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Kinetics and mechanism of pyrrolidine buffer-catalyzed fulvene formation

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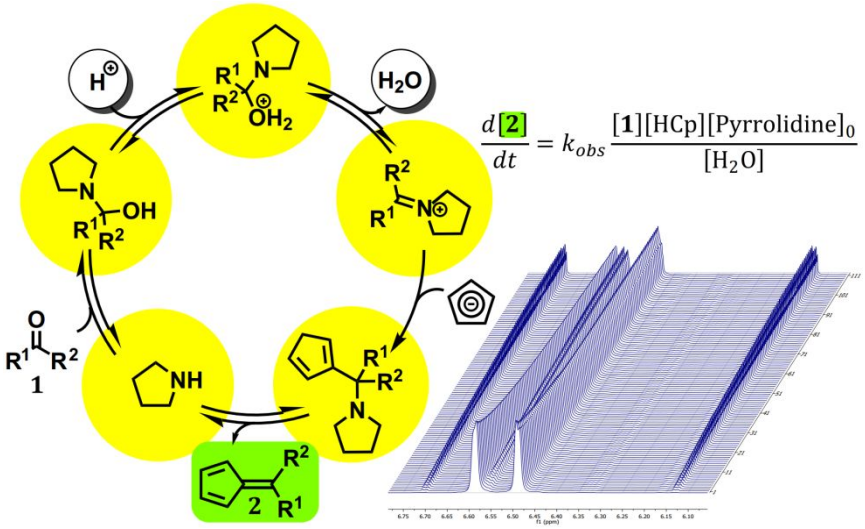


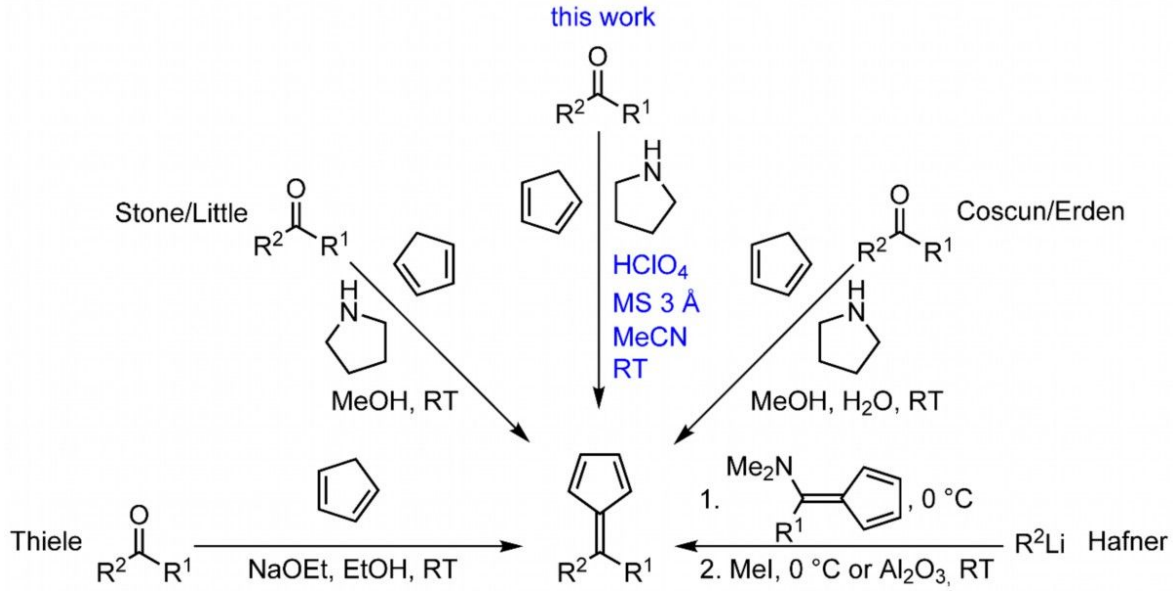
Abstract

Rapid synthesis of fulvenes is achieved using pyrrolidinium/pyrrolidine buffers in anhydrous acetonitrile. Time-dependent UV-Vis absorption and NMR spectroscopy reveal that the rate and yield of fulvene formation depend strongly on both the presence of acid in the medium and the choice of solvent, and are negatively affected by water. Kinetic data have been collected for various substrates, and the synthetic benefits of the adjusted reaction conditions are showcased. Enhancements of reaction rates are found in comparison to literature procedures. α-Unsaturated fulvenes that were previously difficult to access can now be obtained in good yields.

Introduction

Fulvenes are a class of highly reactive intermediates[1,2] with unusual electronic properties[3] and two main applications: the creation of complex polycyclic frameworks through cycloaddition reactions[4-14] and the synthesis of substituted cyclopentadienyl derivatives via nucleophilic addition.[7,15-17] Despite the current interest in these reactions, little has changed in fulvene synthesis methods since Thiele first prepared them in 1900 via condensation of cyclopentadiene and an aldehyde or ketone in presence of sodium ethanolate (Scheme 1).[18] A multistep synthesis was developed by Hafner in 1964, specifically targeting highly electrophilic aldehydes and even enabling the synthesis of the unsubstituted fulvene.[19] Today's

de facto standard is the protocol developed by Stone and Little in 1984,[20] using pyrrolidine or another secondary amine as base, with typical reaction times of 12 min to 48 h in methanol. This reaction is usually accompanied by the formation of various side products resulting from unwanted cycloadditions, and shows significantly decreased yields in the case of even mildly sterically demanding substrates. More recent studies by Erden *et al.* investigated the influence of added water, molecular sieves or tertiary amines on the reaction rates and yields[21] and formulated the rapid and efficient synthesis of specific derivatives, in particular vinylfulvenes.[22] The positive effect of water on iminium-catalyzed reactions in alcoholic solvents has been explained by a shift of the equilibrium between the participating aldehydes and their dialkyl acetals and by assisting the liberation of the catalyst from the products.[23]

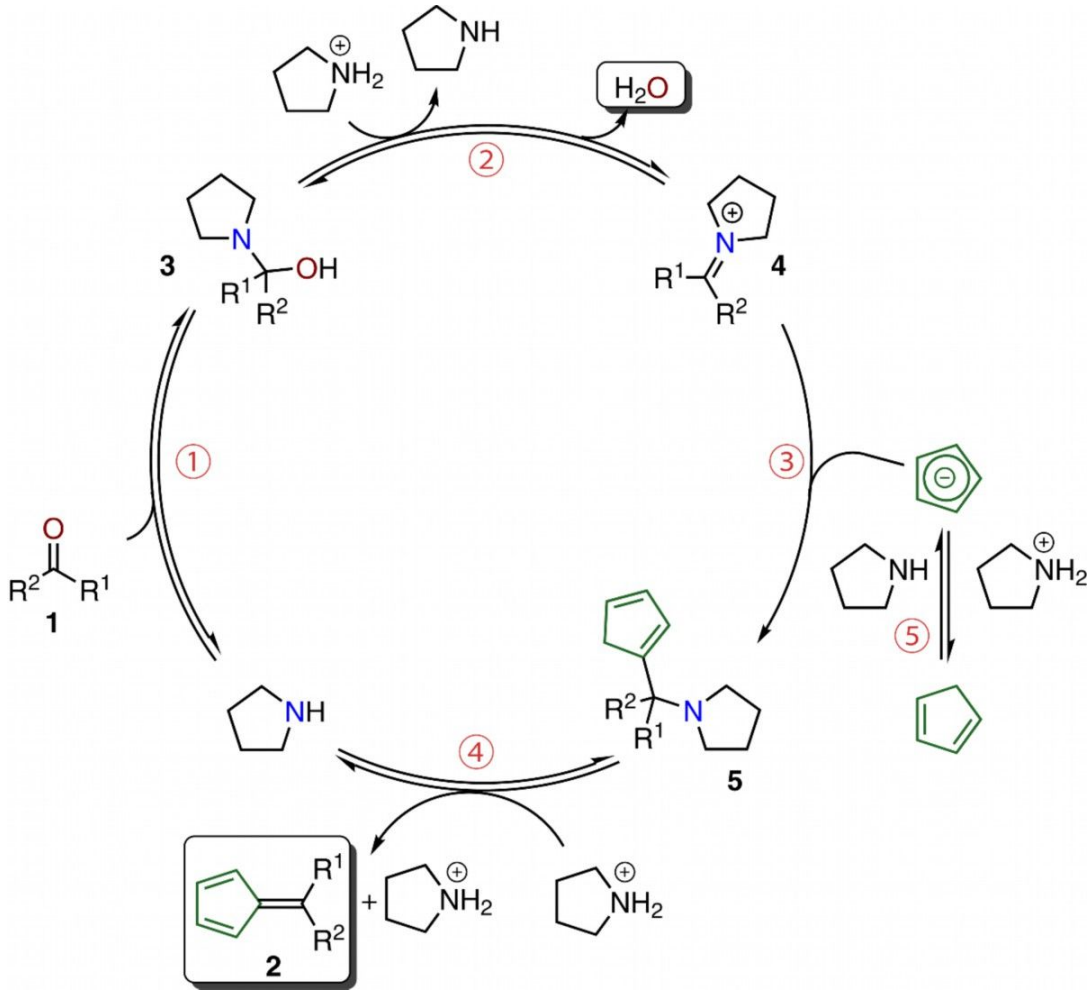


Scheme 1 Routes for the synthesis of fulvenes.

In the context of our pursuit of polycyclopentadienyl-based ligands for organometallic complexes, we explored fulvenes as precursors for cyclopentadienyl groups and thus were motivated to explore the limits of the currently known synthesis routes towards fulvenes. Scattered anecdotal reports[20,24,25] on the rate- or yield-enhancing effect of the addition of various protic species to the secondary amine-catalyzed reaction prompted us to more systematically investigate fulvene synthesis in a buffered medium. Such conditions are indeed known to be beneficial for standard Knoevenagel reactions[26,27] to which fulvene synthesis is closely related. Buffered media were also very recently successfully employed for the organocatalytic synthesis of chiral fulvenes.[28-30] In this work, we demonstrate that it is indeed possible to significantly increase the formation rate of certain fulvenes by employing a pyrrolidine-buffered acetonitrile solution. A kinetic investigation of the catalyzed reactions of two different groups of substrates by NMR and UV-Vis spectroscopy yielded a mechanistic model that rationalizes previous observations. For a first group of substrates, namely 4-substituted benzaldehydes (**1a–e**), only a phenomenological description based on the mechanistic model could be established due to the complexity of the observed reaction network. However, for a second group of substrates, comprising the sterically hindered pivalaldehyde (**1f**), acetone (**1g**), acetophenone (**1h**) and para-substituted acetophenones (**1i–l**), a quantitative reaction kinetic model was derived and tested. Based on this model, we devise a synthesis protocol towards a wide range of substituted fulvenes that results in high yields and purities particularly for the second group of substrates. Side reactions as well as the limitations and substrate-specific optimizations of our synthetic protocol are also discussed.

Results and Discussion

Drawing from the thoroughly investigated mechanism of the Knoevenagel reaction,[31] and in particular from the work of Guyot and Kergomard,[32,33] we propose the formation of fulvenes to proceed via a four-step mechanism, detailed in Scheme 2: the addition of the pyrrolidine catalyst (step ①) is followed by acid-catalyzed elimination of water from the hemi-aminal to form the iminium (step ②), addition of deprotonated cyclopentadiene (step ③) and finally the acid-catalyzed elimination of pyrrolidine (step ④). Direct involvement of cyclopentadiene as nucleophile can be excluded as the iminium **4** undergoes no reaction with cyclopentadiene in the absence of a base.[20]

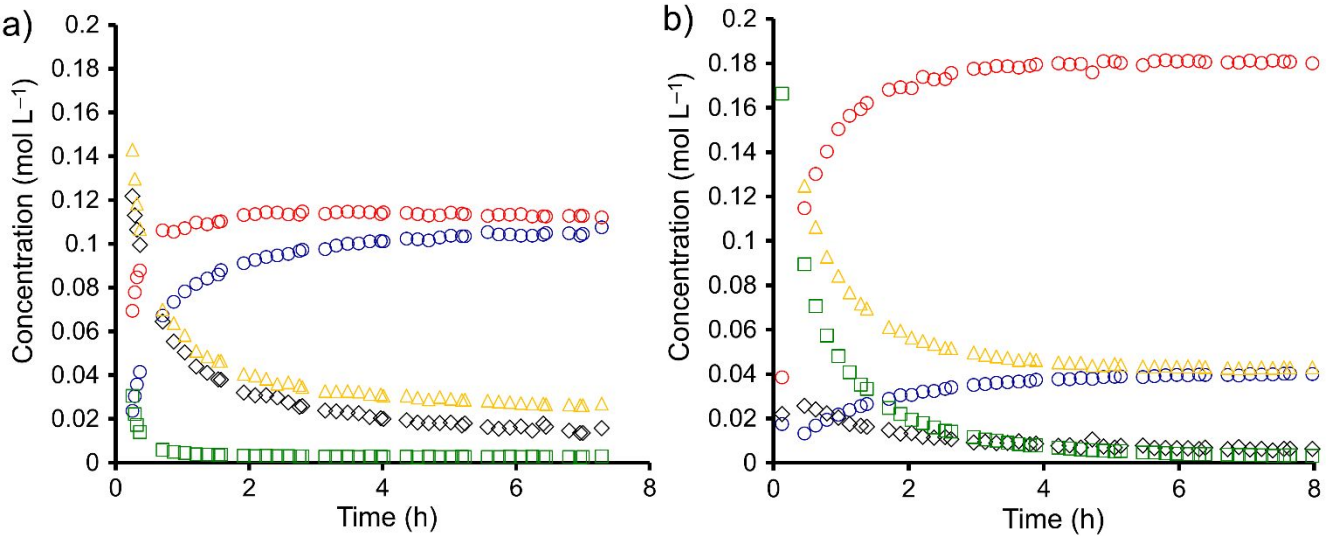


Scheme 2 Catalytic cycle of the pyrrolidine-buffer catalyzed fulvene formation.

Fulvene formation has been reported to be fully reversible for bulky cyclopentadiene derivatives,[34,35] where the final fulvene concentration could be expected to be inversely proportional to water concentration. Furthermore, the formation of ring-deuterated fulvenes from pre-formed fulvenes in the presence of pyrrolidine in CD_3OD indicates the reversibility of step ④ under such conditions.[20] However, at least in the case of pivalaldehyde, on which we initially focused in this study, a final conversion of 100 % is observed for all tested conditions, although addition of water to the reaction solution significantly decelerates the reaction. Therefore, one of the steps ① – ③ must necessarily be irreversible.

Benzaldehydes

To our initial disappointment, for the first group of substrates (benzaldehyde and its 4-substituted derivatives) the use of a pyrrolidinium-pyrrolidine buffer in acetonitrile showed no improvement over the Stone/Little method as modified by Erden (Scheme 1; Table 1, entries **1a**–**e**). NMR investigation of the reaction kinetics (Figure 1) of these substrates indicates the immediate formation of the hemi-aminal (**3a**), iminium (**4a**) and aminal (**6a**) derivatives (see Scheme 2, as well as Scheme S1 in the Supplementary Information for a full representation of side reactions).



Exp.	[**HCp**] / mol·L^{-1}	[**1a**] / mol·L^{-1}	[**Pyr**]$_0$ / mol·L^{-1}	[**HPyr**]$_0$ / mol·L^{-1}
a)	0.24	0.22	0.38	0.038
b)	0.26	0.22	0.082	0.008

Figure 1 Formation of 6-phenylfulvene **2a** (○) by reaction of benzaldehyde **1a** (□) with cyclopentadiene (△) in the presence of an excess (a) and catalytic (b) amount of pyrrolidine and pyrrolidinium perchlorate in acetonitrile, as monitored by ^{1}H NMR. Benzaldehyde is transformed in its pyrrolidine aminal adducts (**3a** and **6a**) (◇, step ① in Scheme 2). 1-(Cyclopentadienylphenylmethyl)pyrrolidine **5a** (○) also forms by addition of pyrrolidine to **2a** (step ④ in Scheme 2).

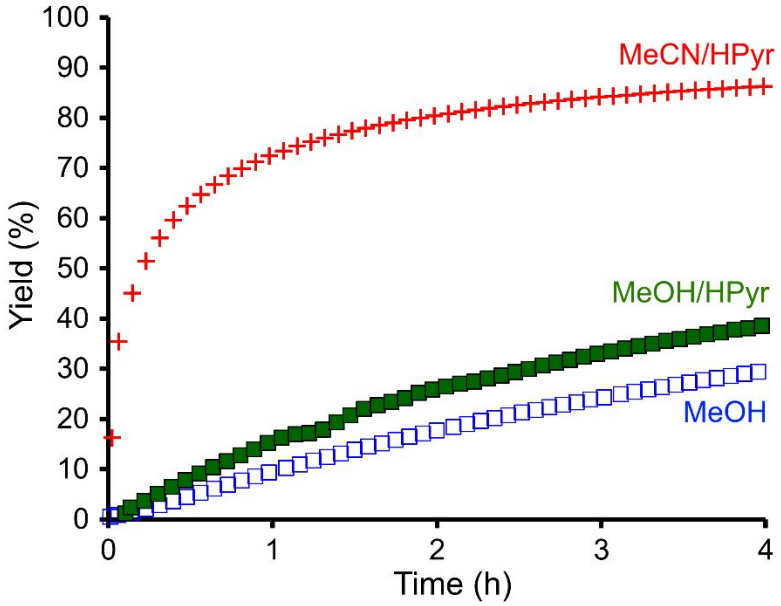
As evident from Figure 1, equilibria ①, ② and ③ are shifted away from the carbonyl **1a** (□) and significant quantities of pyrrolidine aminal adducts (**3a** and **6a,** ◇) are rapidly formed, in agreement with its increased electrophilicity compared to e.g. acetophenone (**1h**). Mirroring that effect, equilibrium ④ is shifted away from the fulvene **2a** (○), and the amine-cyclopentadiene species **5a** (○) forms in significant amounts. Species **5a** forms slower than the corresponding fulvene, and its final concentration scales with the initial pyrrolidine concentration. Although a fraction of the pyrrolidine participates in the formation of **5a,** for substoichiometric pyrrolidine amounts (Figure 1 b) a turnover number of the catalyst pyrrolidine of greater than 1 is observed, indicating reversibility of step ④. In agreement with these observations, we also found that contrarily to the second group of substrates discussed below, the rate of fulvene formation shows a buffer concentration-dependent maximum (at 1 equivalent of pyrrolidine): low catalyst concentrations lead to low reaction rates, but too high concentrations shift the equilibrium in step ④ further away from the product. To obtain near-quantitative yields in short reaction times for moderate catalyst loadings, equilibrium ④ can be shifted back by subsequent reactions with additional electrophiles.[19] For example, addition of methyl iodide to a 4-methoxybenzaldehyde (**1b**)-based reaction

mixture converts species **5b** to the desired fulvene **2b** (Figure S2). Therefore, we recommend the use of low catalyst loadings or subsequent work-up steps[36] for the synthesis of fulvenes from benzaldehydes **1a**–**e**.

Pivalaldehyde

Contrary to the benzaldehydes discussed above, the less electrophilic, sterically hindered substrate pivalaldehyde (**1f**, R^1 = ^{t}Bu, R^2 = H) results in significantly smaller amounts of intermediates present in the reaction mixture, and 1-(cyclopentadienyl-*tert*-butylmethyl)pyrrolidine **5f** cannot be detected by reaction progress NMR. Here, the only intermediate species existing in significant amounts, trackable by ^{1}H NMR, is the corresponding iminium ion **4f** (see Figure S5).

Compared to the reaction of benzaldehydes under Stone/Little conditions[20] (Scheme 1), only a moderate reactivity is observed for pivalaldehyde (**1f**) due to the bulkiness of the substrate. In our effort to enhance fulvene formation from sterically hindered aldehydes we selected pivalaldehyde (**1f**) as our primary model substrate. In a similar search for a more effective method for fulvene formation from a sterically hindered aliphatic aldehyde, van Hijfte and Little[25] found the addition of acid to a methanolic reaction solution to be beneficial. To compare our approach using buffered acetonitrile with the latter method and standard Stone/Little conditions, three measurements of the kinetics of reactions representing the three different protocols for fulvene synthesis were conducted (Figure 2).



	[**HCp**] / mol·L^{-1}	[**1f**] / mol·L^{-1}	[**Pyr**]$_0$ / mol·L^{-1}	[**HPyr**]$_0$ / mol·L^{-1}	Solvent	Method
+	0.15	0.15	0.70	0.05	MeCN	this report
■	0.15	0.15	0.70	0.05	MeOH	van Hijfte/Little[25]
□	0.15	0.15	0.70	0	MeOH	Stone/Little[20]

Figure 2 Formation of 6-*tert*-butylfulvene **2f** by reaction of pivalaldehyde **1f** with cyclopentadiene in the presence of pyrrolidine, as followed by ^{1}H NMR.

The use of buffered acetonitrile strongly enhanced the rate of fulvene formation in comparison to both reference methods, while addition of pyrrolidinium perchlorate (0.3 eq.) to the pyrrolidine-catalyzed (4.3 eq.) reaction of pivalaldehyde with cyclopentadiene in methanol did only slightly improve the reaction

rate (Figure 2). Monitoring the reaction in CD_3OD via ^1H NMR confirmed the expected formation of significant amounts of acetal and hemi-acetal as well as aminal of pivalaldehyde, irrespective of the presence of acid, thus decreasing the reactivity of the carbonyl.[37,38] Deliberate addition of acid, eliminating the need for methanol as a proton source, allowed turning to acetonitrile as the solvent of choice.[39] Indeed, whereas aprotic solvents such as diethyl ether, THF and acetonitrile have been demonstrated to be inferior solvents compared to methanol under standard Stone/Little conditions,[21] we observed an increase of the initial rate of formation of 6-*tert*-butylfulvene (**2f**, R^1 = *t*Bu, R^2 = H) by a factor of 25 upon combined solvent change to acetonitrile and addition of acid (see Figure 2).

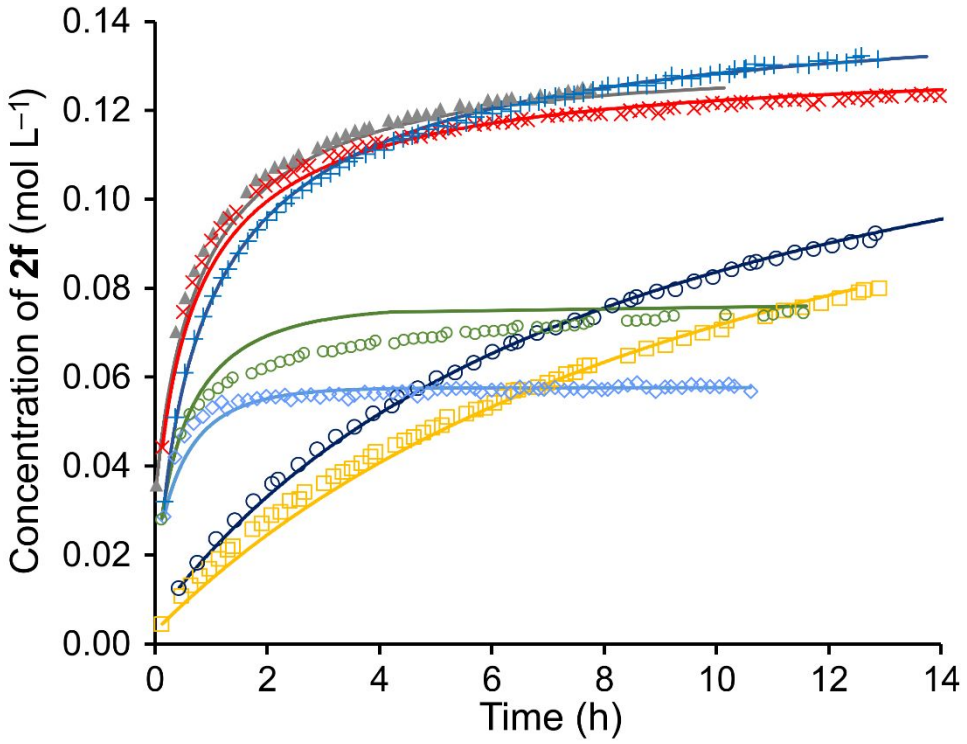
To gain further insight into the mechanism of fulvene formation under such conditions, two series of ^1H NMR kinetic measurements using different initial concentrations of pivalaldehyde **1f**, cyclopentadiene, pyrrolidine, acid and water were performed. Different kinetic models for fulvene formation that can be derived from the mechanism shown in Scheme 2 were tested for the two full datasets.

The correct kinetic model needs to account for a number of findings: The afore-mentioned reversibility of step ④ (*a*) and presence of an irreversible step in the mechanism of fulvene formation, at least observed in case of pivalaldehyde **1f** (*b*). (*c*) Furthermore, the addition of water slows down the reaction, meaning that step ② must be reversible. (*d*) Only minor amounts of intermediates **3**–**5** were detected, implying that both pyrrolidine and pyrrolidinium concentrations remain approximately constant throughout the reaction. (*e*) Increasing the initial concentrations of **1f** and cyclopentadiene each accelerates the reaction. (*f*) The reaction rates are also proportional to the concentrations of pyrrolidine. (*g*) As long as a minimal amount of acid is present to catalyze the elimination steps ② and ④, no effect of the actual acid concentration on the reaction rate is observed. (*h*) Proton exchange reactions, such as the deprotonation of cyclopentadiene (step ⑤), are assumed to be fast equilibria under our buffered conditions.

Different simplified kinetic models resulting from the assumption that only one of the steps ①–④ is rate-limiting were considered; only the scenario in which step ③ is rate-limiting and irreversible is in line with (*a*) – (*g*). With step ③ as the sole rate-determining step, a differential rate law has been derived from the mechanism presented in Scheme 2 (see Supplementary Information for details):

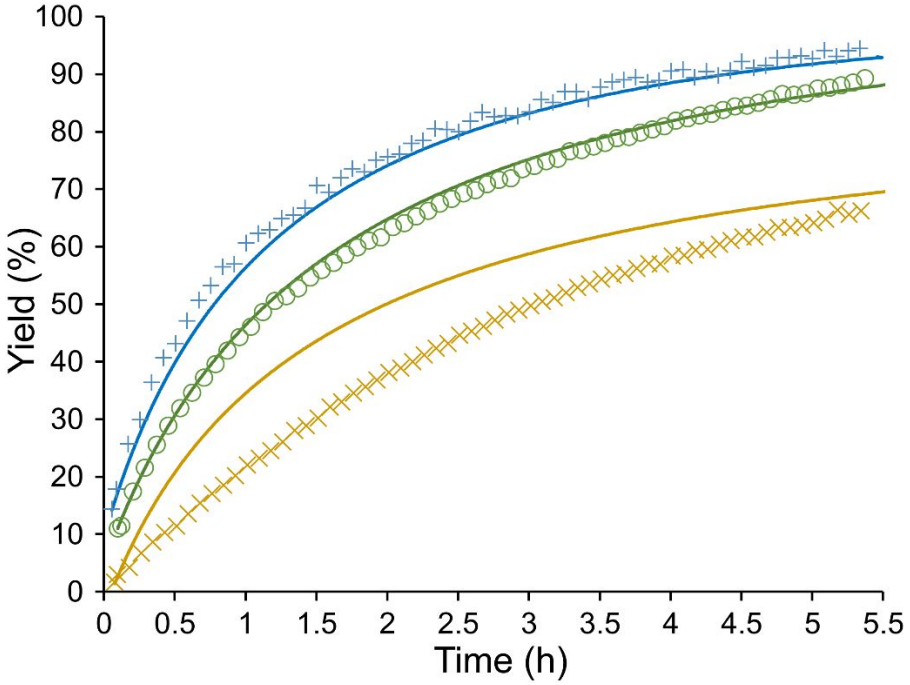
$$\frac{d[\mathbf{2}]}{dt} = k_{\text{obs}} \frac{[\mathbf{1}][\text{HCp}][\text{Pyrrolidine}]_0}{[\text{H}_2\text{O}]} \qquad (1)$$

Here, the observed rate constant k_{obs} is the product of the equilibrium constants for steps ①, ② and ⑤ as well as the rate constant for step ③, $k_{obs} = K_{①}K_{②}K_{⑤}k_{③}$ (see Supplementary Information). Analytical resolution of equation (1) provided a $t = f([\mathbf{2}])$ relation (see Supplementary Information). In the following kinetic analyses, the apparent rate constant k_{obs} (common to all experiments for a given substrate) and the initial water concentration $[H_2O]_0$ (if not directly determined via NMR) are the only free parameters and were determined from a least-squares fit to the experimental data. The simplified model allowed for a satisfactory fit of all datasets obtained for pivalaldehyde **1f** with a minimum of free parameters (Figures 3, 4 and S4).



Exp.		[HCp] / mol·L^{-1}	[1f] / mol·L^{-1}	[Pyr]$_0$ / mol·L^{-1}	[H$_2$O]$_{0,NMR}$ / mol·L^{-1}
a	▲	0.128	0.157	0.594	0.100
b	×	0.138	0.129	0.565	0.071
c	○	0.146	0.161	0.614	**2.064**
d	□	0.137	0.181	0.579	**3.860**
e	◇	**0.058**	0.155	0.589	0.077
f	○	0.140	**0.076**	0.624	0.074
g	+	0.141	0.155	**0.266**	0.047

Figure 3 Variation of reactants, pyrrolidine and water concentrations in the formation of 6-*tert*-butylfulvene **2f** from pivalaldehyde **1f** and cyclopentadiene in the presence of pyrrolidinium perchlorate (a–f: 0.06 M, g: 0,03 M) in acetonitrile, monitored by ^{1}H NMR. Water was deliberately added to experiments c and d. Solid curves represent best fits ($k_{obs,\mathbf{1f}}$ = (7.4±0.1)×10^{-4} s^{-1} M^{-1}) of experiments a–e and g to eq. (1), the curve for the deviating measurement f was extrapolated using the corresponding measured initial concentrations and the same k_{obs}. The water concentration of run d was used as a fitting parameter, obtaining an effective water concentration [H$_2$O]$_{0,eff}$ = (2.9±0.2) M.[40] We attribute the observed systematic deviations to the formation of side products during the reaction (see SI for discussion). Bold table entries highlight intentional concentration deviations between the experiments.



Exp.		[HCp] / mol·L^{-1}	[1f] / mol·L^{-1}	[Pyr]$_0$ / mol·L^{-1}	[HPyr]$_0$ / mol·L^{-1}	[H_2O] / mol·L^{-1}
a	○	0.062	0.114	0.66	0.06	0.2 ± 0.1
b	+	0.063	0.101	0.60	0.03	0.2 ± 0.1
c	×	0.074	0.110	0.53	-	0.2

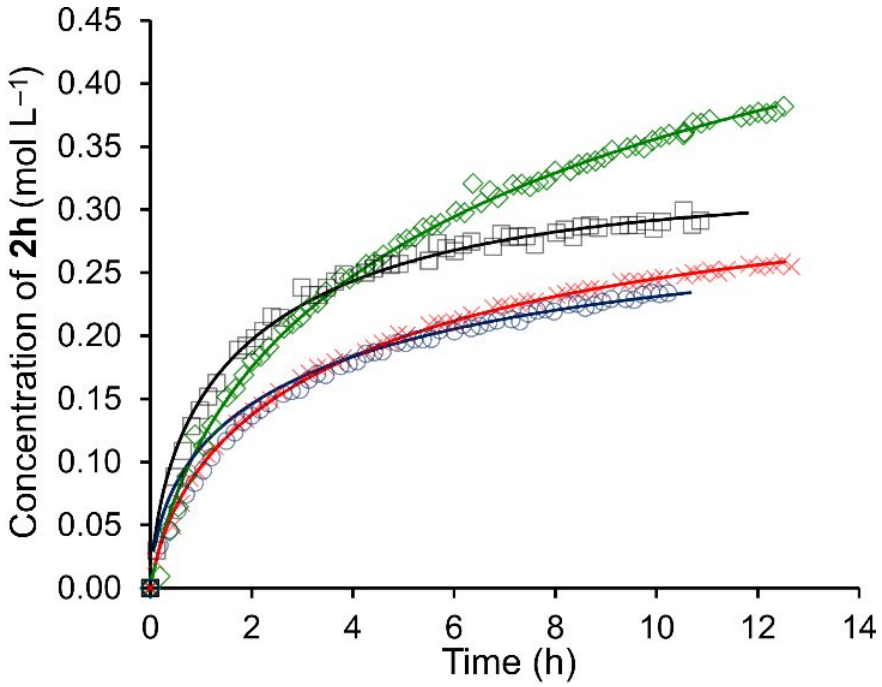
Figure 4 Variation of the acid concentration in the formation of 6-*tert*-butylfulvene **2f** from pivalaldehyde **1f** and cyclopentadiene in the presence of pyrrolidine and variable amounts of pyrrolidinium perchlorate in acetonitrile, monitored by ^{1}H NMR. Solid lines were generated using eq. (1) with $k_{obs,1f}$ = (7.4±0.1)×10^{-4} s^{-1} M^{-1} obtained from the measurements presented in Figure 3, using the water contents of measurement a and b as fitting parameters. The curve corresponding to experiment c was extrapolated using the water content determined directly via ^{1}H-NMR.[40]

The phenomenological kinetic model and eq. (1) imply that removing water from the reaction medium, *e.g.* by addition of molecular sieves, will increase the reaction rate and yield, as side reactions will become less significant. Additionally, while an increase of the amount of base catalyst linearly increases the reaction rate, only a minute amount of acid needs to be present. Indeed, we confirmed that changing the acid concentration (as long as some is present) does not affect the kinetics of the reaction (Figure 4, experiments a and b), in agreement with the non-involvement of the acid in the rate-determining step ③. When no acid is used, the rate-determining step (and possibly the entire mechanism) changes, and the slower reaction observed does not follow the rate law for buffer-catalyzed fulvene formation (eq. (1)), as showcased by the strongly deviating extrapolated curve for experiment c in Figure 4.

Based on these results, for the synthesis of fulvenes from sterically hindered aldehydes comparable to pivalaldehyde **1f** in good yields we recommend the use of a catalytic amount of pyrrolidine, a small amount of acid and an excess of cyclopentadiene, which minimizes side reactions. High catalyst concentrations in the presence of excess aldehyde lead to the formation of dialkylaminomethyl-substituted fulvenes originating from the reaction of 1-(cyclopentadienyl-*tert*-butylmethyl)pyrrolidine (**5f**) with additional **1f** (*cf.* Supplementary Information). Furthermore, we advise continually removing water from the reaction mixture in order to accelerate fulvene formation.

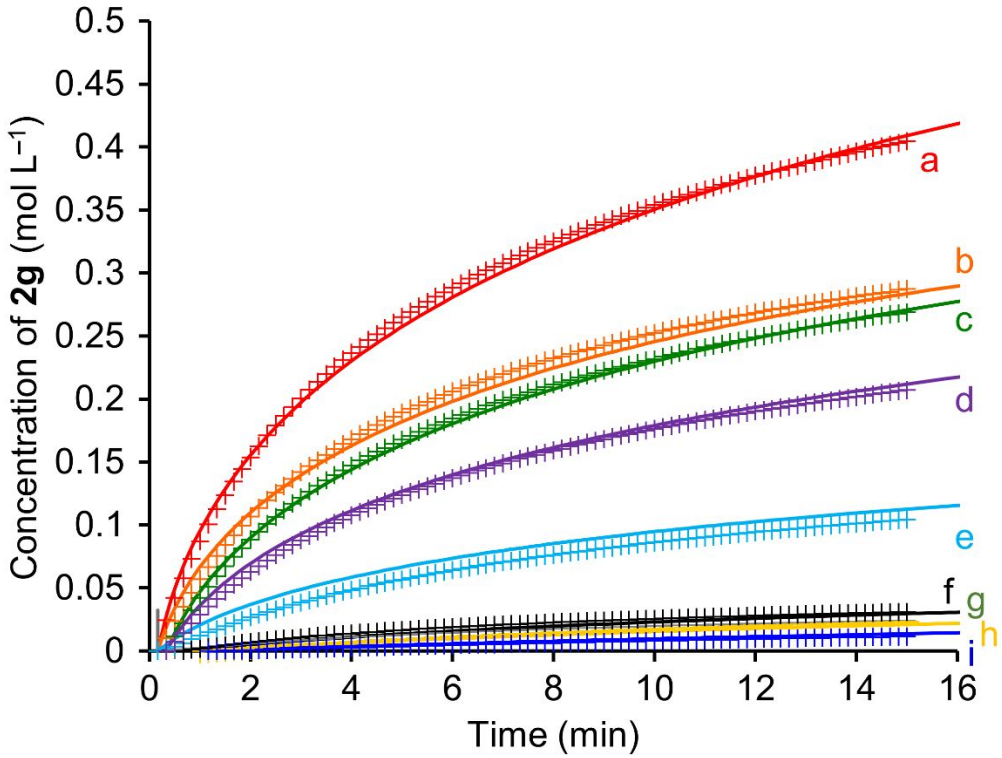
Ketones

The proposed reaction mechanism was also compared against the kinetics of the reaction of two other substrates, acetone (**1g**, R^1 = R^2 = Me) and acetophenone (**1h**, R^1 = Ph, R^2 = Me), varying the concentrations of the reagents and pyrrolidine, and the amount of water added to the medium. The slower reactions of acetophenone were monitored via ^{1}H NMR (see Figure 5). This was impractical for faster reactions involving acetone, where the formation of the yellow-colored fulvenes was followed via UV-visible spectroscopy (see Figure 6).



Exp.		[**1h**] / mol·L^{-1}	[**HCp**] / mol·L^{-1}	[**Pyr**]$_0$ / mol·L^{-1}	[**HPyr**] / mol·L^{-1}	[**H$_2$O**]$_{0,fit}$ / mol·L^{-1}
a	×	0.993	0.303	0.875	0.094	0.052±0.007
b	□	0.971	0.312	1.841	0.200	0.035±0.008
c	○	0.499	0.280	1.815	0.197	0.013±0.005
d	◊	0.980	0.570	0.874	0.096	0.11±0.01

Figure 5 Formation of 6-methyl-6-phenylfulvene **2h** from acetophenone **1h** and cyclopentadiene in the presence of pyrrolidine/pyrrolidinium perchlorate in acetonitrile, monitored by ^{1}H NMR. The solid curve represents the least-squares fit ($k_{obs,\mathbf{1h}}$ = (1.34±0.05)×10^{-5} s^{-1} M^{-1}) of the experimental data using eq. (1); the initial solvent water concentration was used as an individual fitting parameter for each run.[40]



Exp.	[**1g**] / mol·L^{-1}	[**HCp**] / mol·L^{-1}	[**Pyr**]$_0$ / 10^{-3} mol·L^{-1}	[**Hpyr**] / 10^{-3} mol·L^{-1}
a	0.97	0.87	86	77
b	1.01	0.45	89	79
c	0.50	0.90	89	79
d	0.52	0.47	92	83
e	0.27	0.24	96	86
f	0.100	0.085	92	83
g	0.102	0.086	71	84
h	0.104	0.088	48	86
i	0.106	0.090	24	88

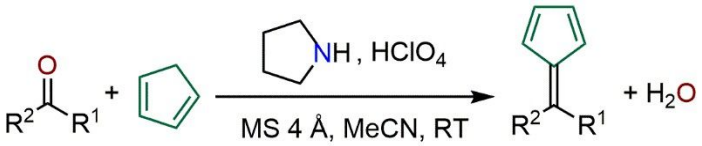
Figure 6 Formation of 6,6-dimethylfulvene **2g** from acetone **1g** and cyclopentadiene (**HCp**) in the presence of pyrrolidine (**Pyr**) and pyrrolidinium perchlorate (**Hpyr**) in acetonitrile, followed by UV-visible spectroscopy. Solid curves represent best fits ($k_{obs,\mathbf{1g}}$ = (4.5±0.5)×10^{-3} s^{-1} M^{-1}, initial solvent water concentration: 0.043±0.001 M) of the experimental data to eq. (1).

The apparent rate constant sharply decreases from acetone **1g** ($k_{obs,\mathbf{1g}}$ = (4.5±0.5)×10^{-3} s^{-1} M^{-1}) to pivalaldehyde **1f** ($k_{obs,\mathbf{1f}}$ = (7.4±0.1)×10^{-4} s^{-1} M^{-1}) and acetophenone **1h** ($k_{obs,\mathbf{1h}}$ = (1.34±0.05)×10^{-5} s^{-1} M^{-1}), as expected for the increasing steric hindrance at the electrophilic center. Corroborating the assignment of the addition step ③ as the rate-determining step, the reaction is accelerated by the addition of an electron-withdrawing group to acetophenone **1h** ($k_{obs,\mathbf{1l}}$ = (2.11±0.07)×10^{-5} s^{-1} M^{-1} for 4-bromoacetophenone **1l**, Figure S7) and decelerated by the addition of electron-donating groups ($k_{obs,\mathbf{1i}}$ = (9.1±0.2)×10^{-6} s^{-1} M^{-1} for 4-methoxyacetophenone **1i** and $k_{obs,\mathbf{1j}}$ = (1.17±0.01)×10^{-5} s^{-1} M^{-1} for 4-methylacetophenone **1j**; Figures S8, S9).

Synthetic applications

We generally recommend a buffer ratio of 20:1 (base:acid), easily formed by addition of a small amount of perchloric acid to the reaction medium containing around 1 equivalent of pyrrolidine. Under those conditions, a variety of fulvenes was obtained (see Table 1) on the gram scale and without need for chromatographic purification. Of particular interest are the high yields obtained in the case of sterically demanding substrates such as pivalaldehyde (**1f**) and acetophenone (**1h**) and enolizable carbonyl derivatives such as acetophenone (**1h**), 2-methylbutanal (**1m**) or 2-phenylpropanal (**1n**). In the latter case, a rapid reaction is of crucial importance if the fulvene is to be isolated before it isomerizes to the vinylcyclopentadienes (see SI). Further improvement is possible by lowering the temperature, which decreases the isomerization rate relative to the formation rate of the fulvene. With increasing steric demand and decreasing electrophilicity of the substrates of the second group, higher catalyst concentrations are advisable. On the other hand, for highly electrophilic substrates (*e.g.* benzaldehydes, first group) a high buffer concentration must be avoided, as reversible addition of the pyrrolidine to the resulting electrophilic fulvenes leads to reduction of the yields. To reduce the formation of dialkylaminomethyl-substituted fulvenes by addition of intermediate **5** to the carbonyl, a side reaction competing with step ③, the use of excess cyclopentadiene is recommended for all substrates.

Table 1 Synthesis of fulvenes



Carbonyl	R^1	R^2	Pyrrolidine (equiv.)	$HClO_4$ (equiv.)	Reaction time	Yield	Reported yield
1a	Ph	H	0.10	0.01	1 d	65 %	70 %[20], 97 %[21]
1b	*p*-MeO-C_6H_4	H	0.10	0.01	1 d	95 %	97 %[21]
1c	*p*-MeS-C_6H_4	H	0.10	0.01	1 d	91 %	-
1d	*p*-OH-C_6H_4	H	1.10	0	1 d	85 %	85 %[21]
1e	*p*-OH-*m*-MeO-C_6H_3	H	1.07	0	1 d	78 %	-
1f	^{t}Bu	H	0.10	0.01	3 h	69 %	90 %[20]
1h	Ph	Me	1.01	0.14	1 d	98 %	74 %[41, *b*]
1i	*p*-MeO-C_6H_4	Me	1.00	0.10	1 d	78 %	61 %[42]
1j	*p*-Me-C_6H_4	Me	1.00	0.10	1 d	88 %	82 %[21]
1k	*p*-Cl-C_6H_4	Me	1.00	0.10	1 d	69 %	56 %[43, *c*]
1l	*p*-Br-C_6H_4	Me	1.00	0.10	1 d	71 %	68 %[43, *c*]
1m	^{s}Bu	H	0.08	0.014	1 d	86 %	-
			0.08	0.014	6 h	91 %	
1n	CHMePh	H	0.99	0.17	1 d	0 %	24 %[44, *b*]
			1.01	1.42	1 d[a]	73 %	
1o	^{n}Bu	H	0.10	0.01	1 d	68 %	56 %[45, *b*]

a) T = –25 °C. *b*) Yield reported following distillation of product. *c*) Product purification not reported.

In line with the collected kinetic data, particular improvements are observed for the different acetophenones tested, as for those substrates the reaction can be rationalized by our model. However, some limitations remain: Diphenylfulvene could not be obtained (from benzophenone) in any appreciable amount, probably because the formation of the iminium intermediate is impossible for steric reasons. Thiele's method (Scheme 1) remains the only known method to prepare this fulvene, and is recommended for all cases where our standard conditions fail because of sterical requirements, providing the corresponding carbonyl is not enolizable. Finally, despite the significant improvement obtained by our method in the fulvene yields from some enolizable carbonyl derivatives (acetophenone **1h,** 2-methylbutanal **1m** and 2-phenylpropanal **1n**), for highly α-acidic carbonyl such as 2-phenylethanal the initially formed enamines are too stable and isomerization to the corresponding vinylcyclopentadienes is too fast for isolation of the fulvenes in any significant amount.

Conclusion

In summary, an improved fulvene synthesis method has been developed, based on the use of a catalyst buffer instead of the traditional pure base, and a shift from acetal-forming methanol to acetonitrile as solvent. Despite some limitations in the case of very bulky or highly electrophilic carbonyl substrates, the increased reaction speed of the reported method allows for the formation of fulvene in high yields and with a high degree of purity. In several cases the as-of-yet difficult isolation of fulvenes derived from enolizable carbonyls now has become possible.

Experimental section

Materials and methods: All preparative reactions were conducted under argon to limit decomposition of the oxygen and heat-sensitive fulvenes. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz Bruker or Agilent spectrometers, using $CDCl_3$ or CD_3CN as solvent. UV spectra were measured in quartz cuvettes using a J&M TIDAS spectrometer in a range from 300 nm to 600 nm. All NMR kinetic measurements were conducted at room temperature 25±1 °C. UV-kinetics were conducted at 21±2 °C. UV-Vis spectroscopy samples were prepared in argon-flushed vessels that were quickly capped immediately after mixing. Non-deuterated solvents (methanol and acetonitrile) where used as received. Fresh commercial samples of benzaldehyde, 2-methylbutanal, 2,2-dimethylpropanal (pivalaldehyde), 2-phenylpropanal and 2-phenylethanal (hyacinthine) were used for fulvene synthesis as received. Pyrrolidine was used as received for NMR- and synthetic experiments or after fractional distillation under argon for UV-kinetics (to avoid interference from colored pyrrolidine oxidation products). Cyclopentadiene was cracked from stabilizer-containing dimer and kept cool and under argon.[46] Diluted stock solutions in acetonitrile stored under argon at –25 °C were used within a week of storage. Molecular sieves (3 Å, VWR) and silica gel (Macherey-Nagel) were used as received. Pyrrolidinium perchlorate was prepared according to the literature.[47] Thin-layer chromatography (TLC) was performed with diethyl ether/pentane mixtures on silica gel-coated aluminum sheets (60 mesh, with F_{254} fluorescence indicator). Details on the sample preparation and data acquisition by ^{1}H-NMR and UV-vis are presented in the Supplementary Information.

General procedure for the synthesis of non-polar fulvenes: To a solution of pyrrolidine (see Table 1 for amounts) and pyrrolidinium perchlorate in acetonitrile (10 mL) were added cyclopentadiene (1.0 mL, 12 mmol), the appropriate carbonyl derivative (0.65 mL or 0.65 g) and molecular sieves (3 Å, 3 g). The reaction was followed by TLC. Upon completion, the reaction mixture was extracted with pentane (4 × 50 mL). The pentane phase was washed with diluted HCl (10 mL, 10 %), filtered through a small amount of silica and the solvent subsequently removed under vacuum.

General procedure for the synthesis of fulvenes containing hydroxyl groups: To a solution of pyrrolidine (see Table 1 for amounts) and pyrrolidinium perchlorate in acetonitrile (2 mL) were added cyclopentadiene (1.0 mL, 12 mmol), the appropriate carbonyl derivative (0.65 mL of liquid carbonyls or 0.65 g of solid carbonyls) and molecular sieves (3 Å, 3 g). The reaction was followed by TLC. Upon completion, the reaction mixture was acidified with diluted HCl (10 ml, 10 %), diluted with water (10 mL) and extracted with diethyl ether (4 × 20 mL). The organic phases were filtered through a small amount of silica and the solvent subsequently removed under vacuum.

6-Phenylfulvene (**2a**): The product **2a** was obtained as an orange solid (643 mg, 65 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.58 (m, 2 H), 7.46–7.40 (m, 2 H), 7.40–7.35 (m, 1 H), 7.24 (br s, 1 H), 6.75–6.71 (m, 1 H), 6.71–6.67 (m, 1 H), 6.56–6.52 (m, 1 H), 6.38–6.34 (m, 1 H) ppm; ^{13}C NMR δ = 145.3 (s), 138.2 (s), 136.4 (s), 130.8 (s), 130.7 (s), 129.0 (s), 128.7 (s), 127.2 (s), 120.4 (s) ppm. The NMR spectral data are in accordance with those reported in the literature.[21]

6-(4'-Methoxyphenyl)fulvene (**2b**): The product **2b** was obtained as an orange solid (932 mg, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.56 (m, 2 H), 7.17 (br s, 1 H), 6.99–6.92 (m, 2 H), 6.75–6.71 (m, 1 H), 6.69–6.65 (m, 1 H), 6.51–6.47 (m, 1 H), 6.35–6.31 (m, 1 H), 3.87 (s, 3 H) ppm; ^{13}C NMR δ = 160.6 (s), 138.3 (s), 134.9 (s), 132.5 (s), 129.8 (s), 129.6 (s), 127.4 (s), 119.9 (s), 114.3 (s), 55.4 (s) ppm. The NMR spectral data are in accordance with those reported in the literature.[21]

6-(4'-Methylthiophenyl)fulvene (**2c**): The product **2c** was obtained as an orange solid (892 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.50 (m, 2 H), 7.32–7.24 (m, 2 H), 7.16 (br s, 1 H), 6.73–6.69 (m, 2 H), 6.69–6.65 (m, 1 H), 6.53–6.50 (m, 1 H), 6.35–6.31 (m, 1 H), 2.53 (s, 3 H) ppm; ^{13}C NMR δ = 144.5 (s), 140.7 (s), 137.7 (s), 135.3 (s), 131.1 (s), 130.4 (s), 127.3 (s), 125.9 (s), 119.9 (s), 15.17 (s) ppm.

6-(4'-Hydroxyphenyl)fulvene (**1d**): The product **2d** was obtained as an orange solid (879 mg, 85 %). ^{1}H NMR (400 MHz, CD_3CN): δ = 7.58–7.54 (m, 2 H), 7.32 (br s, 1 H), 7.19 (br s, 1 H), 6.91–6.86 (m, 2 H), 6.76–6.72 (m, 1 H), 6.66–6.62 (m, 1 H), 6.45–6.41 (m, 1 H), 6.32–6.29 (m, 1 H) ppm. The NMR spectral data are in accordance with those reported in the literature.[21]

6-(4'-Hydroxy-3'-methoxyphenyl)fulvene (**1e**): The product **2e** was obtained as an orange solid (708 mg, 78 %). ^{1}H NMR (400 MHz, CD_3CN): δ = 7.28–7.22 (m, 1 H), 7.22–7.15 (m, 2 H), 6.93–6.84 (m, 1 H), 6.70–6.61 (m, 1 H), 6.48–6.42 (m, 1 H), 6.42–6.27 (m, 1 H), 3.91 (s, 3 H) ppm; ^{13}C NMR δ = 149.3 (s), 148.6 (s), 143.9 (s), 139.9 (s), 135.9 (s), 130.3 (s), 129.9 (s), 128.7 (s), 126.3 (s), 120.6 (s), 116.3 (s), 114.7 (s), 56.8 (s) ppm.

6-*tert*-Butylfulvene (**2f**): The product **2f** was obtained as a yellow oil (553 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70–6.67 (m, 1 H), 6.62–6.58 (m, 1 H), 6.45 (br s, 1 H), 6.42–6.39 (m, 1 H), 6.19–6.15 (m, 1 H), 1.30 (s, 9 H) ppm; ^{13}C NMR δ = 153.7 (s), 134.0 (s), 128.5 (s), 128.4 (s), 119.8 (s), 35.9 (s), 30.9 (s) ppm. UV-Vis (ε): λ = 355 nm (38 M^{-1} cm^{-1}). The ^{1}H-NMR spectral data are in accordance with those reported in the literature.[20]

6-Phenyl-6-methylfulvene (**2h**): The product **2h** was obtained as an orange oil (916 mg, 98 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 5 H), 6.56–6.53 (m, 1 H), 6.51–6.45 (m, 1 H), 6.42–6.36 (m, 1 H), 6.13–6.07 (m, 1 H), 2.45 (s, 3 H) ppm; ^{13}C NMR δ = 149.7 (s), 141.9 (s), 131.8 (s), 131.4 (s), 129.1 (s), 129.1 (s), 128.1 (s), 127.8 (s), 123.6 (s), 121.0 (s), 22.55 (s) ppm.

6-(4'-Bromophenyl)-6-methylfulven (**2l**): The product **2l** was obtained as an orange viscous oil (573 mg, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.52 (m, 2 H), 7.31–7.25 (m, 2 H), 6.67–6.63 (m,

1 H), 6.62–6.58 (m, 1 H), 6.54–6.50 (m, 1 H), 6.18–6.14 (m, 1 H), 2.54 (s, 3 H) ppm; ^{13}C NMR δ = 148.0 (s), 143.7 (s), 140.8 (s) 132.2 (s), 132.0 (s), 131.1 (s), 130.8 (s), 123.3 (s), 122.6 (s), 121.1 (s), 22.42 (s) ppm. The ^{13}C-NMR spectral data are in accordance with those reported in the literature.[43]

6-(4'-Methoxyphenyl)-6-methylfulvene (**2i**): The product **2i** was obtained as an orange viscous oil (757 mg, 78 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.34 (m, 2 H), 6.98–6.91 (m, 2 H), 6.68–6.62 (m, 1 H), 6.60–6.55 (m, 1 H), 6.53–6.48 (m, 1 H), 6.29–6.23 (m, 1 H), 3.87 (s, 3 H), 2.56 (s, 3 H) ppm; ^{13}C NMR δ = 159.9 (s), 149.8 (s), 142.6 (s) 134.4 (s), 131.3 (s), 131.1 (s), 130.9 (s), 123.7 (s), 121.1 (s), 113.4 (s), 55.33 (s), 22.55 (s) ppm. The NMR spectral data are in accordance with those reported in the literature.[42]

6-(4'-Methylphenyl)-6-methylfulvene (**2j**): The product **2j** was obtained as an orange oil (779 mg, 88 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.25 (m, 2 H), 7.21–7.15 (m, 2 H), 6.66–6.60 (m, 1 H), 6.58–6.52 (m, 1 H), 6.50–6.44 (m, 1 H), 6.24–6.18 (m, 1 H), 2.51 (s, 3 H), 2.37 (s, 3 H) ppm; ^{13}C NMR δ = 150.1 (s), 143.1 (s), 139.2 (s) 138.3 (s), 131.3 (s), 129.4 (s), 128.7 (s), 123.8 (s), 121.09 (s), 113.4 (s), 22.65 (s), 21.28 (s) ppm. The NMR spectral data are in accordance with those reported in the literature.[21]

6-(4'-Chlorophenyl)-6-methylfulvene (**2k**): The product **2k** was obtained as an orange viscous oil (703 mg, 69 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.18 (m, 4 H), 6.41–6.37 (m, 1 H), 6.49–6.46 (m, 1 H), 6.41–6.37 (m, 1 H), 6.05–6.02 (m, 1 H), 2.41 (s, 3 H) ppm; ^{13}C NMR δ = 148.0 (s), 143.8 (s), 140.4 (s), 134.3 (s), 132.2 (s), 131.9 (s), 130.5 (s), 128.1 (s), 123.3 (s), 121.1 (s), 22.46 (s) ppm. The ^{13}C-NMR spectral data are in accordance with those reported in the literature.[43]

6-*sec*-Butylfulvene (**2m**): The product **2m** was obtained as a yellow oil (742 mg, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.60–6.55 (m, 1 H), 6.55–6.52 (m, 1 H), 6.52–6.48 (m, 2 H), 6.27–6.20 (m, 2 H), 2.85–2.70 (m, 1 H), 1.61–1.39 (m, 2 H), 1.20–1.13 (d, J = 6.6 Hz, 3 H), 0.93 (t, J = 7.5 Hz, 3 H) ppm; ^{13}C NMR δ = 148.7 (s), 144.8 (s), 132.9 (s), 130.6 (s), 125.7 (s), 119.6(s), 37.3 (s), 30.1 (s), 20.9 (s), 12.0 (s) ppm.

6-(1'-Phenylethyl)fulvene (**2n**): The product **2n** was obtained as a yellow oil (660 mg, 73 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.29 (m, 4 H), 7.29–7.21 (m, 1 H), 6.70–6.59 (m, 2 H), 6.57–6.43 (m, 2 H), 6.30–6.21 (m, 1 H), 4.27–4.13 (m, 1 H), 1.57 (d, J = 7.0 Hz, 3 H) ppm; ^{13}C NMR δ = 145.8 (s), 144.1 (s), 144.0 (s), 133.6 (s), 131.1 (s), 128.6 (s), 127.1 (s), 126.5 (s), 126.1 (s), 119.2 (s), 40.8 (s), 21.4 (s) ppm. The NMR spectral data are in accordance with those reported in the literature.[44]

6-*n*-Butylfulvene (**2o**): The product **2o** was obtained as a yellow oil (556 mg, 68 %). ^{1}H NMR (400 MHz, CD_3CN): δ = 6.60–6.51 (m, 2 H), 6.51–6.42 (m, 2 H), 6.24–6.19 (m, 1 H), 2.61–2.50 (m, 2 H), 1.57–1.48 (m, 2 H), 1.44–1.33 (m, 2 H), 0.94 (t, J = 7.4 Hz, 3 H) ppm; ^{13}C NMR δ = 147.2 (s), 144.5 (s), 133.8 (s), 131.5 (s), 126.7 (s), 120.2 (s), 32.4 (s), 31.4 (s), 23.2 (s), 14.3 (s) ppm. The ^{1}H-NMR spectral data are in accordance with those reported in the literature.[45]

Supplementary material: The following supporting information is available:

Derivation of the rate law and the fitting function for the formation of fulvenes **2a**–**f**; details on the treatment of raw kinetic data, additional NMR kinetic data for the formation of **2i**, **2l** and **2m**; NMR spectra of products **2a** and **2c**–**k**.

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(36) Simpler and more eco-friendly methods than the Hofmann elimination of amines, e.g. filtration through activated alumina, may be used for the removal of pyrrolidine.[19]

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