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

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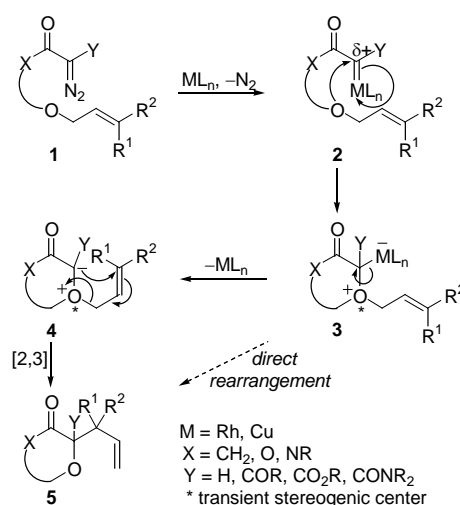
Abstract: Rhodium-, copper- and iridium-catalyzed reactions of the ^{13}C-labelled diazocarbonyl substrates **18*** and **19*** have been performed. Results obtained from copper- and iridium-catalyzed reactions of the ^{13}C labelled α-diazo β-keto ester **19*** indicate that either or both of these reactions do not proceed *via* a free oxonium ylide but instead follow a competing non-ylide route that delivers apparent [2,3]-sigmatropic rearrangement products. In the case of the iridium-catalyzed reaction of α-diazo β-keto ester **19***, results obtained from crossover experiments indicate that the metal-bound ylide formed initially, dissociates to give an iridium enolate and an allyl cation which recombine to form the C–C bond.

Keywords: carbenoid • oxonium ylide • rearrangement • isotopic labelling

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 the groups of Pirrung and Johnson in 1986,[3] 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** that 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 computational data for analogous intramolecular reactions of carbonyl groups with electrophilic metal carbenoids show that metal-bound 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.
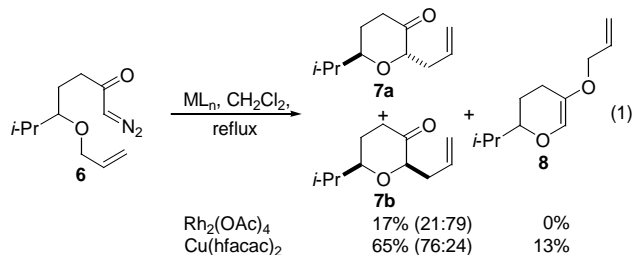
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Scheme 1. Intramolecular reaction of an allylic ether with a metal carbenoid.

M = Rh, Cu
X = CH₂, O, NR
Y = H, COR, CO₂R, CONR₂
* transient stereogenic center

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. It should be appreciated that the intermediacy of a free oxonium ylide or a metal-bound ylide is more than just a question of semantics. If one is to engage in the rational design of new ligands and catalysts to improve diastereomeric product ratios or to render the reaction highly enantioselective, a full understanding of the role of the metal complex in the rearrangement reaction is essential.
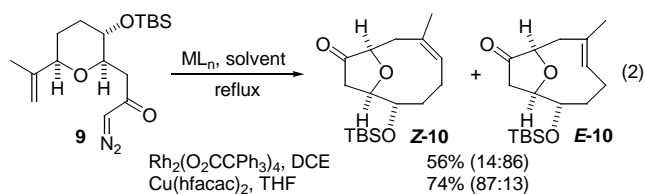
In recent years, the conventional view that the intramolecular reaction of an allylic ether with a metal carbenoid involves a short-lived oxonium ylide has been called in question by observations that are difficult to rationalise mechanistically.[2h,4,5] In the course of detailed studies of the reaction, 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 the diazo ketone **6** with rhodium(II) acetate afforded a mixture of the *cis* and *trans* 2,5-

dialkyldihydro-2*H*-pyran-3(4*H*)-ones **7a** and **7b** with a 21:79 ratio (Eqn. 1).[4f] In contrast, copper-catalyzed reactions produced mixtures of isomers in which the isomer **7a** is the major product; the product ratio was also shown to be highly ligand-dependent. Intriguingly, the reaction mediated by copper(II) 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 using 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.

$$\text{(Eqn. 1)}$$

Reagents/products (Eqn. 1):
6 → **7a** + **7b** + **8**
Rh$_2$(OAc)$_4$ — 17% (21:79), 0%
Cu(hfacac)$_2$ — 65% (76:24), 13%
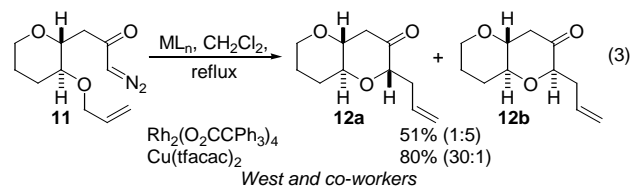ML$_n$, CH$_2$Cl$_2$, reflux

Further recent results from our own work also illustrate the highly catalyst-dependent nature of the reaction. Treatment of the 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 (Eqn. 2).[4n] When rhodium(II) triphenylacetate was employed as the catalyst, the less thermodynamically stable isomer **E-10** was the major product, but when the reaction was performed using Cu(hfacac)$_2$ as the catalyst, the compound **Z-10** was obtained as the major product. Calculations of the energetics of rearrangement of the free oxonium ylide(s) using DFT indicated that the reaction should proceed with low *E*/*Z* selectivity.[4p] The fact that the rearrangement reaction proceeds diastereoselectively and that the isomer ratio can be controlled by choice of the catalyst suggests that a free oxonium ylide is not an intermediate in the reaction.

$$\text{(Eqn. 2)}$$

Reagents/products (Eqn. 2):
9 → **Z-10** + **E-10**
Rh$_2$(O$_2$CCPh$_3$)$_4$, DCE — 56% (14:86)
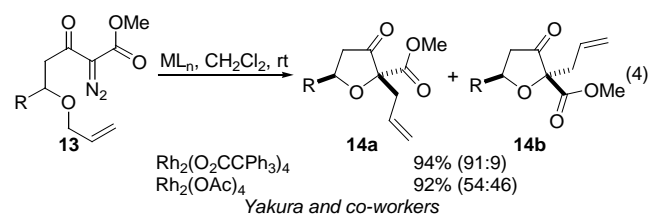Cu(hfacac)$_2$, THF — 74% (87:13)
ML$_n$, solvent, reflux

To account for the catalyst-dependent stereochemical outcome of the reactions above (Eqn. 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 other researchers. 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.[5e] The reaction promoted by rhodiu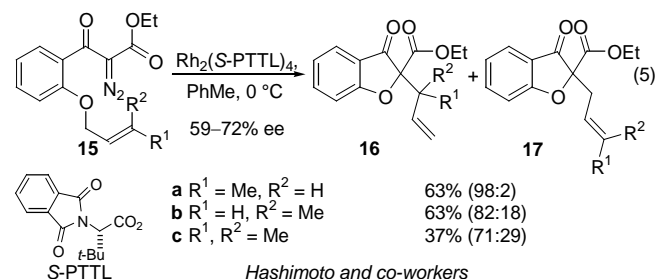m(II) triphenylacetate produced a 1:5 mixture of the diastereomeric bicyclic ethers **12a** and **12b**, whereas the reaction mediated by copper(II) trifluoroacetylacetonate delivered a 30:1 mixture of diastereomers with compound **12a** predominating (Eqn. 3). West and co-workers have also published 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]

$$\text{(3)}$$

Reagents/products (Eqn. 3):
11 → **12a** + **12b**
Rh$_2$(O$_2$CCPh$_3$)$_4$ — 51% (1:5)
Cu(tfacac)$_2$ — 80% (30:1)
ML$_n$, CH$_2$Cl$_2$, reflux
West and co-workers

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** with a 91:9 ratio (Eqn. 4).[9] When the catalyst ligands were changed from triphenylacetate to acetate, the reaction diastereoselectivity was reduced substantially.

$$\text{(4)}$$

Reagents/products (Eqn. 4):
13 → **14a** + **14b**
Rh$_2$(O$_2$CCPh$_3$)$_4$ — 94% (91:9)
Rh$_2$(OAc)$_4$ — 92% (54:46)
ML$_n$, CH$_2$Cl$_2$, rt
Yakura and co-workers

Hashimoto and co-workers have demonstrated that asymmetric reactions of the α-diazo β-keto esters **15a–c** mediated by the chiral rhodium complex Rh$_2$(*S*-PTTL)$_4$ deliver significant amounts of apparent [1,2]-rearrangement products **17a–c** in addition to the expected apparent [2,3]-rearrangement products **16a–c** (Eqn. 5).[7i] The formation of apparent [1,2]-shift products in competition with those arising from a lower energy symmetry-allowed [2,3]-rearrangement reaction and the dependence of product distribution on the substituents adorning the allylic ether is intriguing. It should be noted 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.

$$\text{(5)}$$

Reagents/products (Eqn. 5):
15 → **16** + **17**
Rh$_2$(*S*-PTTL)$_4$, PhMe, 0 °C, 59–72% ee
a R^1 = Me, R^2 = H — 63% (98:2)
b R^1 = H, R^2 = Me — 63% (82:18)
c R^1, R^2 = Me — 37% (71:29)
S-PTTL
Hashimoto and co-workers

Important data regarding the reaction mechanism have also been disclosed by Doyle and co-workers.[10] In early studies, these workers reported highly enantioselective *intermolecular* reactions of simple allyl methyl ethers with carbenoids generated by the reaction of ethyl diazoacetate and chiral rhodium complexes.[10a] 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. More recently, Doyle and co-workers have studied the intramolecular reactions of cyclic ethers with rhodium carbenoids derived from α-diazo β-keto esters to give conformationally restricted bicyclic reactive intermediates that undergo apparent [1,2]- or [2,3]-rearrangement.[10b,c] Based on the invariance of both the isomer ratios and the ratios of the apparent [1,2]- and [2,3]-rearrangement products with catalyst, Doyle and co-workers concluded that these reactions occur through a free oxonium ylide, a finding that contradicts conclusions based on their earlier asymmetric 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] These workers have demonstrated that it is possible to perform analogous enantioselective rearrangement reactions 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 metal-mediated reactions of the simple substrates **18** and **19** to give the benzofuranones **20** and **21** (Eqn 6). The substrates **18** and **19** were selected because the rhodium-catalyzed reactions of these compounds are well documented and the products only contain aliphatic hydrogens in the migrated group, making NMR analysis easier. In their seminal publication, Pirrung and Werner reported that the diazo substrates **18** and **19** underwent rhodium(II) acetate catalyzed cyclization in dichloromethane at room temperature to afford the 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 [Ir(COD)Cl]$_2$ as a potential catalyst for carbenoid generation (Eqn. 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 the direct generation of an iridium carbenoid from diazo carbonyl compound followed by reaction of the presumed iridium carbenoid with an allylic ether.
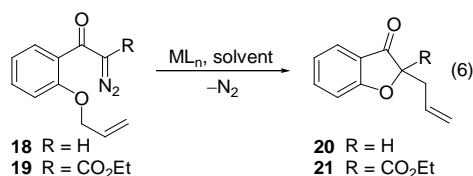

18 R = H
19 R = CO$_2$Et

20 R = H
21 R = CO$_2$Et

Table 1. Copper- and iridium-catalyzed reactions of the diazo ketone **18** and α-diazo β-keto ester **19** to give the benzofuranones **20** and **21**.

Entry	Substrate	Catalyst (mol%)	Solvent	Temp.	Yield[a]
1	**18**	Cu(acac)$_2$ (5)	CH$_2$Cl$_2$	reflux	57%
2	**18**	[Ir(COD)Cl]$_2$ (1)	CH$_2$Cl$_2$	reflux	9%
3	**19**	Cu(acac)$_2$ (10)	DCE	reflux	61%
4	**19**	[Ir(COD)Cl]$_2$ (1)	DCE	reflux	39%

[a] Yield after purification my chromatography.

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

To probe the reaction mechanism we employed substrates **18*** and **19*** that were ^{13}C-labelled at the terminal position of the allylic ether. The use of these ^{13}C-labelled substrates was expected to allow us to detect the formation of apparent [1,2]-shift products analogous to those (**17a–c**) obtained by Hashimoto and co-workers during the rearrangement of from α-diazo β-keto esters **15a–c**,[7i] but without the presence of substituents that might bias the reaction as 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 reactions 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 and concomitant C–C bond formation takes place directly from a metal-associated ylide rather than a free oxonium ylide.
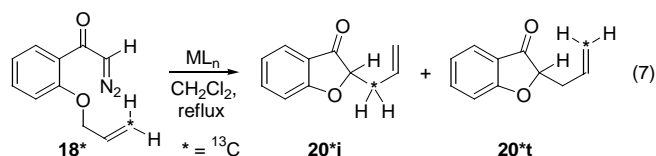
(7)

18*   * = ^{13}C   **20*i**   **20*t**

Table 2. Metal-catalyzed reactions of labelled α-diazo ketone **18***.

Entry	Catalyst	Yield	Ratio **20*i:20*t** ^{1}H NMR	Ratio **20*i:20*t** ^{13}C NMR
1	Rh$_2$(OAc)$_4$	26%	> 99:1	98:2
2	Rh$_2$(O$_2$CCF$_3$)$_4$	62%	99:1	98:2
3	Rh$_2$(O$_2$CCPh$_3$)$_4$	25%	95:5	97:3
4	Cu(hfacac)$_2$	46%	98:2	99:1
5	[Ir(COD)Cl]$_2$	—[a]	52:48	53:47[b]

[a] Trace amounts of the product were obtained. [b] ^{13}C NMR analysis was performed using unpurified product.

Reactions of the substrate **18***, possessing a ^{13}C label at the terminus of the allyl group, to give the products with the label at either the **i**nternal position (**20*i**) or the **t**erminal position (**20*t**) were explored (Eqn. 7). The relative amounts of **20*i** and **20*t** were determined using both ^{1}H and ^{13}C NMR spectroscopy and there was very close agreement between the ratios measured using each technique. Analysis of the product distribution in each case showed that a small but discernible amount of the ketone **20*t**, containing the ^{13}C 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 (entries 1–4, Table 2), but these variations are within experimental error and so the results were inconclusive. However, in the case of the iridium-catalysed reaction (entry 5, Table 2), it was clear that there was almost complete scrambling of the label during the reaction, leading to equal amounts of the 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 the 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 metal-bound ylide is undergoing dissociation to produce an iridium enolate and allylic cation, which recombine to give C–C bond formation, or metal-assisted allyl transfer from *O* to *C* is occurring 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 α-diazo β-keto ester **19*** (Eqn. 8, Table 3). The results obtained using 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 **t**erminal position, was obtained in addition to the expected product **21*i** in which the label

is located at the **i**nternal position of the allyl chain (entries 1–3, Table 3). The ratio of labelled compounds **21*i** to **21*t** was found to be dependent on the nature of the rhodium complex employed as the catalyst; of the three catalysts studied, rhodium(II) triphenylacetate gave the highest proportion of compound **21*t**. A much higher proportion of compound **21*t** was obtained from the copper-catalyzed reactions than from the rhodium-catalyzed reactions and again the ratio of labelled compounds **21*i** to **21*t** was found to be dependent on the specific copper complex used (entries 4–6, Table 3). Finally, the use of [Ir(COD)Cl]$_2$ as the catalyst produced almost equivalent amounts of the labelled products **21*i** and **21*t**, indicating that complete scrambling had occurred (entry 7, Table 3).
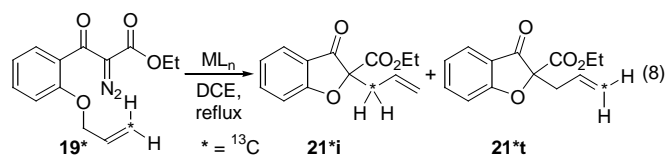

(8)

19*   * = ^{13}C   **21*i**   **21*t**

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$_2$CCF$_3$)$_4$	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	[Ir(COD)Cl]$_2$	37%	45:55	46:54

The dependence of the **21*i** to **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 ratios of **21*i** to **21*t** could be calculated accurately by integration of appropriate signals in the ^{13}C and ^{1}H NMR spectra. As shown in Figure 1, it was easy to determine the product ratio by integration of peaks in the region of the ^{1}H NMR spectrum where signals for the allylic methylene group appear. In the case of unlabelled benzofuranone **21** [spectrum (a)], the protons appear as two apparent ddt centred at δ 3.07 and 2.83 ppm in the ^{1}H NMR spectrum. In the case of the fully labelled compound **21*i** [spectrum (b)], ^{1}H–^{13}C coupling splits the original signals to give four sets of apparent ddt centered at δ 3.20, 2.96, 2.93 and 2.69 ppm. This means that in cases where mixtures of **21*i** and **21*t** are obtained [spectrum (c)] there is clear baseline separation for the signals corresponding to the products **21*i** and **21*t**. Integration of these signals gives ratios that can then be correlated with product ratios obtained from the ^{13}C NMR spectra.
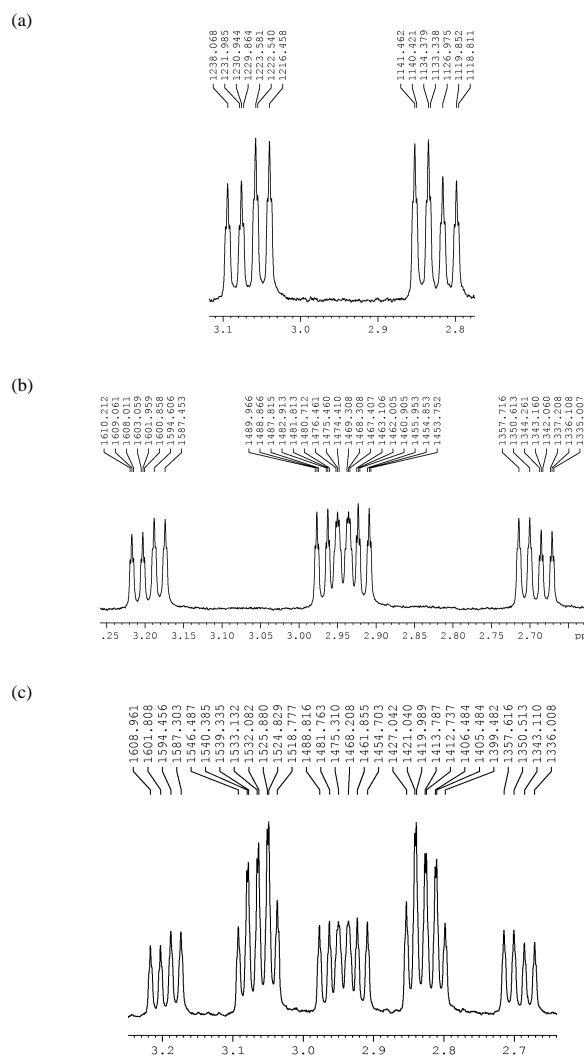
Figure 1. ^{1}H NMR data (δ 2.6–3.3 ppm) for (a) unlabeled **21**, (b) fully labelled **21*i** and (c) a mixture (47:53) of **21*i** and **21*t**.

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***, possessing a ^{13}C label at the terminal position of the allyl group, and **19*d**, possessing on the carbon bearing the **d**iazo group, were treated with a suitable copper or iridium catalyst. In the event that the allyl group is transferred intramolcularly, only the products **21*i**, **21*t** and **21*d** should be observed. However, if there is dissociation of the allyl group prior to C–C bond formation, one would expect to observe formation of the unlabeled crossover product **21** along with the doubly labelled crossover products **21**t** and **21**i**. The compound **21**i** would be easy to identify in the ^{13}C NMR spectrum because ^{13}C–^{13}C 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**.
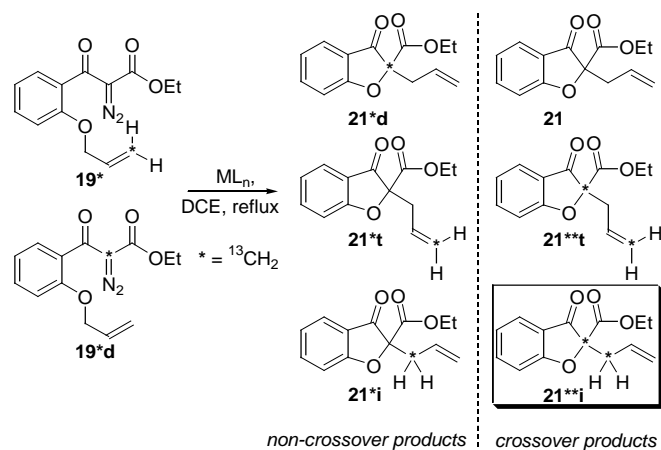
Scheme 2. Cross-over experiment using the labelled substrates **19*** and **19*d**.

When a mixture of **19*** and **19*d** was treated with [Ir(COD)Cl]$_2$ in 1,2-dichloroethane (0.31 M) at reflux a significant amount of the crossover product **21**i** was observed. The compound exhibited a ^{13}C–^{13}C J value of 38 Hz, which is typical of coupling between adjacent sp^3 hybridized ^{13}C centres.[13] The ^{13}C NMR data indicated a **21*i** to **21**i** ratio of approximately 2:1. The amount of doubly-labelled product **21**i** obtained was also found to be concentration-dependent with significantly less of this compound being formed when the reaction was performed at lower concentration (0.041 M). When the same cross-over experiment was repeated using Cu(hfacac)$_2$ in DCE (0.31 M) only traces of the crossover product **21**i** (< 4%) were obtained.

Conclusions

The results of our studies provide important mechanistic insights concerning the course of the intramolecular reaction of carbenoids with allylic ethers. The results obtained from the copper- and rhodium-catalyzed reactions of the ^{13}C labelled diazo ketone **18*** (Eqn. 7) are consistent with a mechanism involving a free oxonium ylide, but do not rule out metal involvement in the rearrangement reaction. In contrast, results of the copper- and iridium-catalyzed reactions of the ^{13}C labelled α-diazo β-keto ester **19*** (Eqn. 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 the substrates **19*** and **19*d** (Scheme 2) suggest that in the case of the iridium-catalyzed reaction, the initial metal-bound ylide dissociates to give an iridium enolate and allylic cation and these recombine to give 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 diazoketone 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, then dried (MgSO$_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel to give the product(s).

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