Rearrangement

Intramolecular Reactions of Metal Carbenoids with Allylic Ethers: Is a Free Ylide Involved in Every Case?

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Abstract: Rhodium-, copper- and iridium-catalyzed reactions of the ¹³C-labelled diazo carbonyl substrates **18*** and **19*** were performed. Results obtained from copper- and iridium-catalyzed reactions of the ¹³C-labelled α -diazo β -keto ester **19*** indicate that either or both of these reactions do not proceed via a free oxonium ylide but instead follow a competing non-ylide route that delivers apparent [2,3]-sigma-

catalyzed reaction of α -diazo β -keto ester **19***, results obtained from crossover experiments indicate that the initially formed metal-bound ylide dissociates to give an iridium enolate and an allyl cation, which recombine to form the C–C bond.

tropic rearrangement products. In the case of the iridium-

Introduction

The intramolecular reaction of an allylic ether with a metal carbenoid and rearrangement of the resulting free oxonium ylide or metal-bound equivalent offers a potentially powerful catalytic approach to the stereoselective construction of cyclic ethers and carbocycles.^[1,2] Since the publication of seminal work by of Pirrung and Werner^[3a] and Johnson and Roskamp^[3b] in 1986, there have been numerous applications of this reaction to the synthesis of functionalised cyclic ethers and carbocycles.^[4–6] Asymmetric variants of the reaction mediated by chiral catalysts have also been developed, but levels of asymmetric induction are frequently modest.^[7]

In the originally proposed and widely assumed reaction mechanism, an electrophilic metal carbenoid **2**, generated by reaction of a metal complex with the diazo substrate **1**, undergoes nucleophilic attack by one of the ether oxygen lone pairs to give a transient metal-bound intermediate **3** (Scheme 1). Dissociation of the metal complex delivers a highly reactive oxonium ylide **4**, which undergoes a symmetry-allowed [2,3]-sigmatropic rearrangement to deliver the observed cyclic ether product(s) **5**. Although the products obtained from the reactions are generally consistent with the intermediacy of the oxonium ylide **4**, the possibility of direct rearrangement of the metal-bound ylide **3** to produce the cyclic ether product(s) **5** cannot be ruled out. The fact that experimental and theoretical data for analogous intramolecular reactions of carbonyl groups with electrophilic metal carbenoids show that metal-bound

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Scheme 1. Intramolecular reaction of an allylic ether with a metal carbenoid.

carbonyl ylides react directly with dipolarophiles suggests that direct rearrangement of the metal-bound ylide **3** might be feasible.^[8] However, it is extremely difficult to tease apart the precise mechanistic details, because the overall process involves four separate reactions and proceeds via three highly reactive and short-lived intermediates (**2–4**) that are present in very low concentrations, precluding spectroscopic detection.

The task of establishing the precise reaction mechanism is also complicated by the possibility that involvement of a free oxonium ylide is dependent on the presence of stabilizing groups on the diazo carbonyl substrate (e.g., ketone, ester, diketone, or keto ester), the nature of the catalyst used to generate the carbenoid and solvent polarity. Indeed, it is conceivable that the course of the reaction could be highly dependent on all of these factors and that the reaction proceeds via a free oxonium ylide in some cases and via a metal-bound ylide in others. The intermediacy of a free oxonium ylide or a metalbound ylide is more than just a question of semantics. If one is to engage in the rational design of new ligands and catalysts

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to improve ratios of diastereomeric products or to render the reaction highly enantioselective, a full understanding of the role of the metal complex in the rearrangement reaction is essential.

In recent years, the conventional view that the intramolecular reaction of an allylic ether with a metal carbenoid involves a short-lived oxonium ylide has been called into question by observations that are difficult to rationalise mechanistically.^[2h,4,5] In the course of detailed studies on the reaction, we have shown that the nature of the catalyst (both metal and ligand) has a profound influence on the yield and stereochemical outcome of individual reactions.[4-6] For example, we observed that reaction of diazo ketone 6 with rhodium(II) acetate afforded a mixture of cis- and trans-2,5-dialkyldihydro-2Hpyran-3(4H)-ones 7a and 7b in 21:79 ratio [Eq. (1)].^[4f] In contrast, copper-catalyzed reactions produced mixtures of isomers in which the isomer 7a was found to be the major product; the product ratio was also shown to be highly ligand dependent. Intriguingly, the reaction mediated by [Cu(hfacac)₂] (hfacac = hexafluoroacetylacetonate) produced the by-product 8 (13% yield). This observation is significant because the ether 8 cannot have arisen from a free oxonium ylide; otherwise, it would have been isolated from reactions performed with the other catalysts and in the same relative amount. In addition, it is highly unlikely that compound 8 could have been produced by concerted migration of the allyl group in the free oxonium ylide because of geometrical constraints in the requisite cyclic transition state.



Further recent results from our own work also illustrate the highly catalyst dependent nature of the reaction. Treatment of diazo ketone **9** with a suitable catalyst delivers a mixture of the isomeric bridged bicyclic ethers (*Z*)-**10** and (*E*)-**10**, and the stereochemical outcome of reaction can be tuned by catalyst selection [Eq. (2), TBS = *tert*-butyldimethylsilyl].^[4n] When rho-dium(II) triphenylacetate was employed as the catalyst, the less thermodynamically stable isomer (*E*)-**10** was the major product, but when the reaction was performed with [Cu(hfacac)₂] as the catalyst, (*Z*)-**10** was obtained as the major product. Density functional calculations of the energetics of rearrangement of the free oxonium ylide(s) indicated that the reaction should proceed with low *E/Z* selectivity.^[4p] The fact that the rearrangement reaction proceeds diastereoselectively and that the



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isomer ratio can be controlled by choice of the catalyst suggests that a free oxonium ylide is not an intermediate in the reaction.

To account for the catalyst-dependent stereochemical outcome of the above reactions [Eqs. (1) and (2)] while maintaining the intermediacy of a free oxonium ylide, it would be necessary for one of the diastereotopic lone pairs to undergo selective nucleophilic attack on the electrophilic metal carbenoid and for the identity of the metal complex to influence the choice of lone pair directly in each case. Furthermore, the free ylide mechanism would require the stereogenic centre (*) created at the oxonium site to be preserved to a large extent during the lifetimes of intermediates **3** and **4** (Scheme 1).

The catalyst dependence of the product distribution from the intramolecular reaction of an allylic ether with a metal carbenoid has been documented by others. For example, West and co-workers observed that the outcome of the metal-mediated reaction of diazo ketone **11** is highly dependent on the catalyst employed.^[Se] The reaction promoted by rhodium(II) triphenylacetate produced a 1:5 mixture of the diastereomeric bicyclic ethers **12a** and **12b**, whereas the reaction mediated by copper(II) trifluoroacetylacetonate delivered a 30:1 mixture of diastereomers with compound **12a** predominating [Eq. (3)]. West and co-workers have also published several examples of reactions in which an ylide or metal-bound ylide generated from a metal carbenoid undergoes apparent [2,3] or [1,2] rearrangement and the stereochemical outcome is influenced by the structure of the catalyst.^[5]



A similar dependence of diastereoselectivity on catalyst structure has been observed in reactions involving carbenoids generated from α -diazo β -keto esters. For example, Yakura and co-workers reported that the reaction of the substrate **13** with rhodium(II) triphenylacetate produces a mixture of the diastereomeric cyclic ethers **14a** and **14b** in 91:9 ratio [Eq. (4)].^[9] When the catalyst ligands were changed from triphenylacetate to acetate, the diastereoselectivity of the reaction was reduced substantially.



Hashimoto and co-workers have demonstrated that asymmetric reactions of the α -diazo β -keto esters **15***a*–*c* mediated by the chiral rhodium complex [Rh₂(*S*-PTTL)₄] deliver significant amounts of apparent [1,2]-rearrangement products **17***a*–*c* in addition to the expected apparent [2,3]-rearrangement prod-

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ucts 16a-c [Eq. (5)].^[7] The formation of apparent [1,2]-shift products in competition with those arising from a lowerenergy symmetry-allowed [2,3]-rearrangement reaction and the dependence of product distribution on the substituents adorning the allylic ether is intriguing. Hashimoto and co-workers did not investigate whether the ratio of the products 16 and 17 is dependent on the catalyst used for carbenoid generation, the solvent or the conditions under which the reaction is performed.



Important data regarding the reaction mechanism have also been disclosed by Doyle and co-workers.^[6f,7f,10] In early studies, they reported highly enantioselective intermolecular reactions of simple allyl methyl ethers with carbenoids generated by the reaction of ethyl diazoacetate and chiral rhodium complexes.^[7f] Direct rearrangement from a metal-bound ylide was proposed to explain the very high levels of asymmetric induction (≈98% ee) obtained from these reactions, and this mechanism was supported by the finding that allylic iodides underwent analogous asymmetric reactions, albeit with lower ee values. More recently, Doyle and co-workers have studied the intramolecular reactions of cyclic ethers with rhodium carbenoids derived from $\alpha\text{-diazo}\ \beta\text{-keto}$ esters to give conformationally restricted bicyclic reactive intermediates that undergo apparent [1,2] or [2,3] rearrangement.^[6f,10] On the basis of the invariance of both the isomer ratios and the ratios of the apparent [1,2]and [2,3]-rearrangement products with catalyst, Doyle and coworkers concluded that these reactions occur through a free oxonium ylide, a finding that contradicts conclusions based on their earlier work.

Finally, evidence for the potential involvement of a metal-associated intermediate in related carbenoid reactions comes from recently published work of Davies and co-workers.[11] They have demonstrated that it is possible to perform analogous enantioselective rearrangement reactions by using chiral rhodium donor/acceptor carbenoids on allylic and propargylic alcohols rather than allylic ethers. In these cases, it is difficult to account for the very high levels of asymmetric induction that are obtained without the involvement of the chiral metal complex in the C-C bond-forming step.

Results and Discussion

We attempted to establish the intermediacy of a free oxonium ylide or a metal-bound ylide (analogous to 3 in Scheme 1) in the key rearrangement reaction by investigating the metalmediated reactions of simple substrates 18 and 19 to give benzofuranones 20 and 21 [Eq. (6)]. Substrates 18 and 19

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were selected because their rhodium-catalyzed reactions are well documented and the products only contain aliphatic hydrogen atoms in the migrated group, making NMR analysis easier. In their seminal publication, Pirrung and Werner reported that diazo substrates 18 and 19 underwent rhodium(II) acetate catalyzed cyclization in dichloromethane at room temperature to afford benzofuranones 20 and 21 in good yield.[3a]



We first conducted a brief survey of copper complexes as catalysts for the cyclization of substrates 18 and 19; we also explored the use of $[{\rm Ir(cod)Cl}_2]$ (cod = 1,5-cyclooctadiene) as a potential catalyst for carbenoid generation [Eq. (6), Table 1]. Although it is known that diazo carbonyl compounds react with iridium complexes and that iridium carbenoids can be generated from sulfur ylides,^[12] we are not aware of any examples of direct generation of an iridium carbenoid from a diazo carbonyl compound followed by reaction of the presumed iridium carbenoid with an allylic ether.

Table 1. Copper- and iridium-catalyzed reactions of the diazo ketone 18and α -diazo β -keto ester 19 to give benzofuranones 20 and 21.							
Entry	Substrate	Catalyst ([mol %])	Solvent	Т	Yield ^[a] [%]		
1	18	[Cu(acac) ₂] (5)	CH ₂ Cl ₂	reflux	57		
2	18	[{Ir(cod)Cl} ₂] (1)	CH_2CI_2	reflux	9		
3	19	[Cu(acac) ₂] (10)	DCE ^[b]	reflux	61		
4	19	$[{Ir(cod)Cl}_2]$ (1)	DCE ^[b]	reflux	39		
[a] Yield after purification by chromatography. [b] 1,2-Dichloroethane.							

The results of preliminary studies showed that the α -diazo carbonyl substrates 18 and 19 react with [Cu(acac)₂] (acac = acetylacetonate) to deliver the expected benzofuranone products 20 and 21 in reasonable yield (Table 1, entries 1 and 3). The iridium-catalyzed reactions (Table 1, entries 2 and 4) were much lower yielding than the copper-catalyzed reactions or the previously reported rhodium-catalyzed reactions, but in the case of substrate 19 a reasonable yield of the expected rearrangement product 21 was obtained.

To probe the reaction mechanism, we employed substrates 18* and 19*, which were ¹³C-labelled at the terminal position of the allylic ether. The use of these ¹³C-labelled substrates was expected to allow us to detect the formation of apparent [1,2]shift products analogous to those (17 a-c) obtained by Hashimoto and co-workers during the rearrangement of α -diazo β -keto esters **15a-c**,^[7h] but without the presence of substituents that might bias the reaction as a consequence of electronic or steric factors. In conducting these experiments, we wished to determine whether the relative amounts of the apparent [2,3]- and [1,2]-rearrangement products were dependent on the catalyst used for carbenoid generation. If all reac-

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tions proceed exclusively through the same metal-free oxonium ylide, the ratio of apparent [2,3]- and [1,2]-rearrangement products should be fixed and independent of the catalyst used to generate the oxonium ylide. Thus, any variations in product distribution with catalyst would indicate that some or all of these reactions proceed through a sequence in which rearrangement with concomitant C–C bond formation takes place directly from a metal-associated ylide rather than a free oxonium ylide [Eq. (7)].



Reactions of substrate **18***, which has a ¹³C label at the terminus of the allyl group, to give products with the label at either the internal position (**20*i**) or the terminal position (**20*t**) were explored [Eq. (7)]. The relative amounts of **20*i** and **20*t** were determined by ¹H and ¹³C NMR spectroscopy, and there was very close agreement between the ratios measured with each technique. Analysis of the product distribution in each case showed that a small but discernible amount of ketone **20*t** containing the ¹³C label at the terminal position of the alkene was generated alongside the expected formal [2,3]rearrangement product **20*i**, in which the label is positioned at the internal (allylic) position. There were small variations in product distribution in the case of rhodium- or copper-catalyzed reactions (Table 2, entries 1–4), but these variations are

Table 2. Metal-catalyzed reactions of labelled α -diazo ketone 18 *.							
Entry	Catalyst	Yield [%]	Ratio 20*i:20*t ¹ H NMR	Ratio 2 0*i:20*t ¹³ C NMR			
1 2 3	$Rh_2(OAc)_4$ $Rh_2(O_2CCF_3)_4$ $Rh_2(O_2CCPh_3)_4$	26 62 25	>99:1 98:2 95:5	98:2 98:2 97:3			
4 5	[Cu(hfacac) ₂] [{lr(cod)Cl} ₂]	46 _ ^[a]	98:2 52:48	99:1 53:47 ^[b]			
[a] Very small amounts of the product were obtained. [b] ¹³ C NMR analysis was performed on unpurified product.							

within experimental error, and so the results were inconclusive. However, in the case of the iridium-catalysed reaction (Table 2, entry 5), almost complete scrambling of the label occurred during the reaction leading to equal amounts of products **20*i** and **20*t**. This result shows that when the iridium catalyst is used to generate the carbenoid, the reaction does not proceed by a pathway involving concerted [2,3]-sigmatropic rearrangement of a free oxonium ylide, even though unlabelled **20** is the product expected from rearrangement of a free oxonium ylide. At this stage there seemed to be two possible explanations for the result of the iridium-catalyzed reaction: the metalbound ylide undergoes dissociation to produce an iridium enolate and allylic cation, which recombine by C–C bond formation, or metal-assisted allyl transfer from O to C occurs with scrambling of the label as a consequence of formation of a symmetrical π -allyl iridium complex.

Attention was then focussed on reactions of the labelled $\alpha\text{-diazo}\ \beta\text{-keto}$ ester 19* [Eq. (8), Table 3]. The results obtained

Table 3. Metal-catalyzed reactions of labelled α -diazo ketone 19 *.							
Entry	Catalyst	Yield [%]	Ratio 21*i:21*t ¹ H NMR	Ratio 21*i:21*t ¹³ C NMR			
1	Rh ₂ (OAc) ₄	76	> 99:1	98:2			
2	$Rh_2(O_2CCF_3)_4$	20	96:4	97:3			
3	Rh ₂ (O ₂ CCPh ₃) ₄	34	95:5	96:4			
4	[Cu(acac) ₂]	43	84:16	85:15			
5	[Cu(hfacac)₂]	75	86:14	87:13			
6	Cu[(MeCN) ₄]PF ₆	63	88:12	90:10			
7	$[{lr(cod)Cl}_2]$	37	44:56	47:53			

with this substrate were more conclusive than those obtained from the reactions of the α -diazo ketone **18***. When a rhodium complex was employed as the catalyst, a very small but detectable quantity of the compound 21*t containing the label at the terminal position was obtained in addition to the expected product 21*i, in which the label is located at the internal position of the allyl chain (Table 3, entries 1-3). The ratio of labelled compounds 21*i:21*t was found to be dependent on the nature of the rhodium complex employed as catalyst; of the three catalysts studied, rhodium(II) triphenylacetate gave the highest proportion of compound 21*t. A much higher proportion of 21*t was obtained from the copper-catalyzed reactions than from the rhodium-catalyzed reactions, and again the 21*i:21*t ratio was found to be dependent on the specific copper complex used (Table 3, entries 4-6). Finally, the use of [{Ir(cod)Cl}2] as catalyst produced almost equal amounts of the labelled products 21*i and 21*t, indicating that complete scrambling had occurred (Table 3, entry 7).



The dependence of the **21*i:21*t** ratio on the catalyst used to generate the carbenoid is inconsistent with the reaction proceeding exclusively through a free ylide. If **21*t** had been formed by [1,2]-rearrangement of a common free oxonium ylide, the proportion of **21*t** would be completely independent of the catalyst used to generate the oxonium ylide; the results presented in Table 3 show that this is not the case.

The **21*i:21*t** ratios could be calculated accurately by integration of appropriate signals in the ¹³C and ¹H NMR spectra. As shown in Figure 1, it was easy to determine the product ratio by integration of peaks in the region of the ¹H NMR spectrum where signals for the allylic methylene group appear. In the case of unlabelled benzofuranone **21** (Figure 1a), the protons appear as two apparent ddt centred at δ =3.07 and 2.83 ppm in the ¹H NMR spectrum. In the case of the fully la-

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Figure 1. ¹H NMR spectra (δ = 2.6–3.3 ppm) for a) unlabelled 21, b) fully labelled 21*i and c) a mixture (47:53) of 21*i and 21*t.

belled compound 21*i (Figure 1b), ¹H-¹³C coupling splits the original signals to give four sets of apparent ddt centred at δ = 3.20, 2.96, 2.93 and 2.69 ppm. This means that if mixtures of 21*i and 21*t are obtained (Figure 1a) there is clear baseline separation for the signals corresponding to products 21*i and 21*t. Integration of these signals gives ratios that can then be correlated with product ratios obtained from the ¹³C NMR spectra.

Having established that there was significant label scrambling during the reaction of 19* when both copper and iridium catalysts were used, we sought to establish whether this resulted from internal transfer or complete dissociation of the allyl group. To do this we designed a crossover experiment in which equal quantities of 19*, having a ¹³C label at the termi-

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nal position of the allyl group, and **19*d**, having a ¹³C label on the carbon atom bearing the diazo group, were treated with a suitable copper or iridium catalyst. In the event that the allyl group is transferred intramolecularly, only products 21*i, 21*t and 21*d should be observed. However, if dissociation of the allyl group occurs prior to C-C bond formation, one would expect to observe formation of the unlabelled crossover product 21 along with the doubly labelled crossover products 21**t and 21**i. Compound 21**i would be easy to identify in the ¹³C NMR spectrum, because ¹³C-¹³C coupling would be evident. In addition, the ratio of crossover to non-crossover products could be determined from the relative amounts of 21**i and 21*i.

When a mixture of 19* and 19*d was treated with [{Ir-(cod)Cl₂] in 1,2-dichloroethane (0.31 M) at reflux, a significant amount of crossover product 21**i was observed. The compound exhibited a ¹³C-¹³C J value of 38 Hz, which is typical of coupling between adjacent sp³-hybridized ¹³C centres.^[13] The ¹³C NMR data indicated a **21*i:21**i** ratio of approximately 2:1. The amount of doubly labelled product 21**i obtained was also found to be concentration-dependent, and significantly less of this compound was formed when the reaction was performed at lower concentration (0.041 M). When the same crossover experiment was repeated with [Cu(hfacac)₂] in 1,2-dichloroethane (DCE, 0.31 M), only traces of crossover product **21**i** (<4%) were obtained.

Conclusion

We have provided important mechanistic insights into the course of the intramolecular reaction of carbenoids with allylic ethers. The results obtained from the copper- and rhodiumcatalyzed reactions of the ¹³C labelled diazo ketone 18* [Eq. (7)] are consistent with a mechanism involving a free oxonium ylide, but do not rule out involvement of the metal centre in the rearrangement reaction. In contrast, results of the copper- and iridium-catalyzed reactions of ¹³C labelled α -diazo β -keto ester 19* [Eq. (8)] indicate that these reactions do not proceed via a free oxonium ylide but instead follow major competing non-ylide routes that deliver apparent [2,3]-sigmatropic rearrangement products. Furthermore, crossover experiments with substrates 19* and 19*d (Scheme 2) suggest that,

Scheme 2. Crossover experiment with labelled substrates 19* and 19* d.

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in the case of the iridium-catalyzed reaction, the initial metalbound ylide dissociates to give an iridium enolate and allylic cation, and these recombine by C–C bond formation. In the case of the copper-catalyzed reaction, intramolecular transfer of the allyl group occurs with little dissociation of the intermediate metal-bound ylide.

Experimental Section

Standard procedure for cyclization reactions of substrates 18 and 19

A solution of diazo ketone in appropriate solvent (1 mL per 0.1 mmol of diazo ketone) was added dropwise to a solution of catalyst (1–10 mol%) in an equivalent volume of the same solvent at reflux, and the reaction was monitored by TLC until completion. The mixture was then cooled to room temperature and the reaction was quenched by the addition of aqueous K_2CO_3 solution. The phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were washed with water followed by brine, dried (MgSO₄) and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel to give the product(s).

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Keywords: carbenoids • cyclization • isotopic labeling • rearrangement • ylides

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FULL PAPER

Differing distributions of ¹³C-labelled rearrangement products in the rhodium-, copper- and iridium-catalyzed reactions of a ¹³C-labelled α -diazo β -keto ester (see scheme) revealed that the copper- and iridium-mediated reactions do not proceed via a common free oxonium ylide intermediate.

Rearrangement

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Intramolecular Reactions of Metal Carbenoids with Allylic Ethers: Is a Free Ylide Involved in Every Case?