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Intramolecular Buchner reaction: experimental and theoretical comparison of the effect of the carbene substituent on the chemoselectivity.

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Abstract. The intramolecular Buchner reaction is a powerful transformation able to dearomatize benzenic rings. However, the competitive C–H insertion of the carbene moiety into benzylic positions still remains a limitation, and the reasons governing this uncomplete chemoselectivity are poorly understood. The carbene substitution, in particular, have been observed to influence strongly the selectivity, though the currently proposed explanation relying on the electrophilicity of the metalcarbene hardly describes some experimental results reported in the literature.

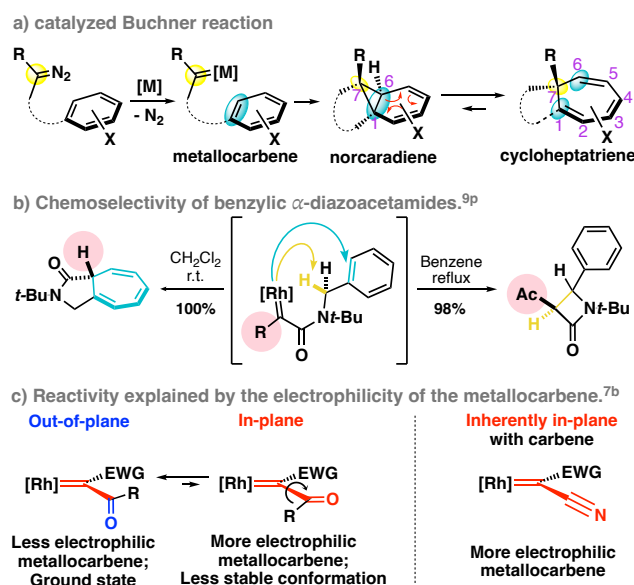
In this article, we present our experimental observations of intramolecular rhodium-catalyzed Buchner reactions, combined with DFT calculations on selected carbene substituents, to propose a complementary explanation for the observed chemoselectivity modification.

Keywords: Buchner reaction; aromatic cyclopropanation; C–H insertion; carbene; rhodium; DFT calculations.

Introduction

Apart from the classical oxidative and reductive dearomatizations,^[1] the Buchner reaction represents an original neutral expansive method to break the aromaticity of phenyl rings. It is permitted by the great reactivity of carbene species, undergoing an unusual cyclopropanation of these otherwise poorly reactive C=C bonds. The resulting bicyclic norcaradiene then lays in equilibrium with the generally more stable cycloheptatriene.^[2] Noteworthy, the Buchner reaction led to some applications in total synthesis,^[3] ruling out its consideration as a simple chemical freak. However, this intriguing yet useful transformation frequently suffers from a lack of selectivity. Indeed, first reported in 1885,^[4] the thermal decomposition of ethyl diazoacetate in benzene was delivering a mixture of regioisomeric compounds due to 1,5-hydrogen shifts. Pioneering work from Linstrumelle and Julia showed in 1970 the first examples of copper as efficient catalyst to promote the Buchner reaction.^[5] Ten years later, the discovery that rhodium complexes could perform the same transformation at a much lower temperature, thus delivering the products more selectively, renewed the interest in the catalyzed Buchner reaction (Scheme 1a).^[6] However the ability of carbenes to undergo insertion in various C–H bonds or addition to isolated alkenes increases the difficulty to selectively target a weakly reactive aromatic unsaturation within the typical complex hydrocarbon skeletons. In this regard, the intramolecular Buchner reaction is more suited to limit the undesired carbene insertions, usually by limiting the number of proximal reactive C–H bonds. Building on Reisman's and Xu's reports showing that cyano-substituted diazo

compounds were highly efficient to get racemic aromatic cyclopropanation under both Rh- and Cu-catalysis,^[7] we recently described an asymmetric intramolecular Buchner reaction, catalyzed by a rhodium complex, using benzylic α -diazo- β -cyanoacetamides with a high chemoselectivity in favor of the Buchner product.^[8]



Scheme 1. Background on the Buchner reaction.

Whereas numerous examples of Rh-catalyzed intramolecular Buchner reaction have been reported in the literature using diazoamides or diazoesters bearing acyl, alkoxycarbonyl, sulfone, phosphonyl or other substituents, highly variable efficiency and selectivity were observed.^[9] Among the parameters influencing the products distribution, the substitution of the

carbene seems to play a crucial role by favoring either benzylic C–H insertion or Buchner products, although the reasons are not yet clearly identified. Striking examples were reported by Doyle, showing that the $\text{Rh}_2(\text{OAc})_4$ decomposition of the *N*-benzyl-*N*-*tert*-butyl- α -diazoacetamide bearing an acetyl group in refluxing benzene lead exclusively to the β -lactam in 98% yield, while the analogous unsubstituted substrate ($\text{R} = \text{H}$) lead to the Buchner product quantitatively in dichloromethane at room temperature (Scheme 1b).^[9p] This report also depicted the crucial role of the *N*-*tert*-butyl moiety, locking the intermediate in a conformation where the aromatic ring is close to the carbenoid center.

These benzylic α -diazoacetamides examples reflect the general difficulty to rationalized the chemoselectivity results present in the literature: not only the substituents are different, but also the solvent, the temperature, the catalyst, the spacer and the aromatic substitution are frequently inhomogeneous, between different publications but also sometime within the same one. Furthermore, the product distribution often remains unclear as solely the major isolated product is frequently reported without mention of other side products observed in the crude mixture. Building on Charette's hypothesis to justify the greater reactivity of cyano-substituted carbenes in rhodium-catalyzed alkene cyclopropanation,^[10] Reisman interestingly proposed that the higher electrophilicity of metalcarbenes favors the aromatic cyclopropanation over the C–H insertion.^[7b] In the ground-state, the π -system of the electron-withdrawing substituent lay out of the plane of the metalcarbene to avoid the conjugated but more energetic conformation, thus leading to a less electrophilic reactive species (Scheme 1c). On the other hand, the catalytic carbene transfer using benzylic α -diazo- β -cyanoacetamides leads to an inherent conjugation of the linear cyano group with the metalcarbene. The resulting highly electrophilic metalcarbene is more susceptible to perform the cyclopropanation of the poorly reactive aromatic unsaturation. Johnson interestingly reported that cyanosubstituted α -diazoesters are also effective partners for the more difficult intermolecular aromatic cyclopropanation.^[11]

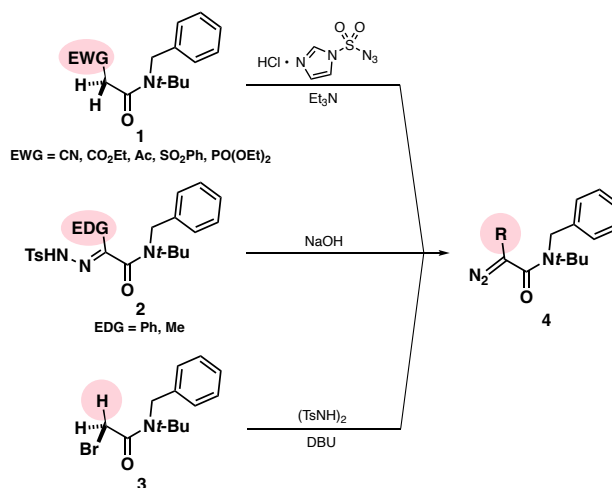
Lei's DFT study of the Buchner reaction of *N*-benzyl-*N*-*iso*-propyl- α -diazoacetamides intending to evaluate the effect of the carbene substituent on the chemoselectivity unfortunately suffers from major contradictions regarding the literature analysis and the interpretation of the calculation results.^[12] In particular, the erroneous interpretation that Reisman would have mainly observed C–H insertion instead of aromatic cyclopropanation in the case of cyano-substituted carbenes induced subsequent inconsistencies. The comparison of the activation energy required for C–H insertions with those combined of the aromatic cyclopropanation and the norcaradiene-cycloheptatriene sigmatropic rearrangement led to the over evaluation of the energy of the second route to fit

with the former postulate. Indeed, under rhodium(II) catalysis, the irreversible aromatic cyclopropanation should independently be compared with the competitive C–H insertion without considering any potential subsequent rearrangement of the norcaradiene.

We therefore decided to perform a combined experimental and DFT analysis of the carbene transfer process using diazoacetamides and the most widely used and efficient rhodium(II) catalysis. *N*-Benzyl-*N*-*tert*-butyl- α -diazoacetamides substituted by selected functional groups were chosen as different groups have already reported carbene transfer reactions with this family of reagents, and the simple and commercially available $\text{Rh}_2(\text{OAc})_4$ catalyst was selected. We report herein the results and the conclusions of these studies intending to provide a more comprehensive and homogeneous description of the chemoselectivities observed.

Results and Discussion

We thus started by preparing a set of *N*-benzyl-*N*-*tert*-butyl- α -diazoacetamides **4** bearing either an electron-withdrawing or -donating group (Scheme 2). The formers were accessed by a traditional diazo transfer procedure using imidazole-1-sulfonyl azide hydrochloride,^[13] while the latter were obtained by basic treatment of tosylhydrazones through a Bamford-Stevens type reaction.^[14] The unsubstituted diazo compound was synthesized according to Fukuyama's procedure (see Supporting Information for details).^[15]

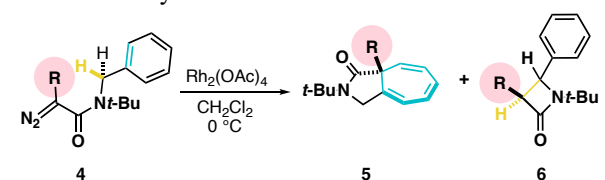


Scheme 2. Synthesis of functionalized diazo compounds.

With the different diazo derivatives in hand, we decided to study their catalytic decomposition in the presence of rhodium(II) acetate, in dichloromethane at 0 °C (Table 1). As previously observed, the decomposition of diazo compounds **4a** and **4b**, respectively unsubstituted and bearing a cyano group, led to the exclusive formation of the Buchner products **5a** and **5b** in 86 and 95% yield, with no trace of C–H insertion product. On the other hand, all the other

electron-withdrawing group-substituted carbenes (**4c-f**) led to the exclusive formation of the C–H insertion products (**6c-f**) in moderate to excellent yields with no trace of Buchner product. The phenyl substituted carbene (**4g**) also afforded solely the β -lactam (**6g**) in 91% yield. As an in-between situation, the carbene substituted with a methyl group (**4h**) delivered a 4.5:1 mixture of C–H insertion (**6h**) and Buchner products (**5h**) in the crude mixture, then isolated in 63% and 18% yields respectively.

Table 1. Influence of the carbene substituent **R** on the chemoselectivity.^{a)}



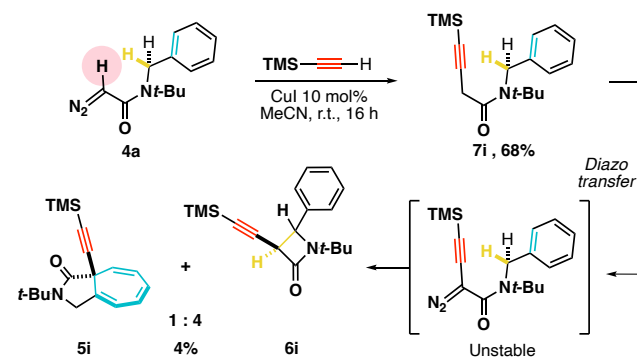
Entry	R	Ratio 5:6 ^(b,c)	Yield 5 ^{d)}	Yield 6 ^{d)}
a	H	1:0	86	0
b	CN	1:0	95	0
c	CO ₂ Et	0:1 (95:5)	0	90 ^{e)}
d	Ac	0:1 (0:100)	0	86 ^{f)}
e	SO ₂ Ph	0:1 (95:5)	0	72 ^{e)}
f	PO(OEt) ₂	0:1 (86:14)	0	50 ^{f)}
g	Ph	0:1 (95:5)	0	91 ^{e)}
h	Me	1:4.5 (100:0)	18	63 ^{e)}

a) Reaction conditions: to a solution of **4** (0.200 mmol, 1.00 eq.) in CH₂Cl₂ (2 mL) at 0 °C, under an argon atmosphere, was added Rh₂(OAc)₄ (4.0 μ mol, 2.0 mol%). The mixture was stirred at this temperature for 2 h. b) Determined by ¹H NMR in the crude mixture. c) Ratio of *cis/trans* of azetidine **6** determined by ¹H NMR in the crude mixture. d) Isolated yield after flash chromatography. e) *Cis* product only. f) *Trans* product only.

Whereas the complete chemoselectivity in favor of the Buchner product with the cyano-substituted diazo compound **4b** could be explained by the previously mentioned electrophilicity of the metallocarbene, the same result observed with **4a** is more difficult to rationalize solely by electronic factors. Moreover, the methyl-substituted carbene derived from **4h** also leads to a non-negligible amount of aromatic cyclopropanation, thus calling for a complementary explanation. Noticing that the Buchner reaction was occurring with the carbene bearing a hydrogen, with the linear thus less sterically demanding cyano group, and also with the small methyl substituent, we decided to test the non-electron-withdrawing linear alkyne substituent. The butyn-3-amide **7i** bearing a TMS alkynyl substituent was prepared from **4a** following a procedure described by Fu (Scheme 3).^[16] Performing the diazo transfer reaction as described previously for the formation of **4b-f** led to an unstable diazo compound starting to decompose in the crude mixture. This uncatalyzed transformation directly resulted in the corresponding free carbene and the formation of a 1:4 mixture of Buchner product **5i** and azetidinone **6i**, in only 4% isolated yield, thus making any precise

interpretation hazardous.^[17] Interestingly, **5i** depicts a much more pronounced norcaradiene character (H⁶ at 3.88 ppm) than the other Buchner products synthesized in this study, although the reasons of the equilibrium shift remain unclear.^[2a] This result shows that the competition between the aromatic cyclopropanation and the C–H insertion intrinsically exists, but the influence of the rhodium catalyst on the chemoselectivity could not be experimentally determined in this case.

Scheme 3. Synthesis and behavior of the alkyne-substituted diazo compound.

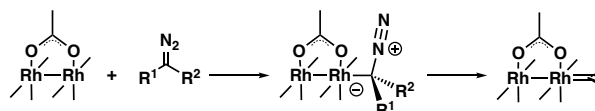


With these results in hand, DFT calculations were undertaken on representative benzylic α -diazoacetamides to rationalize the catalytic experimental results obtained above.

The first hypothesis usually put forward in the literature relies on the electrophilicity of the reactive species, *i.e.* of the metallocarbene. We thus computed the Electron Affinity (EA) of the Rh-based metallocarbene using Density Functional Theory (DFT) (see computational details) with the substituents tested in Table 1. The resulting values (Table S1, in *supporting information*) follow the decreasing order: CN > SO₂Ph > PO(OMe)₂ > Ac > CO₂Me > H > Me, hence consistent with expected EWG or EDG effects known in organic chemistry. The three highest EAs are obtained for the metallocarbene issued from **4b**, **4e** and **4f**, the first yielding solely the Buchner product, while the other two afforded exclusively the insertion product. One of the lowest EA is obtained for the metallocarbene formed with the non-substituted (R = H) diazoacetamide **4a** although it yields exclusively the Buchner product. Clearly the electrophilicity alone is not sufficient to explain the chemoselectivity.

We thus turned to the analysis of computed reaction profiles, in order to disclose the mechanistic details of both C–H insertion and Buchner reactions. Different substituents were studied, corresponding to different reactivity behaviour (R = H, Me, CN and Ac), and chosen for their combined electronic and steric properties. Although a previous analogous analysis had appeared earlier in the literature,^[12] we were motivated by a thorough reinvestigation of their profiles, especially in the light of the present experimental results. We also included the description of the alkyne-TMS derivative which decomposes, yielding the same C–H insertion and Buchner reaction. The well-established stepwise mechanism begins with

the formation of the rhodium carbenoid intermediate with N₂ elimination (Scheme 4).^[12,18]



Scheme 4. Rhodium carbenoid formation.

From this metallocarbene, two possible pathways may lead either to the C–H insertion or to the Buchner product (see Scheme S1). We first investigated the thermodynamic profile of formation of the metallocarbene and N₂ extrusion to assess the DFT approach on one well-known system, namely ethyldiazoacetate (EDA) reacting with Rh₂(OAc)₄, for which experimental enthalpy were determined.^[19] We obtained an enthalpy of 14.3 kcal.mol⁻¹ (Table S2), which reproduces very satisfactorily the experimental values of *ca* 15 kcal.mol⁻¹. We also computed the activation energies of this preliminary step for four diazo compounds of interest (R = H, Me, CN, Ac) and got values similar to the calculated ones already obtained by Lei and coll. for closely related metallocarbenes.^[12] Both conformations of the diazoacetamide, with the C=O and N₂ moieties *cis* or *trans*, were considered, and the *cis* conformer appeared to be more stable and leading to an easier activation to form the metallocarbene (Figure S1).

Figures 1-3 display C–H insertion and Buchner profiles for the substituents H, CN and Ac respectively. The Buchner reaction consists first in a cyclopropanation reaction (transition state TS_{cyc}) followed by the ring expansion (R.E.). This latter step has not been represented here, not only because it occurs after the irreversible thus determining cyclopropanation step, but also for the sake of simplicity, although the activation free energy is shown in Table 2. These activation free energies were calculated taking the lowest energy foot point prior to the TS, *i.e.* either the metallocarbene or the “pre-reactant” issued from the IRC.

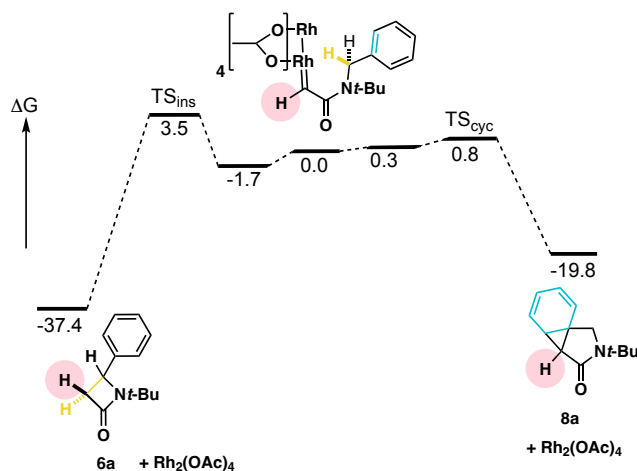


Figure 1. Free energy profile (kcal.mol⁻¹) of C–H insertion (left) and cyclopropanation (right) for R = H. The energy reference is the metallocarbene formed from N₂ extrusion.

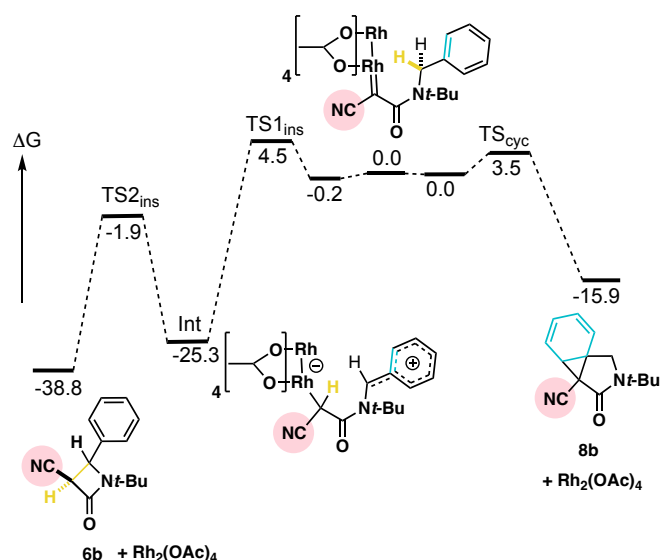


Figure 2. Free energy profile (kcal.mol⁻¹) of C–H insertion (left) and cyclopropanation (right) for R = CN. The energy reference is the metallocarbene formed from N₂ extrusion.

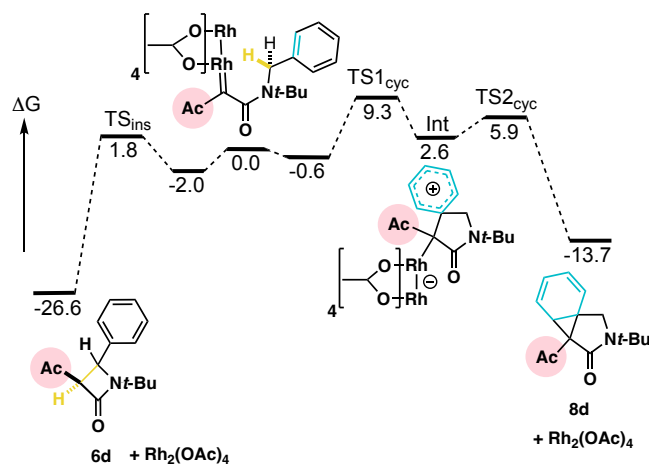


Figure 3. Free energy profile (kcal.mol⁻¹) of C–H insertion (left) and cyclopropanation (right) for R = Ac. The energy reference is the metallocarbene formed from N₂ extrusion.

Experimental conditions (0 °C, 2 h) correspond to a kinetic control of the reaction, thus we turned to an examination of the activation free energies of the stepwise pathways, which are shown in Table 2. Indeed, the low values - less than 10 kcal.mol⁻¹ - of most of the steps are consistent with the low temperature and short reaction times.

Table 2. Free energies of activation (kcal.mol⁻¹) for C–H insertion (CHins) and Buchner (cyclopropanation, Cyc and ring expansion, RE).

substituent	CHins	Cyc	RE
H	5.2	0.8	5.3
CN	4.6; 23.5	3.5	6.7
Ac	3.8	9.9; 3.3	2.6
Me	10.2	12.2	4.1

The trend of activation energies for a substituent is consistent with experimental data within the usual uncertainty in energy calculations, *i.e.* ΔG[‡] (CHins) >

ΔG^\ddagger (Cyc) for R = H, CN and ΔG^\ddagger (CHins) < ΔG^\ddagger (Cyc) for R = Me and Ac. This uncertainty in DFT computations of energies is *ca* 1.5-2 kcal.mol⁻¹ using hybrid functionals and good-quality basis sets, due to intrinsic approximations and numerical errors.^[20] Moreover, a simple calculation shows that a difference of 2 kcal.mol⁻¹ in activation energies yields a 97:3 ratio in the distribution of the resulting two products. Thus, balanced distributions such as in R = Me cannot be quantitatively reproduced by DFT modelling, although we get qualitatively the expected trend (Table 2 and Figure S3). Details about the intermediates and TSs involved in these processes are given in Tables S4-S5 and Figure S2, and about thermodynamic data in Tables S6-S8.

Two particular behaviours call for more comments. In the case of R = CN, we observe a two-step mechanism for the C–H insertion, where the first TS corresponds to a H⁻ transfer to the carbene, without cyclization. Indeed, the same behaviour is described in the paper by Lei although the second step had not been computed.^[12] Examination of the Mulliken charges (Table S4) and of the main interatomic distances point to an intermediate where a H⁻ has moved to the carbene atom leading to a cationic benzylic group and a negatively charged tetraacetato dirhodium group. This step is consistent with previous mechanistic studies pointing to the hydride nature of the H atom during C–H insertion.^[18] Figure 4 and Table S4 gather the main molecular properties of this intermediate.

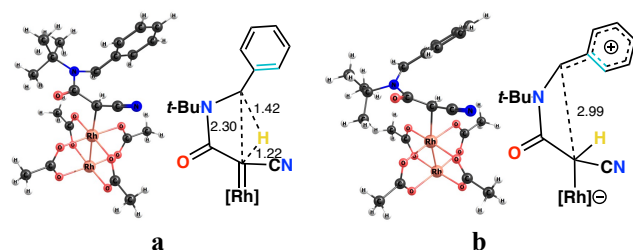


Figure 4. Molecular structure and schematic view of TS1_{ins} (a) and of Int (b) in the C–H insertion for R = CN with some interatomic distances (Å). [Rh] stands for the Rh₂(OAc)₄ part.

Examination of some key-distances in the TS_{ins} for all R substituents in Table S4, namely C_{carb}–H_b and C_{carb}–C_b (see scheme S1 for their definition) show that the H_b atom has been almost fully transferred to the carbene in the first TS, whereas the benzylic C_b is still at more than 2.2 Å of the carbene. However, for R = H and Ac, this carbon-carbon bond is shorter (2.23-2.25 Å) than the one for the cyano derivative (2.30 Å). Thus, the formation of the C_{carb}–C_b bond occurs within the same step for R = H or Ac, whereas for R = CN the C_{carb}–C_b bond is too long and an intermediate is formed. Such behaviour can be explained by the stronger electron withdrawing property of the CN group

compared to R = H or Ac. In the former, the H⁻ transfers even if the C_{carb}–C_b bond is still long (2.3 Å) whereas for the latter, the C_{carb}–C_b distance must be shorter, enough to form the C_{carb}–C_b bond simultaneously with the H transfer.

Another two-step process is observed for the norcaradiene formation with an R = Ac substituent (Figure 3). An intermediate (Int) is obtained by forming a first C_{carb}–C_{Ph} bond in an asynchronous manner (see scheme S1 for their definition), while the second C_{carb}–C_O distance is still long (2.54 Å in the intermediate, see Table S5). Indeed, in the R = Ac case (Figure 5), the first TS exhibits a large C_{carb}–C_O distance (2.65 Å), whereas the TS in one-step profiles for norcaradiene formation show C_{carb} to C_O atoms distances all lower than 2.45 Å (see Figure S2 and Table S5).

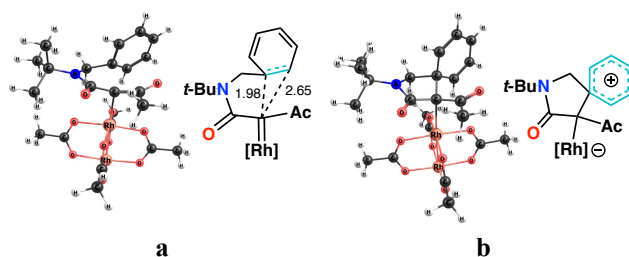


Figure 5. Molecular structure and schematic view of TS1_{cyc} (a) and of Int (b) in the cyclopropanation for R = Ac with some interatomic distances (Å). [Rh] stands for the Rh₂(OAc)₄ part.

It is clear that electrophilicity is the driving force for both attacks and the actual issue is to understand how the two favourable sites (aromatic C=C bond or C–H bond) compete, depending on the substituent.

The analysis of the R = H profile is interesting because of its absence of electronic and steric effects due to the substituent. We observe that the Buchner reaction occurs with a very low activation energy (0.8 kcal.mol⁻¹) while the C–H insertion asks for a slightly higher one (5.1 kcal.mol⁻¹). This means that the dirhodium complex confers enough electrophilicity to the carbene for both reactions to occur. It also shows that intrinsically, the carbene transfer is easier on the aromatic ring. Turning to the other substituents, we observed an increase in the energy of activation for Buchner reaction, from H to CN to Ac, which can be related to the increase in the volume of the substituent. For the latter, due to the carbonyl group pointing towards the aromatic ring, two steps are necessary. For R = Me, which gives less steric hindrance in vicinity of the phenyl ring, one step is enough but with a higher activation energy, maybe related to the Me group which decreases the electrophilic character. The C–H insertion mechanism is less sensitive to the steric hindrance of the R group, because the driving force is, as abovementioned, the transfer of the small H⁻.

Therefore, as we see on Table 2, the activation energy is very close in the three cases R = H, CN, Ac at *ca* 4 – 5 kcal.mol⁻¹. The higher value for Me (10.2 kcal.mol⁻¹) is certainly due to the decreased electrophilicity. In that case, the Buchner reaction becomes competitive.

Finally, the particular reactivity of the alkyne diazo compounds was also investigated. Indeed, the N₂ extrusion reaction to form the carbene without catalyst occurs with a higher activation energy (22.7 kcal.mol⁻¹, Table S2) compared to the formation of the metallocarbene species, but still consistent with a spontaneous uncatalyzed decomposition at room temperature. From the carbene, the activation energies of pathways to C–H insertion and Buchner reactions (Figure S4) were found both very low (respectively 1.3 and 0.3 kcal.mol⁻¹), indicative of a spontaneous conversion in both products. Interestingly, the partial atomic charges of the carbene atom along the reactions (Tables S4-S5) are negative, in contrast to those with a metallocarbene active species. This is consistent with the well-established role of the dinuclear Rh complex to enhance the metallocarbene electrophilicity.

Considering the results of our experiments combined with the DFT calculations, we can conclude that the favoured reaction depends on both the electron withdrawing character, as previously reported, but also of the volume of the R group. Both reactions, the cyclopropanation and the C–H insertion, are in principle favoured with electron withdrawing substituents, but the cyclopropanation is sensitive to the steric hindrance, therefore it can become disfavoured with increased bulkiness, and the C–H insertion thus becomes predominant.

Conclusion

We have studied the rhodium-catalyzed intramolecular carbene transfers using differently substituted benzylic α -diazo- β -cyanoacetamides to rationalize the chemoselectivity observed in the Buchner reaction. Experimental observations combined with DFT calculations allowed to propose that increased electrophilicity of the metallocarbene both facilitate the aromatic addition and the less favorable benzylic C–H insertion. However, the chemoselectivity seems to be governed by the steric hindrance around the carbene moiety. Therefore, the intrinsically disfavoured C–H insertion becomes predominant when hindered carbenes are involved, preventing the approach of the bulky aromatic ring.

Experimental Section

General procedure for the catalyzed carbene transfer reaction: In a round bottom flask under argon was added the studied diazoacetamide (0.200 mmol, 1.00 equiv.) and anhydrous DCM (2 mL). The solution was cooled down to

0 °C and Rh₂(OAc)₄ (1.7 mg, 4.0 μ mol, 2.0 mol%) was added in one portion. The mixture was left warming up slowly to room temperature and was stirred for 24 h. The solvent was then removed under reduced pressure and the residue was purified by flash column chromatography.

Computational details: Density functional calculations were carried out with Orca 5.0,^[21] using the hybrid functional B3LYP^[22] including a D3BJ dispersion correction.^[23] The def2-tzvp basis set^[24] has been used for geometry optimizations in gas phase and subsequent single-points in a solvent continuum (CPCM with dichloromethane). For Rh atoms, a 28-electron core pseudopotential has been used. Numerical harmonic frequencies have been calculated to control the nature of the stationary points and to derive thermodynamic functions.

For further experimental details and compound characterization data, please refer to the Supporting Information.

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