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Communication

# Generating Fischer-Type Rh-Carbenes with Rh-Carbynoids

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**ABSTRACT:** We describe the first catalytic generation of Fischer-type acyloxy Rh(II)-carbenes from carboxylic acids and Rh(II)-carbynoids. This novel class of transient donor/acceptor Rh(II)-carbenes evolved through a cyclopropanation process providing access to densely functionalized cyclopropyl-fused lactones with excellent diastereoselectivity. DFT calculations allowed the analysis of the properties of Rh(II)-carbynoids and acyloxy Rh(II)-carbenes as well as the characterization of the mechanism.

The discovery and development of transient donor/acceptor Rh(II)-carbenes generated from dirhodium paddlewheel catalysts and diazo compounds has represented a breakthrough in the field of carbene transfer catalysis (Figure 1A).[1−3] Aryl, heteroaryl, alkenyl, or alkynyl substituents used as donor groups modulate the reactivity by decreasing the electrophilicity of the Rh(II)-carbene, which often offers exceptional levels of site- and stereoselectivity in intermolecular alkene cyclopropanations and C−H bond insertions (Figure 1A). However, the introduction of heteroatomic functionalities such as acyloxy, hydroxy, alkoxy, or amino as donor groups remains a long-standing problem, due to the lack of appropriate diazo compounds or carbene precursors.[4]

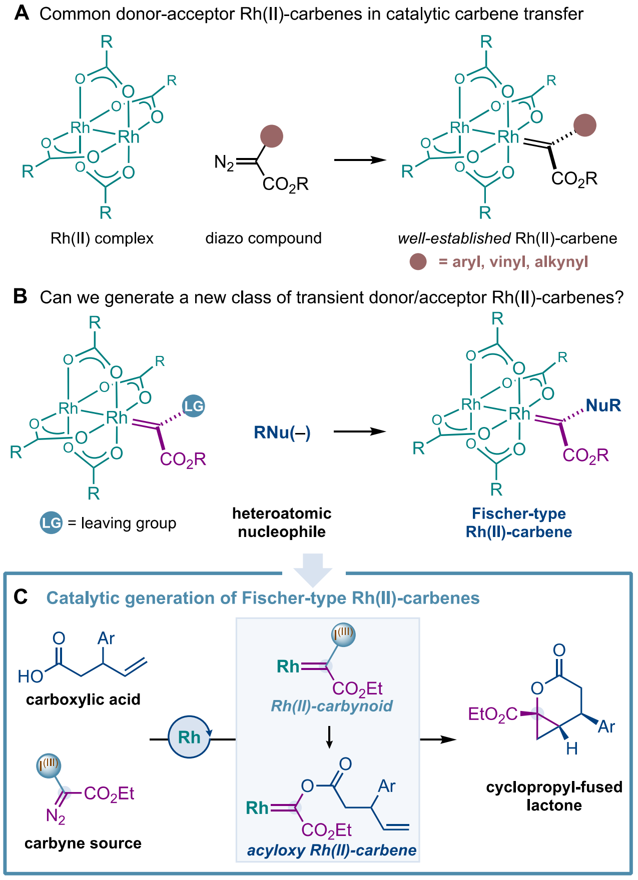

**Figure 1.** Generation of novel donor/acceptor Rh(II)-carbenes.

Novel strategies to generate Rh(II)-carbenes catalytically with such heteroatomic functionalities promise to offer new synthetic applications and advance the field of carbene chemistry. An unexplored strategy to circumvent this problem could involve the attack of heteroatomic nucleophiles to the carbene carbon atom of Rh(II)-carbenes substituted with a leaving group (Figure 1B). If successful, this strategy would also provide a novel approach for the generation of Fischer metal-carbenes,[5] a class of organometallic species that have been rather challenging to generate in a catalytic fashion.[6] There is a small number of catalytic reactions where Fischer carbenes were proposed, and these include the seminal reports by McDonald,[7] Wipf,[8] and Barluenga[9] with W(0) catalysts and recent examples by Kakiuchi,[10] Kusama,[11] Wang,[12] and Tobisu[13] with Rh(I), Cu(I), and Pd(0) catalysts, respectively.[14]

Herein, we present the discovery and development on the use of alkenyl carboxylic acids as nucleophiles for the first catalytic generation of transient acyloxy Rh(II)-carbenes (Figure 1C). The latter species evolved through intramolecular diastereoselective cyclopropanations, leading to complex cyclopropyl-fused lactones. Key to this work was the generation of Rh(II)-carbynoids, a class of Rh(II)-carbenes substituted with a hypervalent iodine(III) as a leaving group.

Our group has pioneered the generation of Rh(II)-carbynoids as carbyne transfer species by selective diazo activation of hypervalent iodine reagents[15] with Rh(II) carboxylate catalysts (Figure 2, ***int-I***).[16] We have demonstrated that Rh(II)-carbynoids were able to transfer the carbynoid

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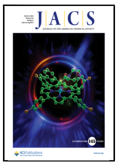

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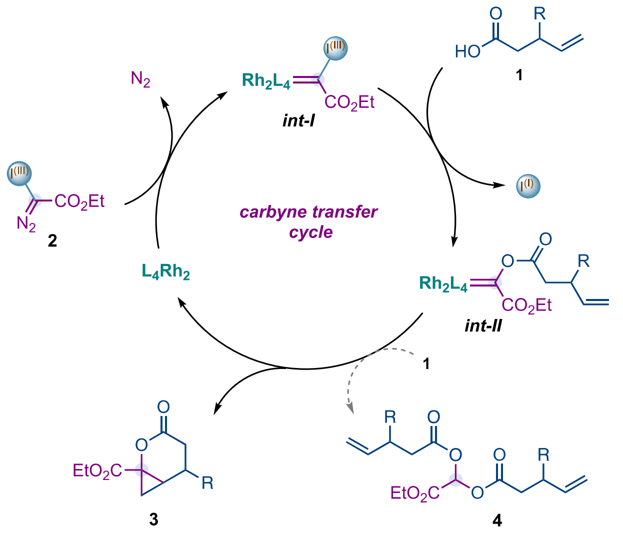
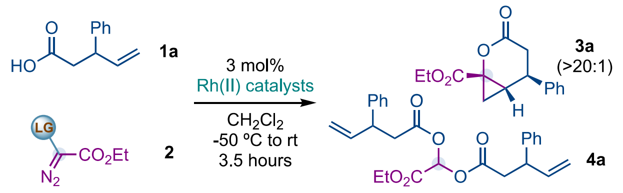


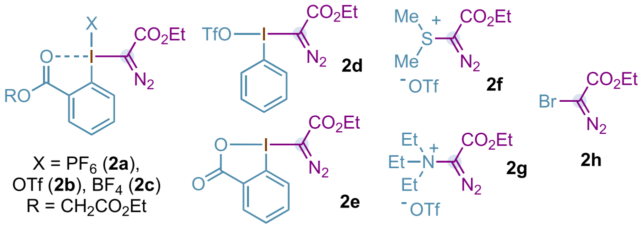
**Figure 2.** Mechanistic hypothesis.

**Table 1. Optimization Studies**[a]



| entry | reagent 2 | ratio 1a:2 | Rh catalyst | yield 3a (4a) [%][b] |
|---|---|---|---|---|
| 1 | **2a** | 2:1 | $Rh_2(OAc)_4$ | 0 (65)[c] |
| 2 | **2a** | 1:1.3 | $Rh_2(OAc)_4$ | 30 (21) |
| 3 | **2a** | 1:1.3 | $Rh_2(Oct)_4$ | 31 (20) |
| 4 | **2a** | 1:1.3 | $Rh_2(Adc)_4$ | 40 (10) |
| 5 | **2a** | 1:1.3 | $Rh_2(esp)_2$ | 64 (<5) |
| 6 | **2b** | 1:1.3 | $Rh_2(esp)_2$ | 52 (<5) |
| 7 | **2c** | 1:1.3 | $Rh_2(esp)_2$ | 43 (7) |
| 8 | **2d** | 1:1.3 | $Rh_2(esp)_2$ | 32 (12) |
| 9 | **2e** | 1:1.3 | $Rh_2(esp)_2$ | 0 (0) |
| 10 | **2a** | 1:1.3 | $Rh_2(esp)_2$ | 72[c] (<5) |
| 11 | **2f** | 1:1.3 | $Rh_2(esp)_2$ | 0 (0) |
| 12 | **2g** | 1:1.3 | $Rh_2(esp)_2$ | 0 (0) |
| 13 | **2h** | 1:1.3 | $Rh_2(esp)_2$ | 0 (0) |

[a] Performed at 0.1 mmol scale by addition of **1a** and **2** over the Rh catalyst in $CH_2Cl_2$ at −50 °C during 30 min and then warmed to rt in 3 h. [b] $^1$H NMR yields used $CH_2Br_2$ as an internal standard; a single diastereoisomer of **3a** was observed (>20:1) in each entry, and **4a** was obtained as an equimolecular mixture of four diastereoisomers. [c] $NaHCO_3$ was added (2 equiv). oct = octanoate. adc = 1-adamantylcarboxylate. esp = *α,α,α′,α′*-tetramethyl-1,3-benzenedipropanoate.



X = $PF_6$ (**2a**), OTf (**2b**), $BF_4$ (**2c**)
R = $CH_2CO_2Et$

ligand to alkenes or alkynes, generating cyclopropyl- or cyclopropenyl-I(III) species that evolved, through the departure of the I(III) group, to synthetically useful allyl or cyclopropenium cations, respectively. Considering the outstanding nucleofuge ability of the hypervalent iodine(III)[17] and high electrophilicity of the Rh-carbynoid (***int-I***), we recently hypothesized that alkenyl carboxylic acids **1** could be sufficiently nucleophilic to displace the iodine(III) group and provide a Fischer-type acyloxy Rh-carbene (Figure 2, ***int-II***). The latter species could then evolve through (a) *intramolecular alkene cyclopropanation* that leads to complex cyclopropyl-fused δ-lactones **3** or (b) *nucleophilic attack* at the carbene carbon atom by acid **1** that would provide acetal **4**.

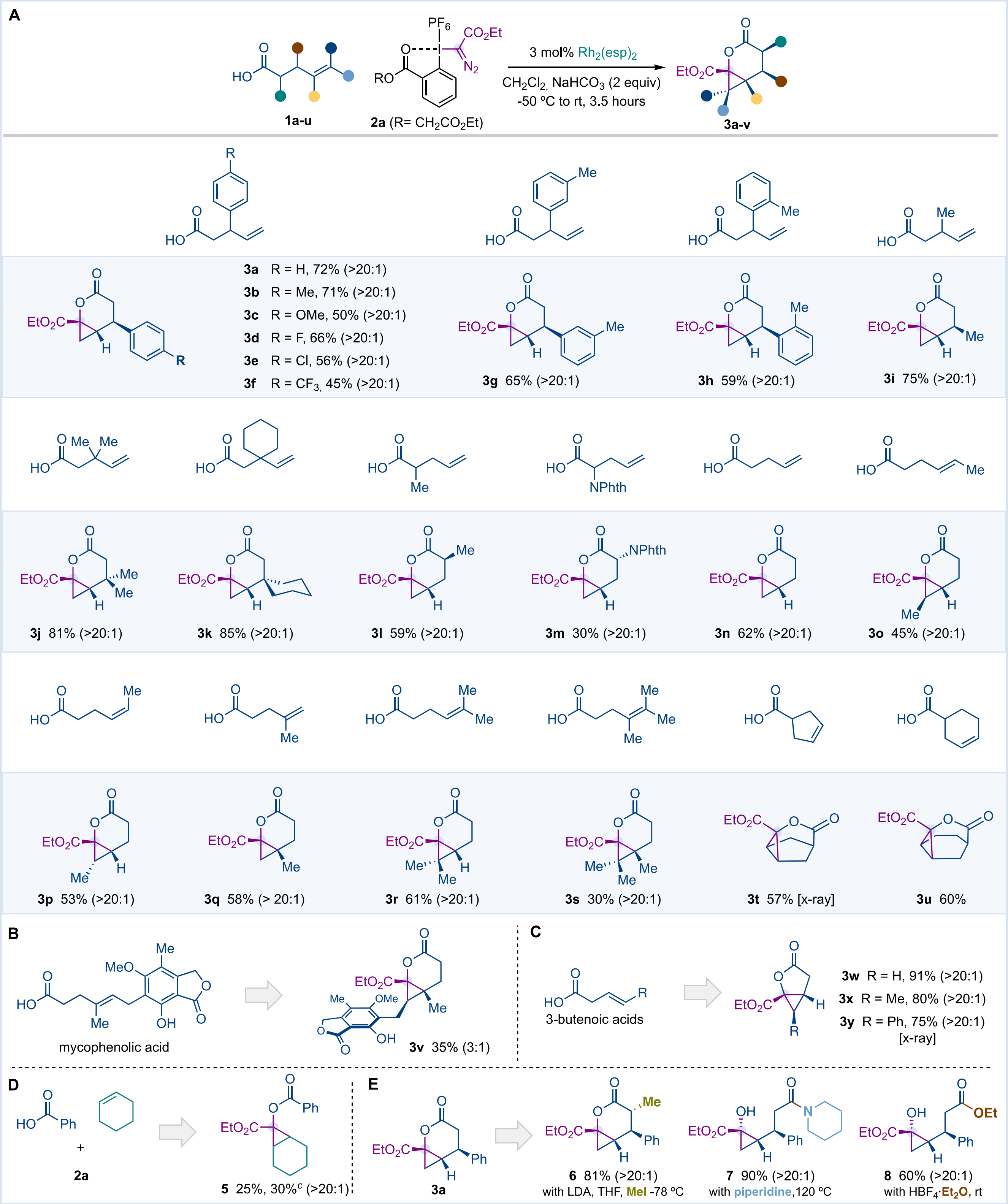
Our envisaged carbyne transfer process with carboxylic acids was initially tested by adding 2 equiv of 3-phenyl-4-pentenoic acid (**1a**) and pseudocyclic hypervalent iodine reagent **2a** as a limiting reagent to a solution of $Rh_2(OAc)_4$ (3 mol %) in $CH_2Cl_2$ at −50 °C (Table 1). Unfortunately, lactone **3a** was not detected, and instead, acetal **4a** was isolated in 65% yield (Table 1, entry 1). This result suggested the generation of a Fischer-type Rh(II)-carbene that underwent nucleophilic attack by **1a**. Remarkably, no products derived from an alkene cyclopropanation were observed.[16a]

After this, by reversing the stoichiometry (ratio **1a**:**2a**, 1:1.3), we were delighted to observe 30% yield of the desired lactone **3a** accompanied by a 20% yield of **4a** (entry 2). **3a** was obtained as a single diastereoisomer (>20:1), where the ester group from the Rh(II)-carbynoid, the aryl ring, and the internal olefinic C−H bond from **1a** are in the *syn* disposition. Then, we argued that a way to increase the efficiency of the reaction, by decreasing **4a** formation, could rely on the use of sterically demanding rhodium catalysts. While the use of $Rh_2(Oct)_4$ provided similar results to $Rh_2(OAc)_4$ (entry 3), $Rh_2(Adc)_4$ and Du Bois' catalyst $Rh_2(esp)_2$[18] increased the efficiency of the cyclization while disfavoring formation of **4a** (entries 4, 5). With $Rh_2(esp)_2$, we evaluated the effect of the counteranion and structural nature of **2** and found that while triflate and tetrafluoroborate reagents **2b**,**c** and linear reagent **2d** were less efficient (entries 6−8), cyclic derivative **2e** provided no conversion to **3a** (entry 9). In addition, we observed that sodium bicarbonate (2 equiv) slightly improved the efficiency of the reaction (entry 10).[19] Finally, alternative diazo compounds substituted with sulfonium,[20,21] ammonium,[20] or bromide[22] (**2f**−**h**, entries 11−13) were ineffective in promoting formation of **3a**/**4a**.

Control experiments showed that tetrabutylammonium salt or methyl ester derivative derived from 3-phenylpent-4-enoic acid were unreactive, which underlines a key role of the carboxylic acid functionality for the generation of the acyloxy Rh(II)-carbene. Further controls showed that no reaction takes place between **1a** and **2a**, which indicates that generation of ***int-II*** from a presumable *α*-acyloxy diazoacetate derivative is highly unlikely.[23]

With the optimized conditions, we investigated the scope of this carbyne transfer reaction with a range of alkenyl carboxylic acids (Table 2A−C). We found that 4-pentenoic acids with *para*-substituted aromatic rings at C3 provided δ-lactones **3b**−**f** with excellent diastereoselectivity (>20:1). Moreover, *meta*- and *ortho*-substitution on the aromatic rings was tolerated as well as alkyl substitution at C3 (**3i**). It was believed that geminal substitution at C3 could be detrimental in the cyclopropanation event for steric reasons. In contrast to our beliefs, we were glad to observe that lactones **3j**,**k** were obtained with high efficiency and that could be explained by a

**Table 2. Scope of the Catalytic Carbyne Transfer with Alkenyl Carboxylic Acids**[a,b]



[a] Performed with **1** (0.20 mmol, 1 equiv), **2a** (0.26 mmol, 1.3 equiv), and $Rh_2(esp)_2$ (0.006 mmol, 3 mol %) in $CH_2Cl_2$ (0.08 M). Yields are reported on the basis of isolated pure product. [b] The diastereoselectivity ratio indicated in parentheses was determined by $^1H$ NMR analysis of the reaction crude mixture. NPhth = phthalimide. [c] Reaction performed at 0 °C.

Thorpe−Ingold effect. On the other hand, C2 substitution with alkyl or protected amino groups provided **3l,m** as single diastereoisomers, and the unsubstituted derivative 4-pentenoic acid led to **3n** in moderate yield.

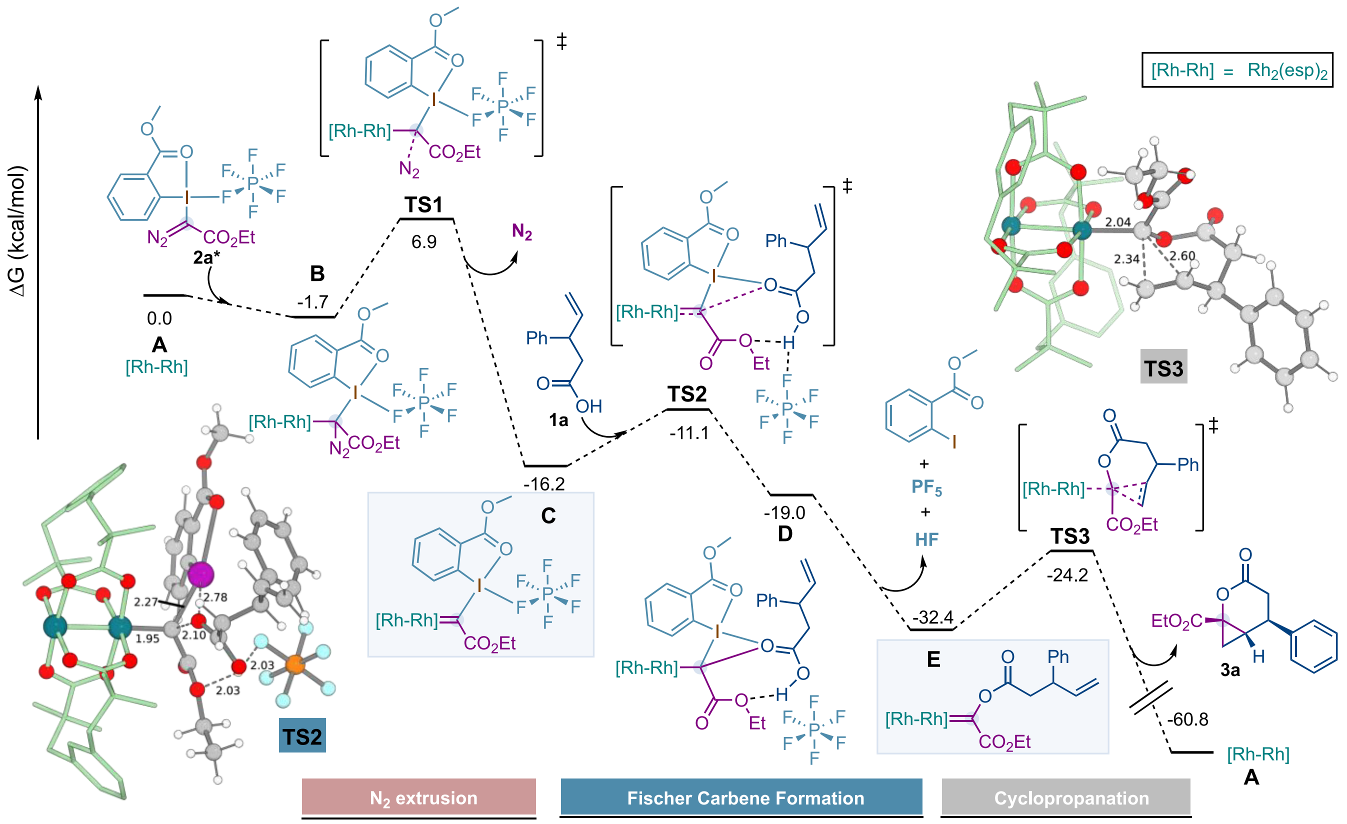


**Figure 3.** Free energy profile for the catalyzed reaction between **1a** and **2a*** with Rh$_2$(esp)$_2$.

After this, we evaluated the alkene substitution and observed that the stereochemistry of the double bond is preserved in the final products (**3o,p**). Tri- and tetrasubstituted alkenes typically undergo carbene allylic C−H bond insertion for alternative donor/acceptor Rh(II)-carbenes.[24,25] However, our acyloxy Rh(II)-carbene preferred to evolve via cyclopropanation and delivered penta- and hexasubstituted cyclopropanes **3r,s**. Furthemore, carboxylic acids substituted with cyclic alkenes, such as cyclopentene or cyclohexene, were converted to complex tricyclic lactones **3t,u**. Moreover, our carbyne transfer process was applied in the late-stage functionalization of mycophenolic acid (Table 2B, **3v**), an immunosuppressant agent used to prevent rejection following organ transplantation. Furthermore, 3-butenoic acids could be converted into $\gamma$-lactones **3w−y** with high efficiency (Table 2C). Under the optimized reaction conditions, we were glad to observe intermolecular cyclopropanation using benzoic acid, cyclohexene, and reagent **2a** albeit in low yield (**5**, 25−30%, >20:1; Table 2D). Attempts to improve the efficiency by changing the stoichiometry, temperature, base, or catalyst were unsuccessful (see the Supporting Information for details).[26]

Derivatizations of **3a** were performed by methylation via lithium enolate to provided **6** as a single diastereoisomer[27] and by amidation or esterification to provided cyclopropanols **7** and **8**, respectively (Table 2E).[28] The latter results formally represent the cyclopropanation of an alkene with a Rh(II)-carbene substituted with a hydroxy as a donor group.[29]

Later, we studied computationally the mechanism for the formation of lactone **3a**. We applied a B3LYP-D3BJ method in solvent to the study of the reaction with acid **1a** reagent **2a*** and Rh$_2$(esp)$_2$ as the catalyst. The full system was considered in the calculations, with the only exception that the pendant R group in **2a**, (R = CH$_2$CO$_2$Et, see Table 2A) was replaced by a methyl group for the sake of conformational simplicity. A simplified version of the resulting free energy profile is shown in Figure 3, and full computational details are supplied in the Supporting Information.[30]

The initial reaction between **2a*** and Rh$_2$(esp)$_2$ follows the well-established path for the formation of metallocarbenic species either with dirhodium complexes[31] or coinage metal complexes.[32] A dinitrogen moiety is extruded from the precursor, and the metal-carbene bond is formed, resulting in the Rh-carbynoid **C**.

The 3D structure of **C**, presented in Figure 4 from two different views, has reasonable geometrical parameters, with Rh−C distances and C−I distances of 1.92 and 2.19 Å,

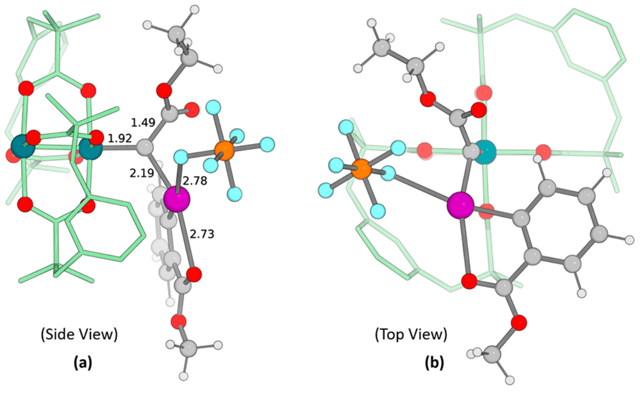


**Figure 4.** Computed geometry of Rh-carbynoid **C** with (a) side and (b) top views. For structural clarity, hydrogens are omitted, and carbon atoms are shown in tube format in the esp ligand.

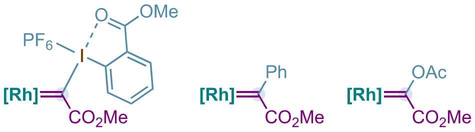
respectively. Remarkably, the $PF_6^-$ counterion and the carbonyl ester group in the *ortho* position of the Ar−I(III) moiety remain attached to the iodine center (F−I, 2.78 Å; O−I, 2.73 Å) in the nonpolar medium, with a distorted square planar arrangement around iodine and the carbonyl group. The two substituents on the carbene are nearly eclipsed with the nearest O−Rh bond of the bimetallic core, with 12.5 and −5.3° dihedral angles for $CO_2Et$ and the Ar−I(III) substituent, respectively (Figure 4b). Furthermore, the ethyl group of $CO_2Et$ and the aryl group of the Ar−I(III) substituent are placed away from the esp units. The angle between Rh−Rh−$C_{carbene}$ is 166.9°, and the carbene carbon is slightly pyramidal ($\angle Rh-C_{carbene}-C_{CO2Et}-I_{IAr} = 165°$), which may be due to steric interaction of the Ar−I(III) group with the esp ligand. It is also worth mentioning that the two phenyl groups in the esp ligands are by no means in a symmetric arrangement, with one of them much closer to the carbynoid ligand.

Rh(II)-carbynoid **C** interacts with **1a** through transition state **TS2** and evolves to intermediate **D**. The latter can go through a series of low barrier fragmentations detailed in the Supporting Information and evolve finally to the Fischer carbene **E**. From here, the cyclopropane formation occurs in a single step through **TS3** (8.2 kcal/mol barrier) where the phenyl ring from the carboxylate moiety and the dirhodium are displayed in favorable *pseudo*-equatorial positions to prevent steric clashes.

The role of the usually inert $PF_6^-$ counterion as a proton abstraction agent deserves some comment. We are in no way claiming that HF will be a side product of the reaction, as it will immediately react with the $HCO_3^-$ excess present in the medium to regenerate $PF_6^-$, in a step that has not been included in the profile for simplicity. We consider however that it emphasizes a defining feature of Rh(II)-carbynoid **C** in abstracting the proton from carboxylic acids.[33]

We finally analyzed computationally the Rh(II)-carbynoids and Fischer Rh(II)-carbene complexes and compared their properties with a donor/acceptor derivative substituted with a phenyl ring (Table 3). The metal moiety was slightly simplified from that used in the mechanistic study above, as the $Rh_2(OAc)_4$ was used instead of $Rh_2(esp)_2$. We first analyzed the metal complexes through charge decomposition analysis (CDA), which separates the metal-carbene bonding interaction into ligand to metal $\sigma$ donation and metal to ligand $\pi$ back-donation.[34] Remarkably, for the carbynoid, the $\sigma$ donation (0.245) is the lowest, and the back-donation (0.123) is the highest. This means that the ligand transfers less electronic density to the dirhodium core of the system in comparison with the Rh-carbenes substituted with phenyl or acetoxy. However, the Rh(II)-carbynoid complex is a stronger electrophile, as shown by the much more negative LUMO energy, and the significantly higher electrophilicity index $\omega$.[35] This seeming contradiction is explained by the presence of the formally cationic hypervalent iodine attached to carbon. In contrast, the acetoxy Rh(II)-carbene is the least electrophilic of the three complexes and has the highest LUMO energy.

**Table 3. Calculated Values of Charge Donation ($d$) and Back Donation ($b$)[a] from the Carbene Ligand to Rhodium, LUMO Energies (eV), and Electrophilicity Indices ($\omega$)[a]**



| | | | |
|---|---|---|---|
| donation (d) | 0.245 | 0.275 | 0.313 |
| back donation (b) | 0.123 | 0.037 | 0.066 |
| d-b | 0.122 | 0.238 | 0.247 |
| $\varepsilon_{LUMO}$ (eV) | -4.083 | -3.496 | -2.931 |
| ω | 5.78 | 4.68 | 3.30 |

[a] $d$ and $b$ values are obtained by charge decomposition analysis. [Rh] = $Rh_2(OAc)_4$.

In summary, we have disclosed a carbyne transfer process that catalytically transforms alkenyl carboxylic acids into complex cyclopropyl-fused lactones by the formation of two single C−C bonds and one C−O bond at the carbyne carbon atom. Relevant on this work was the catalytic generation, from a Rh(II)-carbynoid, of a new class of donor/acceptor Rh(II)-carbene substituted with an acyloxy group that can be considered a Fischer-type carbene. This new way of accessing Fischer-type carbenes in a catalytic fashion is remarkably different to recent approaches,[10−13] and DFT calculations unveiled key features of both Rh(II)-carbynoid and acyloxy Rh(II)-carbene.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c00012.

Experimental procedures and spectral data (PDF)

### Accession Codes

CCDC 2192080 and 2238826 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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