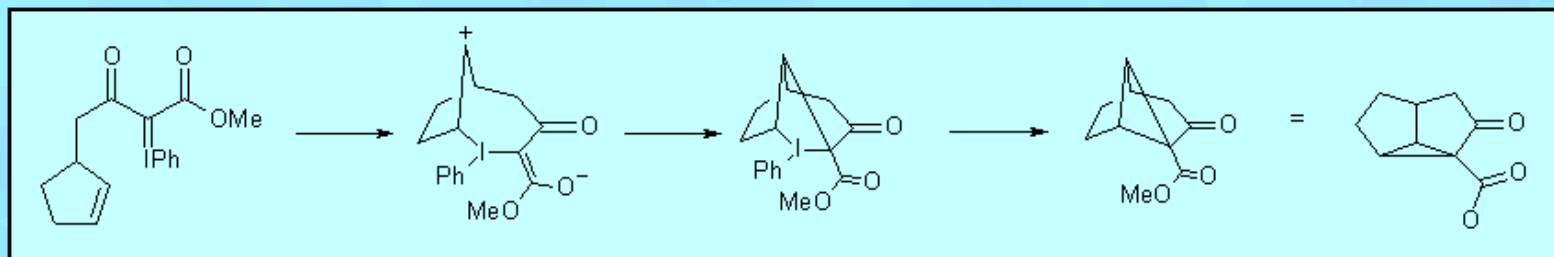
Introduction

Phenylidonium ylides are potential substitutes for diazo compounds in photochemical,^{1,2} thermal,^{1,3} and

transition metal-catalyzed reactions. Although most of these reactions are believed to proceed *via* carbenes or metal carbenoids, the experimental support in favor of the involvement of these intermediates is scarce. Some years ago we presented evidence for metal carbenoid pathways in Rh(II)-catalyzed cyclopropanation and CH insertion reactions.⁵

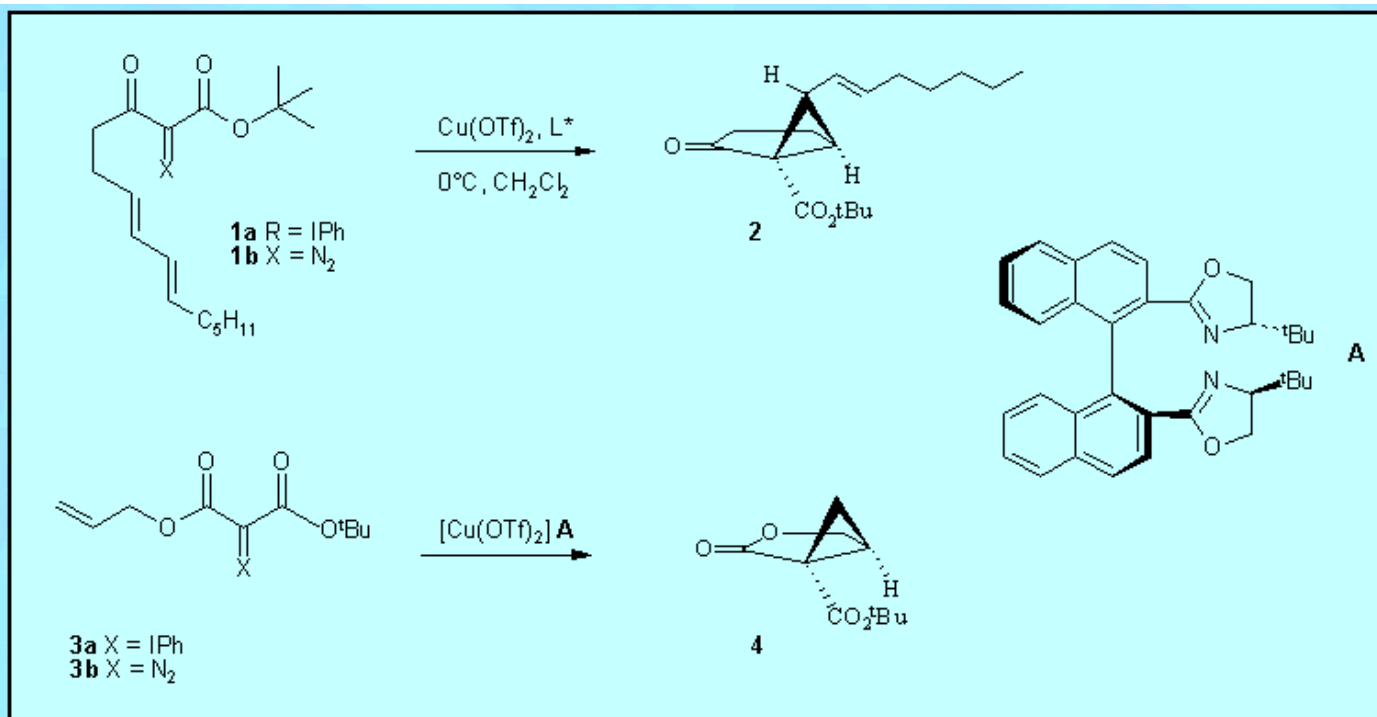
The Cu(I) - catalyzed decomposition of phenyliodonium ylides in the presence of olefins affords cyclopropanes. A mechanism involving electrophilic addition of the iodonium center to the double bond followed by reductive elimination of PhI, as shown in Scheme 1 has been proposed for this transformation. A carbene or metal carbenoid mechanism was specifically ruled out.⁶

Scheme 1



Recently we reported the intramolecular cyclopropanation of phenyliodonium ylides derived from acetoacetates and malonates with [Cu(OTf)₂] in the presence of chiral ligands. Thus, the reaction of ylide **1a** afforded **2** with the binaphthalene derived oxazoline **A** as ligand in 48 % yield and with 68 % ee (Scheme 2).⁷

Scheme 2



This result is inconsistent with the mechanism proposed by Moriarty. If the reaction proceeds *via* electrophilic attack of the iodonium center on the double bond, the metal is not involved in the reaction and, therefore, no asymmetric induction should occur. On the other hand, if a carbenoid mechanism applies, the enantioselectivity resulting upon decomposition of **1a** should be identical to that obtained with the corresponding diazo compound **1b** provided the same chiral ligand is used. Conclusive evidence for metal carbenoid intermediates upon Cu-catalyzed decomposition of diazo compounds has been reported.⁸ Unfortunately, the conventionally used chiral Cu-catalysts proved to be insufficiently reactive for decomposition of **1b** or of similar diazocompounds derived from β -ketoesters and other 1,3-dicarbonyl compounds under conditions suitable for reaction of phenyliodonium ylides. Typically, the ylide **3a** underwent intramolecular cyclopropanation with [Cu(OTf)₂] and ligand **A** in CH₂Cl₂ at 0 °C to provide **4** in 34 % yield and 30 % ee, but decomposition of the corresponding diazo compound **3b** required heating in trifluorotoluene at 100 °C. In general enantioselectivity increases with decreasing temperature and, therefore, a higher enantioselectivity for the reaction of **3a** was expected. Surprisingly, however, the product **4** resulting from diazo decomposition of **3b** had a higher enantiomeric excess (72 % ee, 51 % yield) than that resulting from **3a**. The intramolecular cyclopropanation of **3a** and **3b** in the presence of other chiral ligands revealed remarkable inconsistencies. With some ligands the enantioselectivity observed upon reaction of the ylide was higher than that from diazo decomposition, and with others the trend was inverted. These discrepancies suggest that the cyclopropanation with phenyliodonium ylide may not entirely proceed *via* a metal carbenoid, but also *via* some other, uncatalyzed pathway as suggested by Moriarty. Indeed, uncatalyzed intramolecular cyclopropanations of phenyliodonium ylides have been observed previously.^{5,6}

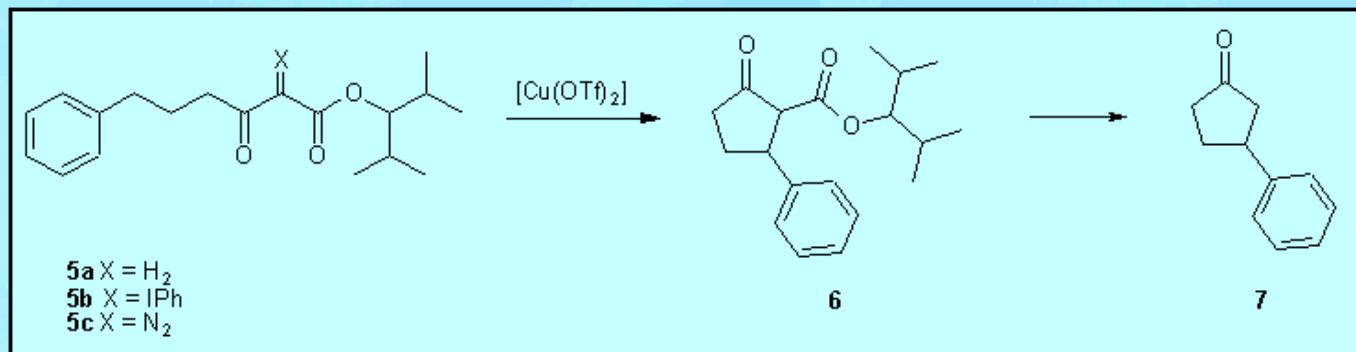
The mechanism of Moriarty for uncatalyzed cyclopropanations with phenyliodonium ylides is plausible, but this mechanism should not apply to uncatalyzed CH bond insertions. Indeed, no insertion products upon uncatalyzed decomposition of phenyliodonium ylides at ambient temperatures have ever been observed or reported. The phenyliodonium ylide derived from diethylmalonate does indeed insert into the CH bonds of cyclohexane, but this

reaction requires a temperature of 100 °C, and it is believed to proceed *via* a free carbene.¹ We reasoned that comparison of enantioselectivities in CH bond insertions resulting from Cu-catalyzed decompositions of phenyliodonium ylides and of the corresponding diazo compounds, respectively, would not be affected by the irregularities occurring in cyclopropanations, and would, therefore, allow more meaningful conclusions on the reaction mechanism.

Results and Discussion

The phenyliodonium ylide **5b** was synthesized by reaction of the hydrocarbon **5a**⁹ with $\text{PhI}(\text{OAc})_2$.¹⁰ Exposure of **5b** to $[\text{Cu}(\text{OTf})_2]$ in CH_2Cl_2 at 0 °C in the presence of chiral ligands **B** – **E** resulted in intramolecular CH insertion and afforded the cyclopentanone carboxylate **6**. The enantioselectivity of the reaction was established on the ketone **7** (g. c., DAICEL, Lipodex B), which was obtained *via* ester hydrolysis of **6** (HBr / EtOH) and subsequent decarboxylation of the intermediate β -ketoacid. Reactions with the diazo compound **5c** were carried out in 1,2-dichloroethane at 65 °C. The results are summarized in Table 1.

Scheme 3



In general, we find that the Cu-catalyzed insertions proceed with acceptable yields from the ylide. The occurrence of CH insertions upon catalysis with Cu is remarkable in itself, since it is well known, that Cu-catalysts are the catalysts of choice for cyclopropanations. However, this preference is only significant when cyclopropanation and insertion pathways are competitive, and this is not the case with **5b** and **5c**. Other Cu-catalyzed CH insertions of diazocompounds have been reported.¹¹ The yields of insertion product **6** resulting from the reaction of the ylide **5b** are generally higher than those of the diazo decomposition. This is a consequence of the notorious low reactivity of diazo esters and diazo ketones derived from β -dicarbonyl compounds, which require temperatures of up to 80 °C with Cu-catalysts and with dirhodium(II)-carboxamidates.¹² Phenyliodonium ylides are significantly more reactive and may be decomposed already at 0 °C with Cu-catalysts or Rh(II)-carboxamidates. This enhanced reactivity in comparison of that of diazo compounds constitutes the main aspect of interest of phenyliodonium ylides.

Ligands

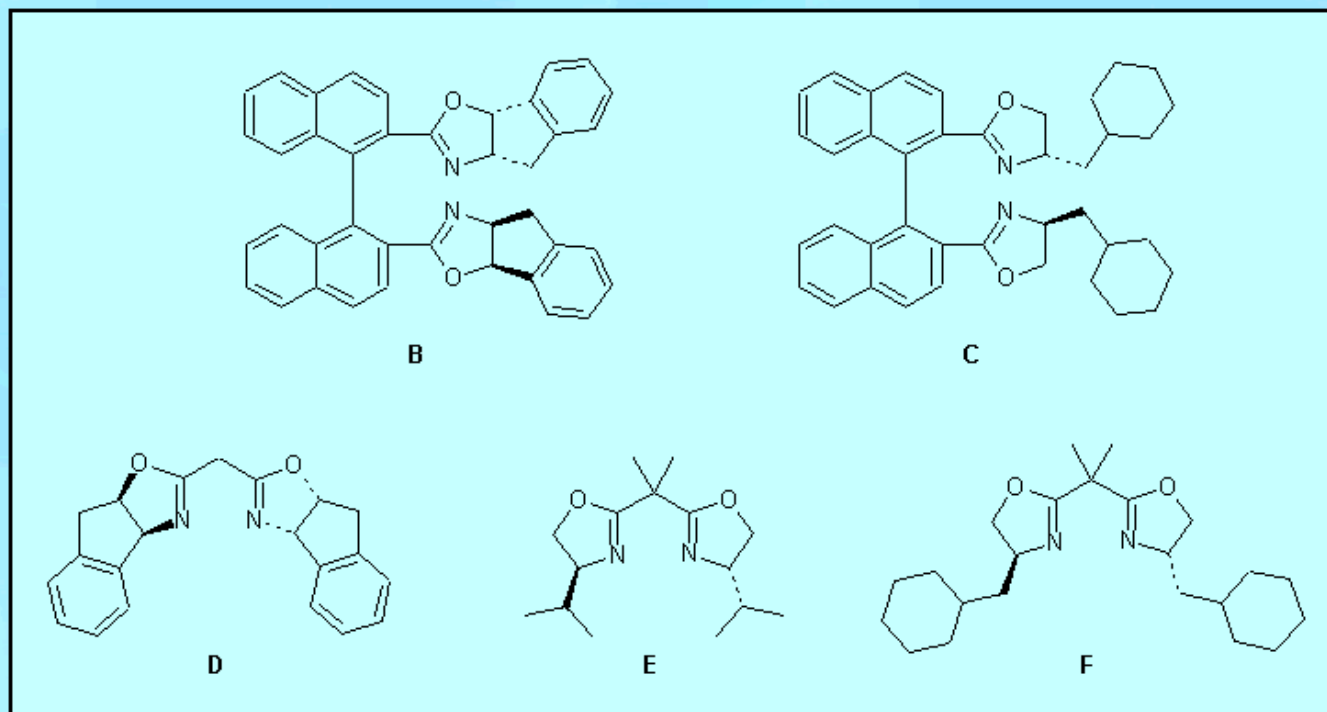


Table 1. Yields and enantioselectivities in intramolecular CH insertions of phenyliodonium ylide **5b** and diazo ketoester **5c**

Entry	Ligand	Yield from 5b (%)	ee from 5b (%)	Yield from 5c (%)	ee from 5c (%)
1	B	47	67	17	51
2	C	46	59	35	60
3	D	52	72	14	31
4	E	51	42	38	15
5	F	49	38	32	18

The enantioselectivity resulting from ylide decomposition is with all ligands higher than that from diazo decomposition. This trend was to be expected on the grounds of the different temperatures of the reactions. In addition, catalyst stability becomes a problem at elevated temperatures, and the low ee's observed in some of the reactions may be due to partial degradation of the catalyst. The intriguing irregularities in the enantioselectivities of Cu-catalyzed cyclopropanations of phenyliodonium ylides and diazo compounds do clearly not occur in the CH insertion reactions. These observations are not only of mechanistic interest; they also extend the synthetic potential of phenyliodonium ylides.

Conclusion

To our knowledge, these are the first enantioselective CH insertions observed upon Cu-catalyzed decompositions of phenyliodonium ylides. The results show clearly that the reactions proceed in the intimate vicinity of the chiral catalyst, and that the mechanism proposed by Moriarty for cyclopropanations cannot apply to the CH insertions. A carbenoid mechanism is generally accepted for CH insertions resulting from transition metal-catalyzed diazo decomposition, and the same mechanism should apply to the reaction of phenyliodonium ylides. This mechanism requires retention of configuration at the center undergoing insertion. Verification of the stereochemistry of the Cu-catalyzed CH insertion of phenyliodonium ylides is currently in progress in this laboratory.

Acknowledgements.

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