

## RESEARCH ARTICLE

# Generation and reactivity of phenylhydroxycarbenes in solution

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## Abstract

We provide evidence for the first successful generation of phenylhydroxycarbene and 4-trifluoromethylphenylhydroxycarbene in solution. The carbene tautomers of the corresponding benzaldehyde derivatives had been prepared under cryogenic matrix-isolation conditions before but their reactivity, apart from a prototypical quantum mechanical tunneling [1,2]-H-shift reaction, had not been studied. Here our strategy is to employ suitable carbene precursors for the McFadyen–Stevens reaction, to generate the parent and the *para*-CF<sub>3</sub>-substituted phenylhydroxycarbenes, and to react them with benzaldehyde or acetone in a highly facile, allowed six-electron carbonyl-ene reaction toward the corresponding  $\alpha$ -hydroxy ketones. Our findings are supported by computations at the DLPNO-CCSD(T)/cc-pVQZ//B3LYP/def2-TZVP level of theory.

## KEYWORDS

carbene, carbonyl-ene reaction, tunneling

## 1 | INTRODUCTION

Even though hydroxymethylene (hydroxycarbene, H– $\ddot{C}$ –OH) had been implicated in the photocatalytic formation of carbohydrates as early as 1921<sup>[1]</sup> and was recognized as the high-energy and highly reactive tautomer of formaldehyde,<sup>[2–6]</sup> it was first prepared and characterized under matrix isolation conditions at cryogenic temperatures only in 2008.<sup>[7]</sup> Parent hydroxymethylene undergoes a tunneling reaction *via* [1,2]-H-shift to formaldehyde with a half-life of 2 h. With the analogously prepared methylhydroxycarbene, the kinetically favored reaction to the corresponding enol does not occur, leading to the new reaction paradigm of *tunneling control* where the thermodynamically favored product forms preferentially through a quantum mechanical tunneling

reaction.<sup>[8–10]</sup> Hydroxymethylene and the entire hydroxycarbene family now can routinely be prepared through CO<sub>2</sub> extrusion from  $\alpha$ -keto carboxylic acids, and hydroxycarbenes undergo tunneling with half-lives typically in the range of several hours.<sup>[8,10–12]</sup> The behavior of phenylhydroxycarbene (**1**) and some of its derivatives has been well studied.<sup>[11–13]</sup> In contrast to other phenyl-substituted carbenes like phenylcarbene and phenylchlorocarbene, it does not undergo a ring expansion reaction.<sup>[14–16]</sup> Under cryogenic conditions **1** shows H-tunneling to benzaldehyde with a measured first-order-decay half-life of  $\tau = 2\text{--}3$  h at cryogenic temperatures.<sup>[12]</sup> In subsequent studies, (*o*-methoxyphenyl)glyoxylic acid was used to generate *o*-methoxyphenylhydroxycarbene,<sup>[11]</sup> which, however, was not observed. Instead, a C–H-bond insertion to

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2,3-dihydrobenzofuran-3-ol took place. Alternative hydroxycarbene reactivity was reported for the reactions toward sugar formation. In a bimolecular reaction several hydroxycarbene derivatives have been shown to react in a nearly barrierless carbonyl-ene reaction with aldehydes and ketones.<sup>[17]</sup> This is made possible through an allowed, highly facile (extremely low barrier) six-electron carbonyl-ene reaction,<sup>[18]</sup> which is mechanistically close to the Alder-ene reaction,<sup>[19,20]</sup> through five-membered ring transition structures where the carbene lone pair replaces the olefinic double bond of the Alder-ene reaction.

The standard procedure for the generation of hydroxycarbenes *via* pyrolysis of  $\alpha$ -keto carboxylic acids cannot be transferred into solution for two reasons. First, the free carbene will very rapidly be protonated by the acidic starting materials. Second, the activation barrier for CO<sub>2</sub> extrusion is too high ( $\sim 40$  kcal mol<sup>-1</sup>) for the temperatures to be conveniently reached with typical organic solvents.

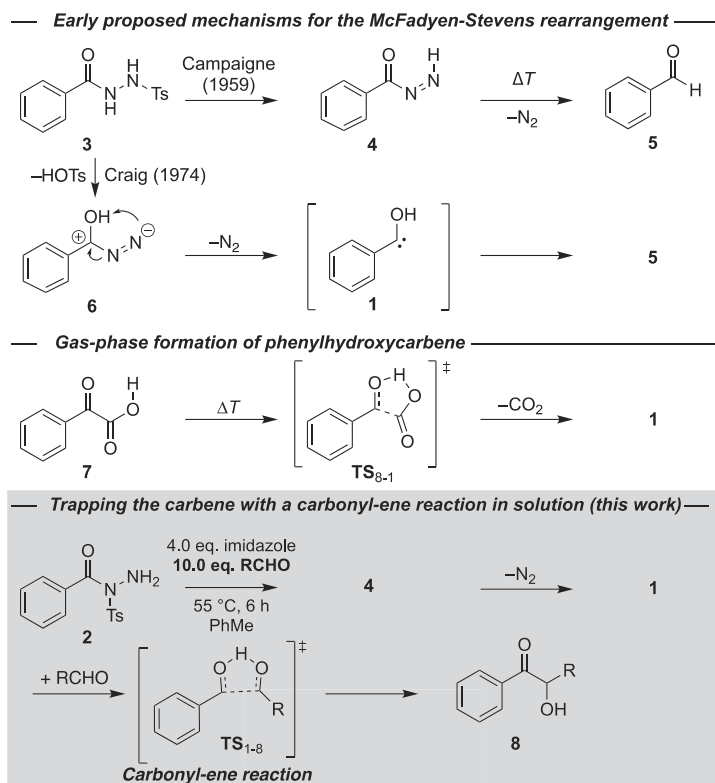
An alternative may be offered by the long known McFadyen-Stevens reaction that converts acids to aldehydes.<sup>[21]</sup> For example, it has been reported that benzenesulphonacyl hydrazide (**3**) derived from benzoic acid undergoes N<sub>2</sub> extrusion at 160 °C to give benzaldehyde (**5**) upon treatment with alkaline carbonates (Scheme 1).<sup>[21]</sup> One of the first postulated mechanism was a one-step elimination through acyldiimide

intermediate **4**.<sup>[22,25]</sup> In 1974, Matin *et al.* reinvestigated the reaction and were first to suggest **1** as an intermediate.<sup>[23]</sup> As the McFadyen-Stevens reaction originally needs harsh conditions, Iwai *et al.* introduced derivatives of **2** as more reactive starting materials, which allows the use of weak bases (e.g., imidazole) and much lower temperatures (55 °C).<sup>[24]</sup> Mechanistic studies imply the intermediacy of **1** so that we deemed **2** as a suitable precursor for the generation of **1** and related hydroxycarbenes in solution.

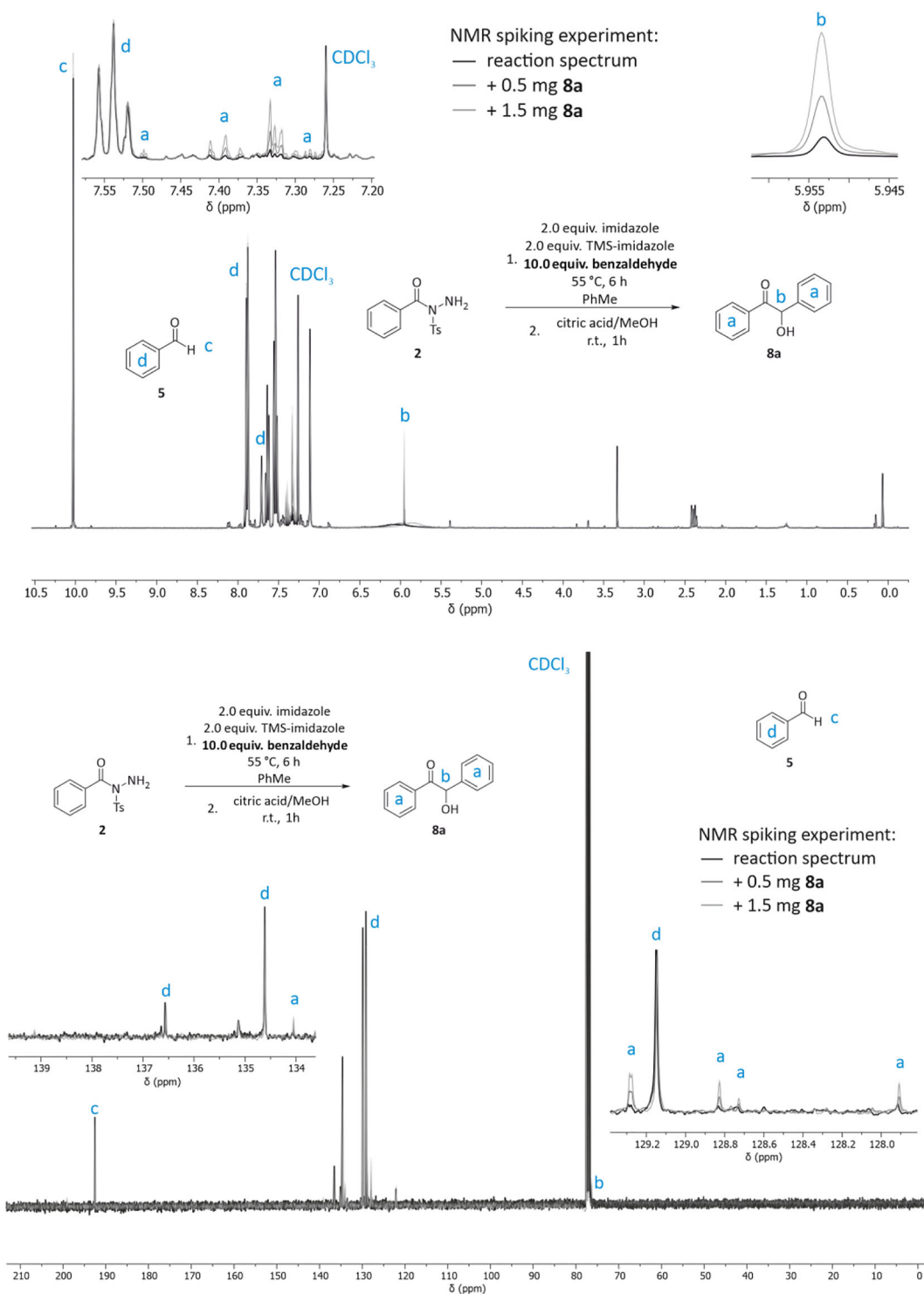
Here we provide evidence for the intermediacy of **1** in solution through using it as a reactant for bimolecular reactions that are indicative for the involvement of a carbene. We thereby draw on nearly barrierless and therefore fast, diffusion-controlled carbonyl-ene reactions of **1** with aldehydes or ketones yielding  $\alpha$ -hydroxyketones (acetoin).<sup>[17]</sup>

## 2 | RESULTS AND DISCUSSION

Because we cannot directly detect **1** in solution due to its high reactivity, we decided to trap it through the established carbonyl-ene reaction.<sup>[18]</sup> We first used the Fukuyama protocol employing imidazole/TMS-imidazole as bases in toluene<sup>[24]</sup> with the hope that in situ generated **1** reacts with **5** that forms during the reaction. To increase the probability of trapping **1**, we added a large



**SCHEME 1** Early proposals of the mechanism of McFadyen-Stevens reaction.<sup>[22,23]</sup> Generation of phenylhydroxycarbene (**1**) in the gas-phase<sup>[12]</sup> and trapping **1** in solution<sup>[24]</sup>



**FIGURE 1** Top: nuclear magnetic resonance (NMR) spectra of benzoin derived from the reactions of precursor **2** via the reaction of intermediate **1** with benzaldehyde in solution. The  $^1\text{H}$ -NMR spectrum (400 MHz,  $\text{CDCl}_3$ ) was recorded after acidic work up of the resulting reaction mixture performing a McFadyen–Stevens reaction and subsequent spiking by adding 0.5 and 1.5 mg of pure **8a**. Bottom: NMR spectra of benzoin derived from the reactions of precursor **2** via the reaction of intermediate **1** with benzaldehyde in solution. The  $^{13}\text{C}$ -NMR spectrum (100 MHz,  $\text{CDCl}_3$ ) was recorded after acidic work up of the resulting reaction mixture performing a McFadyen–Stevens reaction and subsequent spiking by adding 0.5 and 1.5 mg of pure **8a**

excess of 10 equiv. of **5** to the reaction mixture. After work up with citric acid to neutralize and remove the bases, we obtained a yellow oil. The nuclear magnetic resonance (NMR) spectrum (Figure 1) shows full conversion of **2** and the spectral signature of benzoin **8a** (R = Ph). The characteristic peak of **8a** in the  $^1\text{H}$ -NMR spectrum is the singlet at 5.96 ppm (b) for the HCOH group. Even though the aromatic region is crowded due to the presence of **5**, the multiplets at 7.93–7.26 ppm (a) can be assigned to **8a**, as evident from spiking experiments with externally prepared authentic **8a** (Figure 1). The strong singlet at 10.03 ppm (d) belongs to the carbonyl proton of remaining **5**, as do the multiplets at 7.91–7.51 ppm (c). In the  $^{13}\text{C}$ -NMR spectrum, we are also able to identify key signals belonging to **8a** with exception of all quarternary and the hydroxyl carbon atoms (Figure 1). Note that the potential background reaction *without 2* did not produce benzoin (Figure S1). We also did not observe the formation of 1,2-diphenylethanol as the C–H-bond insertion product of toluene and **1**. Cannizzaro products typical for McFadyen–Stevens reactions were also not detected.<sup>[26,27]</sup>

For further proof of the formation of **1** in solution, we used acetone (**9**) as a reactant to perform a cross-reaction to that should produce 2-hydroxy-2-methylpropiophenone (**8b**, R=CH<sub>3</sub>) using the same conditions as before. Integration of the  $^1\text{H}$ -NMR spectrum indicates the formation of **5** as the McFadyen–Stevens product and **8b**, which is evident from the multiplets at 8.03–7.51 (overlap with **5**) and 7.50–7.43 ppm (a). The broad singlet at 2.75 ppm corresponds to the OH function (Figure S2). During spiking with pure **8b**, the singlet shifts to low field because of concentration changes. The characteristic signal of **8b** is the singlet of the methyl groups at 1.64 ppm (c). The formation of **8a** as a side product of **1** reacting with **9** was not observed due to the small amount of **5**. In the  $^{13}\text{C}$ -NMR spectrum (Figure S3) the peaks at 133.9, 133.1, 129.8, and 128.6 ppm (b) can be assigned to aromatic carbons of **8**; the methyl groups appear characteristically at 28.6 ppm (d). The carbonyl carbon (a) and COH (c) are not observed without spiking (Figure S3) due to their low intensity. Peaks at 134.6, 129.9, and 129.2 were assigned to **5** *via* comparison with pure **5** (Figure S3).

To avoid the formation of phenylsiloxycarbene as a potential intermediate, we simplified the reaction

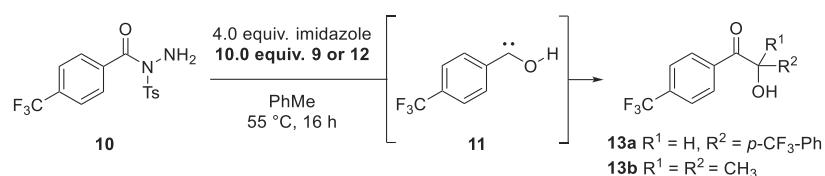
conditions by not using TMS-imidazole. Instead, we used a large excess (4.00 equiv.) of imidazole as the base and extended the reaction time to 16 h at 55 °C. Under these conditions, we also obtained **8a** with an NMR yield of 6% and **8b** with 15%. The yields were determined with *p*-nitrobenzaldehyde as the internal standard.

In a cross-reaction with another phenylhydroxycarbene derivative, we used the para-substituted trifluoromethyl precursor **10** under the simplified reaction conditions (Scheme 2). We attempted to react **11** with 4-trifluoromethylbenzaldehyde (**12**) but did not observe the benzoin derivative **13a**. The electron-withdrawing group of **12** apparently led to a significantly decreased reactivity of the carbonyl moiety.

Success was achieved with **9** as reactant for trapping **11**, leading to hydroxyketone **13b**. Besides the formation of **12** as a side product, we observed in  $^1\text{H}$ -NMR spectrum a singlet at 1.62 ppm, which is characteristic for the methyl groups of **13b** (NMR yield of 14%).

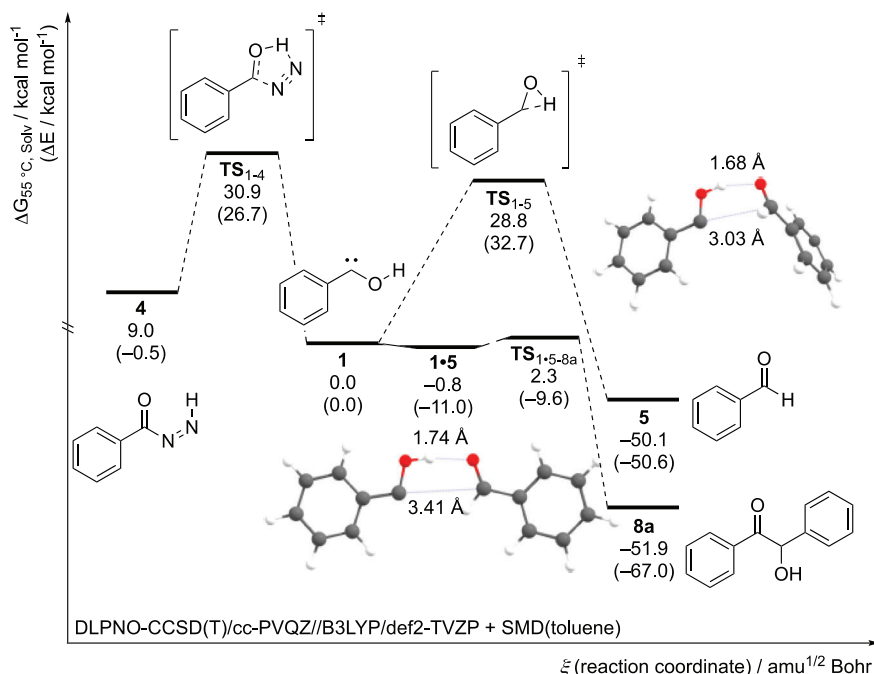
### 3 | COMPUTATIONS

To support our findings, we computed the potential energy hypersurface (PES) of the reactions above. We performed geometry optimizations at the B3LYP/def2-TZVP<sup>[28]</sup> level of theory and improved the relative energies with single point energy computations at DLPNO-CCSD(T)/cc-pVQZ.<sup>[29,30]</sup> With adding thermal corrections for 55 °C and solvation energies with the SMD-solvent model<sup>[31]</sup> with toluene as the solvent, the computed PES should capture the key features of our experiments. Starting from elimination product **4**, **1** forms *via* nitrogen extrusion through a five-membered cyclic transition structure (TS<sub>1-4</sub>) with a free activation barrier of 21.9 kcal mol<sup>-1</sup> ( $\Delta^\ddagger G_{55^\circ\text{C, Solv}}$ , DLPNO-CCSD(T)/cc-pVQZ//B3LYP/def2-TZVP level of theory—these energies are used throughout). In earlier gas-phase studies,<sup>[12]</sup> the activation barrier for CO<sub>2</sub> extrusion of phenylglyoxylic acid (**7**) to **1** is 36.7 kcal mol<sup>-1</sup> (M06-2X/cc-pVDZ). The formation of **8a** in solution follows a concerted reaction mechanism, with **1** forming with **5** C<sub>s</sub>-complex **1•5**, which is 0.8 kcal mol<sup>-1</sup> lower in energy than **1**. This leads straight into a carbonyl-ene like five-center-six-electron transition structure TS<sub>1.5-8a</sub>. After the out-of-plane



**SCHEME 2** Generation of 4-trifluoromethylphenylhydroxycarbene **11** in solution and trapping reactions

**FIGURE 2** Potential energy hypersurface of nitrogen extrusion of **4** to **1** and the reaction with benzaldehyde to benzoin **8a**. Computations at the DLPNO-CCSD(T)/cc-pVQZ//B3LYP/def2-TZVP level of theory with temperature and SMD (toluene)-solvent corrections. N<sub>2</sub> is not depicted but included in the computations



rotation of the benzaldehyde moiety, benzoin **8a** forms (Figure 2).

Besides benzoin formation, **1** can undergo a typical [1,2]-H-shift with a barrier of 28.8 kcal mol<sup>-1</sup> (via  $\text{TS}_{1-5}$ ) to **5** (Figure 2). To rationalize why the yields would be so low for a nearly barrierless reaction, we wondered whether the background quantum mechanical [1,2]-H-tunneling shift from **1** to **5** could effectively compete by consuming **1** at 55 °C. We anticipated that the half-life of 2.5 h of this reaction at 10 K will be significantly shortened at higher temperatures owing to vibrationally assisted tunneling<sup>[32]</sup> and an effectively thinner barrier width.<sup>[9,10]</sup> We computed the tunneling half-lives of the [1,2]-H-shift of **1** and **11** (vide infra) toward the corresponding aldehydes **5** and **12** using canonical variational theory (CVT) in conjunction with small curvature tunneling (SCT)<sup>[33]</sup> at the B3LYP/def2-TZVP level of theory. At a temperature of 55 °C the half-lives are merely  $\tau = 84$  s for **1** and  $\tau = 41$  ns for **11**, respectively. Hence, the low yields for the hydroxyketone products are likely due to a fast tunneling background reaction to the corresponding aldehydes.

In the cross-reaction of **1** with acetone (**9**), a transition structure could not be located, which is likely to be due to the exceedingly low barrier. The reaction proceeds directly to 2-hydroxy-2-methyl-phenylpropanone **13b** (Figure S7).

Introducing a trifluoromethyl group in *para*-position does not affect N<sub>2</sub> extrusion much; the activation barrier is similar to the parent case (Figure S9). The [1,2]-H-shift barrier is slightly higher than for the parent case, resulting in a longer half-life but a transition structure for

this hydrogen shift could also not be located. For the formation of **13a**, the activation barrier is 5.4 kcal mol<sup>-1</sup> (2.3 kcal mol<sup>-1</sup> more than for **8a**). Therefore, the barrier is high enough that only the background reaction toward **5** takes places by a thermal and tunneling<sup>[1,2]</sup> H-shift.

## 4 | CONCLUSIONS

We used new precursors for the McFadyen–Stevens reaction to generate the hydroxycarbenes **1** and **11** in toluene solution *via* base-initiated N<sub>2</sub> extrusion. As the hydroxycarbene intermediates cannot be identified directly spectroscopically owing to their high reactivity and short tunneling half-lives (computed to be 84 s and 41 ns) we reacted them with benzaldehyde or acetone. The formation of their corresponding acetoin *via* a very facile, essentially barrierless carbonyl-ene is suggested as evidence for the intermediacy of the carbenes in solution. Our findings are well supported by computations at the DLPNO-CCSD(T)/cc-pVQZ level of theory.

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## CONFLICT OF INTEREST

The authors declare no competing interests.

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