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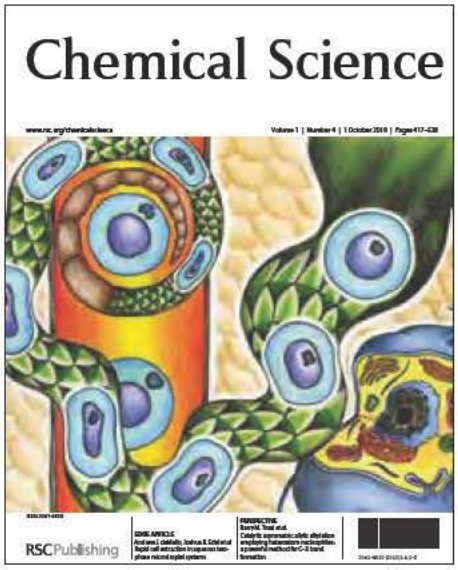

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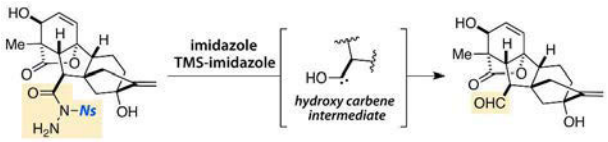

Modified McFadyen-Stevens reaction from *N,N*-acylsulfonyl hydrazine to the corresponding aldehyde was developed. Exploration of the reaction mechanism revealed the intermediacy of hydroxy carbene intermediate. (24 words)

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EDGE ARTICLE

Modified McFadyen-Stevens Reaction for a Versatile Synthesis of Aliphatic/Aromatic Aldehydes: Design, Optimization, and Mechanistic Investigations

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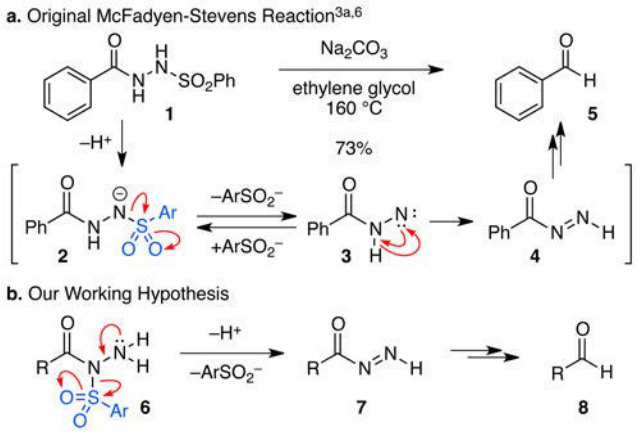
The traditional McFadyen-Stevens reaction requires harsh alkaline reaction conditions, thus precluding application to the synthesis of aliphatic aldehydes. Our modified McFadyen-Stevens reaction enables the transformation from the *N*,*N*-acylsulfonyl hydrazine to the corresponding aldehyde upon treatment with an imidazole–TMS imidazole combination without relying on oxidative or reductive reagents. The reduced basicity and in situ protection of the resulting aldehyde widens the substrate scope to include aliphatic aldehydes, even ones bearing an α-hydrogen atom. Close examination of the side reactions for particular substrates in combination with theoretical considerations via DFT calculations led to a mechanistic understanding of the McFadyen-Stevens reaction involving an acyl diazene and a hydroxy carbene as reasonable intermediates.

Introduction

Aldehydes are one of the most utilized synthetic units because they are important precursors to a variety of structural motifs. Thus, the development of a novel synthetic methodology for preparing this functionality has regained much attention and a number of methods have been established to date. Nonetheless, within the context of synthesizing complex structures and functionalities, it often remains difficult to specify an adequate preparative method for the targeted aldehyde, indicating the need for further development in this field. Most preparative methods have focused on the oxidation of alcohols,[1] and not a reductive approach from the carboxylic acid or its derivatives.[2] Thus, as part of our on-going research toward the development of efficient redox transformations with distinct functional groups, we began exploring novel reductive transformations into aldehydes.

Among the various known methods for transformation of carboxylic acid into aldehyde, the traditional McFadyen-Stevens reaction[3] still holds a unique position. Under the original conditions reported in 1936, *N*,*N'*-acylbenzenesulfonyl hydrazine **1** that is easily prepared via condensation between benzenesulfonyl hydrazide and carboxylic acid is treated with potassium carbonate in ethylene glycol at 160 °C. The aldehyde



Scheme 1. Traditional McFadyen-Stevens reaction and our working hypothesis

is obtained from the corresponding carboxylic acid *without using any oxidants or reductants* (Scheme 1a).[4] Unfortunately, the harsh alkaline reaction conditions, which might cause an aldol reaction or a Cannizzaro reaction, hampered the expansion of the scope to include preparation of aliphatic aldehydes. To solve this problem, several improvements on the reaction conditions have been devised.[5] After Sprecher's first application to synthesize aliphatic aldehyde without an α-hydrogen,[5b] Babad widened the substrate scope to include those bearing an α-hydrogen atom by rapidly distilling the aldehyde from the reaction mixture.[5c] Shechter then reported the merit of flash vacuum pyrolysis (FVP) to prepare volatile aliphatic aldehydes.[5f] Despite these

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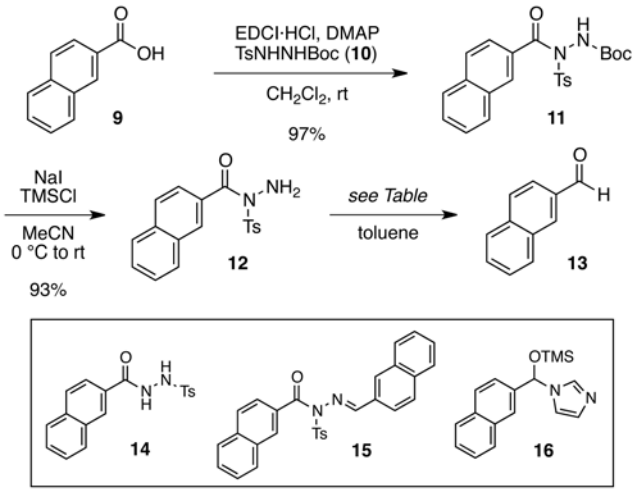
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data and copies of NMR spectral data. CCDC 911911. See DOI: 10.1039/b000000x/

Table 1. Optimization of the reaction conditions.[a]



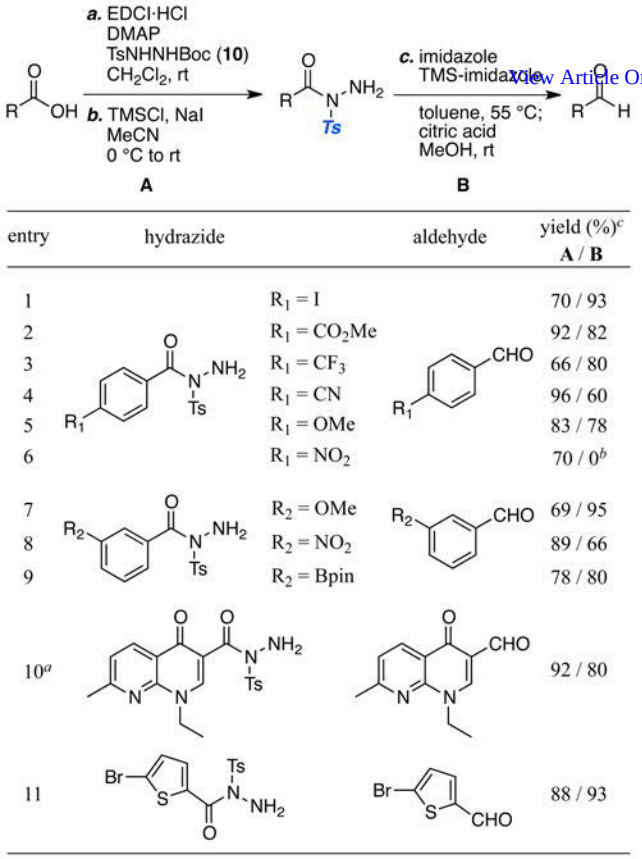
entry	base[b]/additive[c]	temp. (°C)	time (h)	yield (%)[d] 13	14	15
1	–/–	80	18	0	32	30
2	Et_3N/–	80	15	0	65	15
3	DBU/–	rt	0.5	46	45	0
4	*N*-methylimidazole/–	rt	20	35	45	0
5	imidazole/–	rt	18	83	0	0
6	imidazole/–	50	6	87	0	3
7	imidazole/TMS-imidazole	55	4	99	0	0

[a]Reaction was performed under Ar. [b]2.0 eq of base were used. [c]2.0 eq of additive were used. [d]Yield of the isolated product.

improvements and the exclusion of redox reagents, the McFadyen-Stevens reaction of aliphatic substrates remains unpopular.

Herein we disclose a milder preparative method for the acyl diazene intermediate to broaden the scope of this reaction to include base-sensitive aliphatic aldehydes. Craig's seminal mechanistic study[6] indicated that the reversible elimination of the benzenesulfinate ion from **2** and N-H insertion of nitrene **3** to give acyl diazene intermediate **4** can reasonably explain the formation of aldehyde via the McFadyen-Stevens reaction. They proposed that the decomposition of acyl diazene **4** and the concomitant loss of dinitrogen lead to the formation of aldehyde **5**. We planned to change the position of the sulfonyl group as in *N*,*N*-acylsulfonylhydrazine[7] **6** in analogy to our previous studies for preparation of α-diazoacetates[8] and oximes[9] via β-elimination of the sulfinate ion to form hetero-hetero double bonds[10] (Scheme 1b). Because the slow N-H insertion process from nitrene **3** is responsible for the high temperature required in the traditional McFadyen-Stevens reaction,[6] we expected that the more facile elimination of the sulfinate ion from **6**, which would directly lead to the identical acyl diazene **7**, would reduce the reaction temperature. Additionally, because the higher electron density of the neighboring nitrogen atom would facilitate the elimination of a sulfinate ion from **6**, an even weaker base could be employed for the reaction, thereby suppressing the side reactions.

Table 2. Synthesis of aromatic aldehydes.

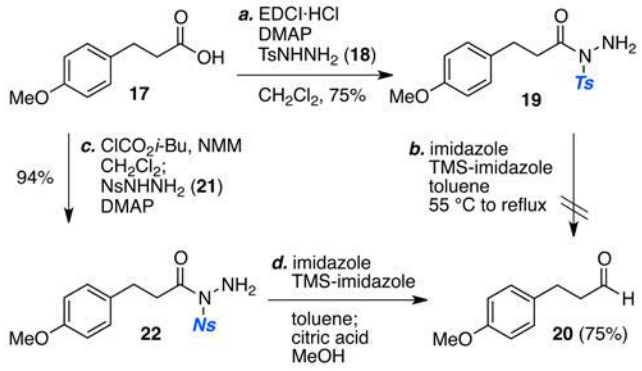


Reagents and conditions: (a) EDCI·HCl (1.2 eq), DMAP (0.10 eq), TsNHNHBoc (**10**, 1.0 eq), CH_2Cl_2, 0 °C to rt; (b) TMSCl (2.0 eq), NaI (3.0 eq), MeCN, 0 °C to rt; (c) imidazole (2.0 eq), TMS-imidazole (2.0 eq), toluene, 55 °C; citric acid (10 eq), MeOH, rt. [a]HATU (1.1 eq) was used in step a. [b]Methyl ester was obtained instead via the formation of acyl imidazole intermediate. [c]Yield of isolated product.

Results and Discussion

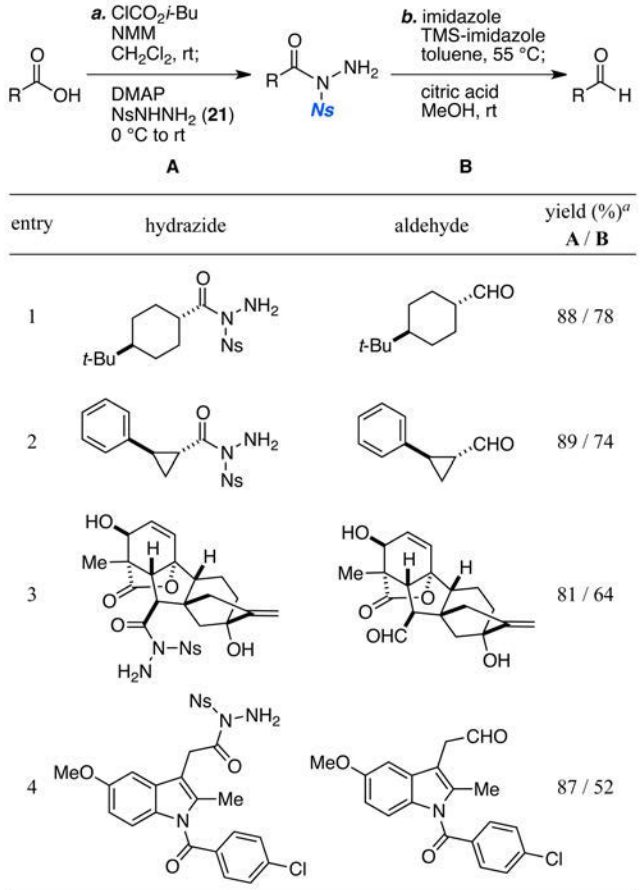
Development of the Reaction Conditions.

We initially examined the synthesis of aromatic aldehyde to investigate the viability of our working hypothesis. To this end, 2-naphthoic acid **9** and *N*,*N'-tert*-butoxycarbonyl-*p*-toluenesulfonyl hydrazine **10** were condensed using modified Bihel's procedure[7b] followed by removal of the Boc group of **11** by treatment with trimethylsilyl iodide to give *N*,*N*-2-naphthoyl-toluenesulfonyl hydrazine **12**. Table 1 shows the results from the attempted synthesis of naphthaldehyde **13** from **12**. Heating in toluene alone or in the presence of Et_3N at 80 °C caused the transposition of the acyl group to the adjacent nitrogen atom to form stable *N*,*N'*-2-naphthoyl-*p*-toluenesulfonyl hydrazine **14** with concomitant formation of a small amount of hydrazone **15**, indicative of the formation of 2-naphthaldehyde **13** (entries 1, 2). Gratifyingly, the desired 2-naphthaldehyde was observed when **12** was treated with DBU or *N*-methylimidazole at room temperature, albeit with the formation of a significant amount of **14** (entries 3, 4). Transformation to aldehyde **13** was most efficiently performed when imidazole was used as the base, with



Scheme 2. Difference between tosyl and nosyl groups for preparation of aliphatic aldehydes. Reagents and conditions: (a) EDCI·HCl (1.2 eq), DMAP (0.2 eq), $TsNHNH_2$ (**18**, 1.2 eq), CH_2Cl_2, rt, 75%; (b) imidazole (2.0 eq), TMS-imidazole (2.0 eq), toluene, 55 °C to reflux; (c) $ClCO_2i$-Bu (1.1 eq), *N*-methylmorpholine (1.1 eq), CH_2Cl_2, rt; $NsNHNH_2$ (**21**, 1.2 eq), DMAP (0.2 eq), 0 °C to rt, 94%; (d) imidazole (2.0 eq), TMS-imidazole (2.0 eq), toluene, 55 °C; citric acid (10 eq), MeOH, rt, 75%.

Table 3. Synthesis of aliphatic aldehydes.



Reagents and conditions: (a) $ClCO_2i$-Bu (1.1 eq), *N*-methylmorpholine (1.1 eq), CH_2Cl_2, rt; $NsNHNH_2$ (**21**, 1.2 eq), DMAP (0.2 eq), 0 °C to rt; (b) imidazole (2.0 eq), TMS-imidazole (2.0 eq), toluene, 55 °C; citric acid (10 eq), MeOH, rt. [a]Yield of isolated and purified product.

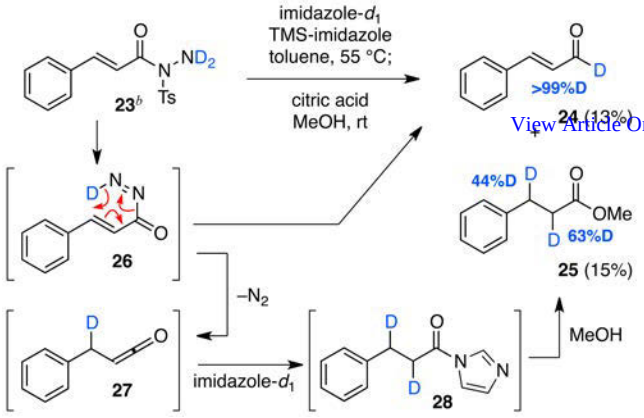
none of the rearranged product observed at room temperature (entry 5). Since acceleration of the reaction at higher temperature resulted in the formation of a small amount of hydrazone **15** (entry 6), in situ protection of the aldehyde was deemed necessary. After extensive experimentation, TMS-imidazole proved to be the ideal reagent to circumvent the formation of hydrazone **15** because facile formation of hemiaminal **16** masked the reactive aldehyde, which, upon acidic workup, regenerated aldehyde **13** in high yield.

We next examined the applicability of this methodology to the other aromatic carboxylic acids (Table 2). Under the standard reaction conditions discussed above, benzoic acids with *para*- (entries 1–5) or *meta*- (entries 7–9) substitutions could be efficiently converted to the corresponding aldehydes. The reaction conditions were mild enough that even the pinacol borate moiety survived the transformation (entry 9). For the substrates with electron withdrawing substituents, the yields were either moderate (entries 3, 8) or, in the case of *p*-nitro group, zero in step B (entry 6) due to the formation of the acyl imidazole, resulting in the formation of the methyl ester after treatment with citric acid in methanol. The quinolone antibiotic nalidixic acid was successfully converted into the corresponding aldehyde[11] without affecting the pyridine and the carbonyl moieties[12] (entry 10). 5-Bromo-2-thiophenecarboxylic acid was also a good substrate (entry 11).

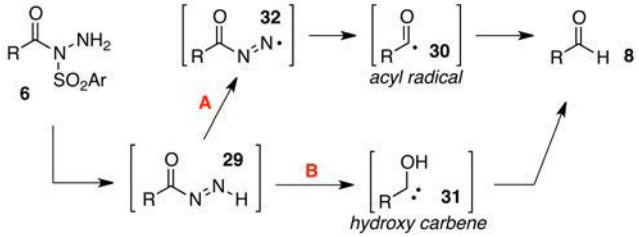
One of the serious limitations of the traditional McFadyen-Stevens reaction is difficulty in preparing aliphatic aldehydes, especially the ones bearing α-hydrogen. Thus, we next envisioned the application of our modified McFadyen-Stevens reaction to aliphatic substrates. To this end, 3-(4-methoxyphenyl)propionic acid **17** was chosen as the substrate. Aliphatic substrate **19** was prepared by condensation with $TsNHNH_2$ in the presence of DMAP according to the report by Tanino and Namba[7f] (Scheme 2). To our disappointment, the reaction of **19** did not proceed under the conditions used to synthesize aromatic aldehydes, even in refluxing toluene. Comparing the ^1H NMR spectra of aromatic substrate **12** and aliphatic substrate **19** revealed a substantial difference between the chemical shifts of the N-H signals (4.6 ppm for **12** and 4.2 ppm for **19**), indicative of the reduced acidity of N-H proton in **19**. Thus, the tosyl group was replaced with a more electron-withdrawing, 2-nitrobenzenesulfonyl (nosyl) group,[13] which is expected to cause more facile elimination of the sulfinate ion. Gratifyingly, use of a nosyl group dramatically increased the reactivity. When treated with imidazole and TMS-imidazole at 55 °C, *N*,*N*-acyl-nosyl hydrazine **22**, prepared via a mixed anhydride method from **17** and 2-nitrobenzenesulfonyl hydrazine **21**,[14] underwent smooth elimination of the sulfinate to give, after an acidic workup with citric acid in methanol, the desired aldehyde **20** in 75% yield. In situ protection of the aldehyde with TMS-imidazole was needed to prevent the formation of the corresponding hydrazone. The above results constitute the establishment of a new McFadyen-Stevens–type reaction, which is applicable to aliphatic aldehyde bearing an α-hydrogen atom.

We next investigated the scope and limitations of the method for synthesis of aliphatic aldehydes. 4-*tert*-Butylcyclohexanecarboxylic acid (Table 3, entry 1) and *trans*-2-phenylcyclopropane-1-carboxylic acid (entry 2), which both bear two alkyl groups at the α-position, were excellent substrates for the two-step transformation into the corresponding aldehydes.

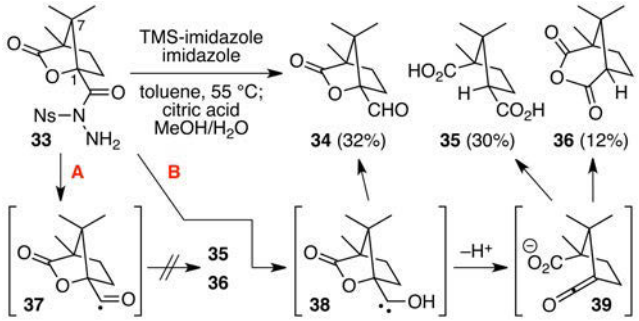
Preparation of gibberellin A_3-7-carboxyaldehyde[15] from gibberellic acid was also examined (entry 3). Thus, gibberellic acid was condensed with $NsNHNH_2$ to afford selectively the desired hydrazide without affecting the two hydroxy groups. After treatment with imidazole and TMS-imidazole, the reaction mixture was treated with citric acid and potassium fluoride in methanol to give gibberellin A_3-7-carboxyaldehyde in 64% yield without cumbersome protection/deprotection steps. Entry 4 represents the transformation of indomethacin into the corresponding aldehyde. Due to the difficulty of this transformation, low yields have been reported for both the one-step reduction of acid chloride[16] and the oxidation of the alcohol.[17] This rather unexpected difficulty was attributed to the unstable nature of the indole acetaldehyde moiety[18] and the presence of the reactive *p*-chlorobenzoyl group.[19] In our case, the reaction successfully gave indomethacin aldehyde in 52% yield. The moderate yield is attributed to the instability of the aldehyde, which slowly decomposed upon standing at room temperature. Thus, we have successfully demonstrated the two-step preparation of aliphatic aldehydes from carboxylic acids via the modified McFadyen-Stevens reaction.



Scheme 3. Evidence of acyldiazene intermediate.[a] Reagents and conditions: imidazole (2.0 eq), TMS-imidazole (2.0 eq), toluene, 55 °C; citric acid (10 eq), MeOH, rt. [a]Methyl cinnamate (49%) was also obtained in the reaction. See supporting information for details. [b]**23** was prepared by treatment with CD_3OD followed by evaporation under reduced pressure. Deuterium content was determined by ^1H NMR analysis.



Scheme 4. Possible reaction pathway of our modified McFadyen-Stevens reaction.



Scheme 5. Evidence against the radical pathway. Reagents and Conditions: imidazole (2.0 eq), TMS-imidazole (2.0 eq), toluene, 55 °C; citric acid (10 eq), MeOH, rt.

Mechanistic Studies.

We next focused on the mechanism of our modified McFadyen-Stevens reaction represented by the transformation of *N,N*-acylsulfonylhydrazine **6** to aldehyde **8**. Initially, we tried to verify the formation of the acyl diazene intermediate from our working hypothesis in Scheme 1b using deuterated cinnamate **23** as a substrate (Scheme 3). When **23** was submitted to the conditions to form the aldehyde, the desired deuterated cinnamaldehyde (**24**) was obtained (13%) with concomitant formation of methyl hydrocinnamate (**25**) in 15% yield bearing the partially deuterated methylenes at the α- and β-positions to the carbonyl functionality. The reaction affording **25** could be reasonably explained by the intermediacy of acyl diazene **26**. Diazene rearrangement[10a-d,20] from **26** would form deuterated ketene **27**, which would subsequently be trapped by imidazole-d_1 to give **28**. **28** would then be transformed into methyl ester **25** during the acidic workup. Hence, this result successfully corroborates the intermediacy of acyl diazene **26**.

For the reaction from **6** to aldehyde **8** via acyl diazene intermediate **29**, two reaction pathways are plausible, namely, via acyl radical **30** or hydroxy carbene **31** (Scheme 4).[21] It has been postulated that acyl radical **30**, which could be generated via acyl diazenyl radical **32**, is the precursor to aldehydes from acyl hydrazides under oxidative conditions of Kalb-Gross–type reactions.[22] A similar scenario involving radical species could reasonably explain the formation of aldehyde in the McFadyen-Stevens reaction (mechanism **A**).[23,24] Craig proposed another viable mechanism where hydroxy carbene intermediate **31** plays a key role.[6] Because hydroxy carbene is a well-known precursor to the corresponding aldehyde,[25] this route is considered as the alternative pathway (mechanism **B**).[6] Thus, we designed an experiment to determine which intermediate is more plausible in our case.

After extensive experimentation, the results using camphanic acid as the substrate cast light on this issue (Scheme 5). Among the three reaction products from **33**—aldehyde **34**, dicarboxylic acid **35**, and cyclic acid anhydride **36**—the latter two, **35** and **36** would indicate cleavage of the C1–O bond. If the reaction involves acyl radical intermediate **37**, C1–C7 cleavage would preferentially proceed to give a tertiary radical instead of C1–O cleavage. Entry 2 of Table 3 also indicates that the cyclopropane ring next to the carbonyl moiety remains intact throughout the reaction, which is inconsistent with the involvement of cyclopropyl carbinyl radical species because cyclopropane would preferentially be opened.[26] In the presence of 1.0 eq of Galvinoxyl free radical, the yield of the reaction from **12** to **13**

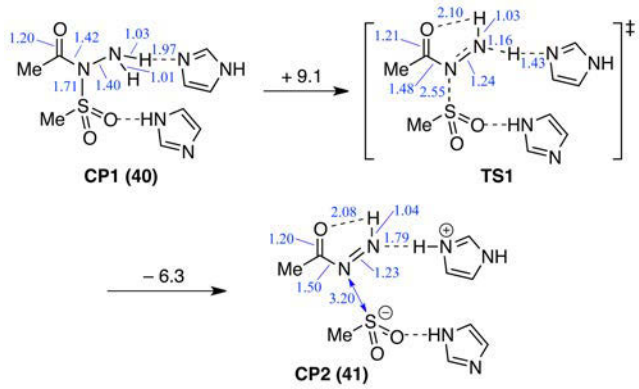


Figure 1. Elimination pathway of the sulfinyl group from acyl hydrazine in the presence of imidazole. Energy changes (ΔG) and bond lengths at the M062X/6-31+G(d) level are shown in kcal/mol and Å, respectively.

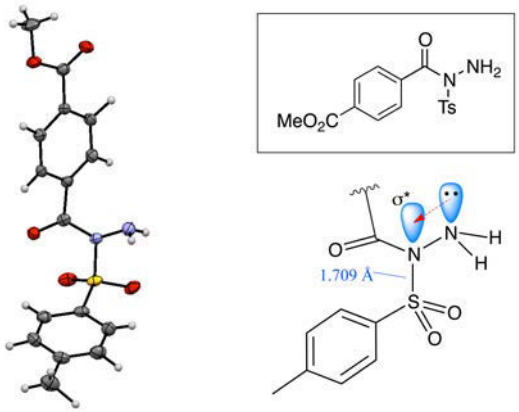


Figure 2. ORTEP drawing of methyl 4-(1-tosylhydrazine-carbonyl)benzoate (Table 2, entry 2, CCDC 911911) and rationale for the elongation of the *N*–*S* bond.

did not change at all, which also contradicts the radical pathway. On the other hand, the scenario involving hydroxy carbene intermediate **38** could rationally explain these experimental results. The formation of **35** and **36** can be understood considering the ring-opening reaction from singlet[27] hydroxy carbene intermediate **38** through the formation of ketene intermediate **39**. Thus, between the two possible mechanisms, the one involving the hydroxy carbene intermediate, not the acyl radical species, should warrant further mechanistic investigations.

To further justify the proposed reaction pathway, density functional theory (DFT) calculations were performed with *N*,*N*-acetylmesylhydrazine **40** as the model substrate. Figure 1 shows the reaction and energy profile of the elimination step to give acyl diazene intermediate **41** at the M062X/6-31+G(d) level. While energetically plausible elimination pathways were not obtained in the absence of base, addition of imidazole substantially influenced the activation energy for the elimination of the sulfinyl group, leading to acyl diazene intermediate **41** (Fig. 1). The low activation energy (+9.1 kcal/mol) could be reasonably explained by the elimination reaction facilitated by the push–pull synergy of the two imidazole molecules through hydrogen bonding. The importance of hydrogen bonding, both as a donor and an acceptor,

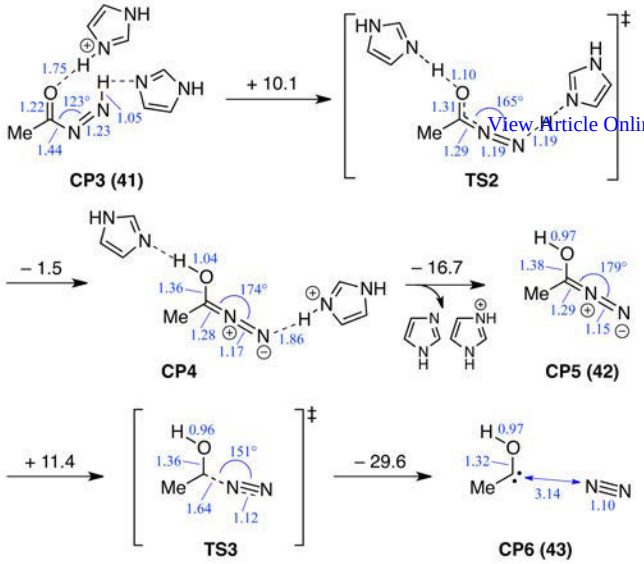


Figure 3. Generation of hydroxy carbene from acyl diazene in the presence of imidazole and imidazolium ion. Energy changes (ΔG), bond lengths, and angles at the M062X/6-31+G(d) level are shown in kcal/mol, Å, and degrees, respectively.

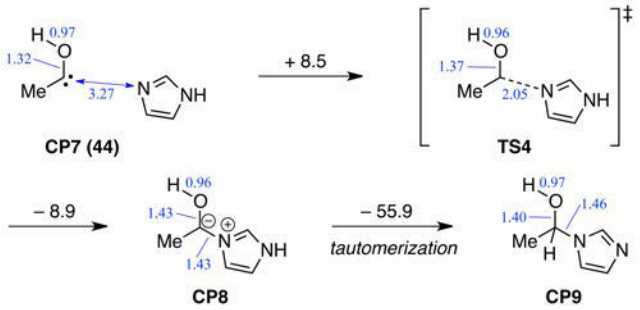


Figure 4. Pathway from hydroxy carbene. Energy changes (ΔG) and bond lengths at the M062X/6-31+G(d) level are shown in kcal/mol and Å, respectively.

was further confirmed by the experimental data employing Et_3N, DBU, or *N*-methylimidazole as a base instead of imidazole (Table 1). These computational results are consistent with the experimental fact that only the imidazole substantially accelerates the elimination step and results in the smooth formation of aldehyde.

X-ray crystallographic analysis of methyl 4-(1-tosylhydrazine-carbonyl)benzoate (Fig. 2) also supports the calculated elimination pathway. The elongated *N*–*S* bond (1.709(2) Å) compared to the ordinary one for a secondary sulfonamide (*ca.* 1.642 Å)[28] suggests that the lone pair electron of the terminal nitrogen atom is situated collaterally next to the σ* orbital of the *N*–*S* bond. The orientation of these orbitals appeared to be ideal for elimination. In fact, a complex of **40** and two imidazoles (i.e. **CP1**) in the DFT calculation (Fig. 1) had a similar orientation for the sulfonylhydrazine moiety with the almost identical length for the *N*–*S* bond (1.71 Å), confirming the validity of the calculation.

We next examined the elimination of dinitrogen from acyl diazene **41** to the corresponding hydroxy carbene by means of a DFT calculation. Figure 3 shows the most likely reaction pathway where a proton from the terminal nitrogen migrates to the

carbonyl oxygen and subsequent tautomerization with the aid of imidazole/imidazolium to afford α-hydroxy diazoalkane intermediate **42** with a low activation energy (+10.1 kcal/mol). Disconnection of the diazo moiety from **42** occurs smoothly along the intrinsic reaction coordinate with a low activation energy (11.4 kcal/mol) and leads to a hydroxy carbene. The large stabilization energy of the last stage (–29.6 kcal/mol) can be attributed to the formation of a dinitrogen molecule, which provides the driving force for the present reaction. These computational results further support the involvement of the hydroxy carbene intermediate.

Since the above investigations indicate that the hydroxy carbene is the probable intermediate, we speculate that the hydroxy carbene would react with the imidazole to gain further stabilization.[29] A DFT calculation on this transformation supports our assumption (Fig. 4). The reaction of hydroxy carbene **43** with imidazole occurs smoothly with a low energy barrier, and affords the hemiaminal with a great stabilization (–55.9 kcal/mol). This adduct would rapidly react with TMS-imidazole to give the final intermediate, silylated hemiaminal, which is similar to **16**. The DFT results support the experimental difficulty in trapping the hydroxy carbene intermediate.[30] In addition to the overall large energetic gain, the fact that each step in the present reaction requires a rather low activation energy supports the experimental result that the reaction proceeds even at room temperature.

Conclusions

In conclusion, our modified McFadyen-Stevens reaction enables the transformation from carboxylic acid to the corresponding aldehyde by means of the decomposition of *N*,*N*-acylsulfonyl hydrazine in the presence of imidazole and TMS-imidazole. This protocol has expanded the scope of the substrates to include aliphatic aldehydes bearing an α-hydrogen atom, which were previously difficult to prepare. The side reactions on the special aliphatic carboxylic acids provided insights into the mechanism for our modified McFadyen-Stevens reaction, demonstrating the intermediacy of a hydroxy carbene. DFT calculations further confirm the mode of action where the reaction proceeds via the decomposition of an acyl diazene and a subsequent reaction between imidazole and hydroxy carbene intermediate. The present mechanistic study also indicates that the traditional McFadyen-Stevens reaction would also involve the hydroxy carbene intermediate. We believe this newly introduced aldehyde synthesis, which does not require an oxidative or reductive transformation, will play an important role in the synthesis of multifunctional complex molecules.

Computational Details

All calculations were carried with the Gaussian 09 program package.[31] The global reaction route mapping method (GRRM)[32] based on Gaussian 09 was utilized to locate all local equilibrium and TS structures as well as to optimize the geometries. The molecular structures and harmonic vibrational frequencies were obtained using the hybrid density functional method based on M062X.[33] We used 6–31+G* for the other atoms. Geometry optimization and vibrational analysis were performed at the same level. All stationary points were optimized without symmetry assumptions and were characterized by normal coordinate analysis at the same level of theory (number of imaginary frequencies, NIMAG, 0 for minima and 1 for TSs). The intrinsic reaction coordinate (IRC) method was used to track the minimum energy paths from transition structures to the corresponding local minima.[34]

Experimental Section

Preparation of 2-Naphthaldehyde (13).

To a solution of 2-naphthoic acid (**9**, 172 mg, 1.00 mmol) in dichloromethane (10 mL) at room temperature was added *N*-ethyl-*N*'-(3-dimethylaminopropyl) carbodiimide hydrochloride (230.0 mg, 1.20 mmol), *N*,*N*-dimethylamino pyridine (12.2 mg, 0.10 mmol) and *N*-tosyl-*N'*-*tert*-buthoxycarbonylhydrazine (**10**, 286 mg, 1.00 mmol). After stirring for 2 h, the solution was quenched with saturated NH_4Cl aq. (5 mL). The resulting mixture was partitioned between EtOAc (20 mL) and water (5 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (20 mL) twice. The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (15% EtOAc in *n*-hexane) to afford *tert*-butyl 2-(naphthalene-2-carbonyl)-2-tosylhydrazinecarboxylate (**11**) as a white solid. R*f* = 0.53 (*n*-hexane/EtOAc = 2:1, UV, Ce-PMA); Mp 157.5–157.8 °C; IR (neat, cm^{-1}) 1734, 1715, 1700, 1507, 1249; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.15 (s, 1H), 8.09 (d, *J* = 8.2 Hz, 2H), 7.85-7.81 (m, 3H), 7.63 (br, 1H), 7.59-7.50 (m, 2H), 7.37 (d, *J* = 7.8 Hz, 2H), 7.19 (brs, 1H), 2.46 (s, 3H), 1.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 154.2, 147.1, 145.3, 134.9, 134.2, 130.7, 129.7, 129.2, 128.8, 128.4, 83.3, 28.0, 21.7; HRMS calcd for $C_{20}H_{21}N_3NaO_5S$ ([M + Na^+]) 463.1304, found 463.1299. To a solution of **11** (436 mg, 0.99 mmol) in acetonitrile (7.0 mL, 0.07 M) at 0 °C was added NaI (3.0 eq) and TMSCl (2.0 eq). After stirring for 30 min at room temperature, the solution was quenched with saturated aq. NH_4Cl (5 mL). The resulting mixture was partitioned between EtOAc (30 mL) and water (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (30 mL) twice. The combined organic extract was washed with saturated $Na_2S_2O_3$ aq. (20 mL) and brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (20 to 50%, EtOAc in *n*-hexane,) to afford *N*,*N*-(naphthalene-2-carbonyl)tosylhydrazide (**12**, 313 mg, 0.92 mmol, 93%) as white crystals. R*f* = 0.68 (*n*-hexane/EtOAc = 2:1, UV, Ce-PMA); Mp 160.5–160.9 °C; IR (neat, cm^{-1}) 1681, 1354, 1291, 1168; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.31 (s, 1H), 7.93-7.86 (m, 5H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.61-7.52 (m, 2H), 7.36 (d, *J* = 8.3 Hz, 2H), 4.52 (s, 2H), 2.46 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 145.2, 134.9, 133.5, 131.9, 130.9, 130.7, 129.4, 129.0, 128.9, 128.1, 127.6, 127.2, 126.5, 125.4, 21.5; HRMS calcd for $C_{20}H_{21}N_3NaO_5S$ ([M + Na^+]) 363.0779, found 463.0781. To a solution of **12** (313 mg, 0.92 mmol) in toluene (9.2 mL) was added TMS-imidazole (2.0 eq) at room temperature. After stirring for 5 min, the reaction mixture was added imidazole (2.0 eq) and stirring was continued at 55 °C. After 6 h, the reaction mixture was added 1.0 M citric acid in MeOH (6 mL) at room

temperature and stirred for further 1 h. The resulting solution was partitioned between saturated $NaHCO_3$ aq. (6 mL) and EtOAc (10 mL). The organic phase was collected and the aqueous phase was extracted with EtOAc (10 mL) twice. The combined organic extract was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (10 to 15%, EtOAc in *n*-hexane) to afford 2-naphthaldehyde (**13**, 90.3 mg, 0.58 mmol, 98%) as white powder. R*f* = 0.68 (*n*-hexane/EtOAc = 2:1, UV, Ce-PMA); Mp 58.5–59.0 °C; IR (neat, cm^{-1}) 1695, 1627, 1451, 1364, 1267; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.17 (dd, J = 7.3, 1.8 Hz, 1H), 8.35 (s, 1H), 8.02-7.91 (m, 4H), 7.67-7.58 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 192.2, 136.5, 134.5, 134.1, 132.6, 129.5, 129.1, 128.1, 127.1, 122.8; HRMS calcd for $C_{20}H_{21}N_3NaO_5S$ ([M^+]) 156.0575, found 156.0571.

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Notes and references

1 *Science of Synthesis*, ed. R. Brückner, Georg Thieme Verlag: Stuttgart, 2006; Vol. 25.

2 (a) R. A. W. Johnstone, in *Comprehenseive Organic Synthesis*, ed. B. M. Trost and I. Freming, Pergamon, Oxford, 1991, Vol 8, Parts 1.11, pp 259-281; (b) A. P. Davis, in *Comprehenseive Organic Synthesis*, ed. B. M. Trost and I. Freming, Pergamon, Oxford, 1991, Vol 8, Parts 1.12, pp 283-305.

3 (a) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 1936, 584-587; (b) E. Mosettig, *Org. React.*, 1954, **8**, 218-257.

4 (a) J. M. Grosheintz and H. O. L. Fischer, *J. Am. Chem. Soc.*, 1941, **63**, 2021-2022; (b) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, 1955, **55**, 511-549; (c) A. Reissert, *Ber.*, 1905, **38**, 1603-1614.

5 (a) M. S. Newman and E. G. Caflisch, Jr., *J. Am. Chem. Soc.*, 1958, **80**, 862-864; (b) M. Sprecher, M. Feldkimel and M. Wilchek, *J. Org. Chem.*, 1961, **26**, 3664-3666; (c) H. Babad, W. Herbert and A. W. Stiles, *Tetrahedron Lett.*, 1966, **7**, 2927-2931; (d) S. Cacchi and G. Paolucchi, *Gazz. Chim. Ital.*, 1974, **104**, 221-223; (e) C. C. Dudman, P. Grice and C. B. Reese, *Tetrahedron Lett.*, 1980, **21**, 4645-4648; (f) M. Nair and H. Shechter, *J. Chem. Soc., Chem. Commun.*, 1978, 793.

6 S. Matin, J. Craig and R. Chan, *J. Org. Chem.*, 1974, **39**, 2285-2289.

7 (a) A. Ruwet and M. Renson, *Bull. Soc. Chim. Belg.*, 1966, **75**, 157-168; (b) F. Bihel, M. Hellal and J.-J. Bourguignon, *Synthesis*, 2007, 3791-3796; (c) L. Grehn and U. Ragnarsson, *Tetrahedron*, 1999, **55**, 4843-4852; (d) U. Ragnarsson, L. Grehn, J. Koppel, O. Loog, O. Tšubrik, A. Bredikhin, U. Mäeorg and I. Koppel, *J. Org. Chem.*, 2005, **70**, 5916-5921; (e) K. Namba, Y. Kaihara, H. Yamamoto, H. Imagawa, K. Tanino, R. M. Williams and M. Nishizawa, *Chem. Eur. J.*, 2009, **15**, 6560-6563; (f) K. Namba, I. Shoji, M. Nishizawa and K. Tanino, *Org. Lett.*, 2009, **11**, 4970-4973.

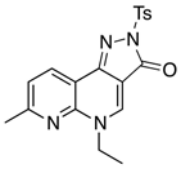
8 T. Toma, J. Shimokawa and T. Fukuyama, *Org. Lett.*, 2007, **9**, 3195-3197.

9 K. Kitahara, T. Toma, J. Shimokawa and T. Fukuyama, *Org. Lett.*, 2008, **10**, 2259-2261.

10 (a) T. Sato, I. Homma and S. Nakamura, *Tetrahedron Lett.*, 1969, **10**, 871-874; (b) A. G. Myers and P. J. Kukkola, *J. Am. Chem. Soc.*, 1990, **112**, 8208-8210; (c) A. G. Myers and B. Zheng, *J. Am. Chem. Soc.*, 1996, **118**, 4492-4493; (d) A. G. Myers and B. Zheng, *Tetrahedron Lett.*, 1996, **37**, 4841-4844; (e) A. G. Myers, M. Movassaghi and B. Zheng, *J. Am. Chem. Soc.*, 1997, **119**, 8572-8573; (f) D. A. Mundal, K. E. Lutz and R. J. Thomson, *J. Am. Chem. Soc.*, 2012, **134**, 5782-5785.

11 (a) A. Bugaut, K. Bathany, J.-M. Schmitter and B. Rayner, *Tetrahedron Lett.*, 2005, **46**, 687-690; (b) A. Bugaut, J.-J. Toulmé and B. Rayner, *Org. Biomol. Chem.*, 2006, **4**, 4082-4088.

12 Pure TMSI was necessary in the second step. In situ-generated TMSI afforded the five-membered cyclic sulfonyl hydrazone.



13 T. Kan and T. Fukuyama, *J. Chem. Soc., Chem. Commun.*, 2004, 353-359.

14 A. G. Myers, B. Zheng and M. Movassaghi, *J. Org. Chem.*, 1997, **62**, 7507-7507.

15 (a) M. Lischewski and G. Adam, *Tetrahedron Lett.*, 1974, **15**, 2835-2836; (b) M. Lischewski and G. Adam, *Tetrahedron Lett.*, 1975, **16**, 2569-2570.

16 D. della Bella, A. Carenzi, D. Chiarino, F. Pellacini, *Eur. Pat.* 87201313.1, Jan 27, 1987.

17 E. J. Glamkowski, G. Gal and M. Sletzinger, *J. Med. Chem.*, 1973, **16**, 176-177.

18 R. A. Gray, *Arch. Biochem. Biophys.*, 1959, **81**, 480-488.

19 (a) T. Y. Shen, S. Lucas, L. H. Sarett, A. Rosegray, G. W. Nuss, J. D. Willett, R. L. Ellis, F. W. Holly, A. R. Matzuk, A. N. Wilson, C. A. Winter, T. B. Windholz, E. A. Risley, C. H. Stammer, W. J. Holtz and B. E. Witzel, *J. Am. Chem. Soc.*, 1963, **85**, 488-489; (b) H. Yamamoto, *Bull. Chem. Soc. Jpn.*, 1967, **40**, 425-425.

20 (a) E. J. Corey, D. E. Cane and L. Libit, *J. Am. Chem. Soc.*, 1971, **93**, 7016-7021; (b) R. O. Hutchins, C. A. Milewski and B. E. Maryanoff, *J. Am. Chem. Soc.*, 1973, **95**, 3662-3668; (c) R. O. Hutchins, M. Kacher and L. Rua, *J. Org. Chem.*, 1975, **40**, 923-926; (d) G. W. Kabalka, D. T. C. Yang and J. D. Baker, Jr., *J. Org. Chem.*, 1976, **41**, 574-575; (e) G. W. Kabalka and J. H. Chandler, *Synth. Commun.*, 1979, **9**, 275-279; (f) A. G. Myers, N. S. Finney and E. Y. Kuo, *Tetrahedron Lett.*, 1989, **30**, 5747-5750; (g) A. G. Myers and N. S. Finney, *J. Am. Chem. Soc.*, 1990, **112**, 9641-9643.

21 An acyl anion intermediate was previously postulated for the McFadyen-Stevens reaction.[a] Although the formation of an anion intermediate from acyl diazene has yet to be completely excluded, Bumgardner's unsuccessful attempt to form the acyl anion by solvolysis of diacyl diazene[23] provided evidence that the acyl anion is not a plausible intermediate. Our DFT calculation also indicated that deprotonation of acyldiazene to give the corresponding anion (**CP10** to **CP11**) would not occur due to the high energy activation barrier (29.6 kcal/mol). Thus, the pathway from the acyldiazene anion via the acyl anion is not discussed. (a) D. Cram, J. Bradshaw, *J. Am. Chem. Soc.* **1963**, *85*, 1108-1118.

22 (a) L. Kalb and O. Gross, *Chem. Ber.*, 1926, **59**, 727-737; (b) R. Braslau, M. O. Anderson, F. Rivera, A. Jimenez, T. Haddad and J. R. Axon, *Tetrahedron*, 2002, **58**, 5513-5523; (c) T. Taniguchi, Y. Sugiura, H. Zaimoku and H. Ishibashi, *Angew. Chem. Int. Ed.*, 2010, **49**, 10154-10157; (d) T. Taniguchi, H. Zaimoku and H. Ishibashi, *Chem. Eur. J.*, 2011, **17**, 4307-4312; (e) S. Bath, N. M. Laso, H. Lopez-Ruiz, B. Quiclet-Sire and S. Z. Zard, *J. Chem. Soc., Chem. Commun.*, 2003, 204-205.

23 Bumgardner observed the formation of an acyl radical intermediate during solvolysis of diacyl diazene without employing an oxidant. C. L. Bumgardner, S. T. Purrington, P. T. Huang, *J. Org. Chem.* 1983, **48**, 2287-2289.

24 Kosower proposed a degradation pathway of phenyl diazene involving a bimolecular exchange of the hydrogen atom and subsequent release of dinitrogen. This proposal successfully explains Myers' result that the alkyl diazene decomposed via radical intermediate.[10e] (a) P. K. C. Huang, E. M. Kosower, *J. Am. Chem. Soc.* 1968, **90**, 2367. (b) A. G. Myers, M. Movassaghi, B. Zheng, *Tetrahedron Lett.* 1997, **38**, 6569-6572.

25 Hydroxy carbene is a well-known precursor to aldehyde,[a-c] and its mechanism was only recently understood. According to the seminal work by Schreiner,[d-g] isolated hydroxy carbene is slowly transformed into the corresponding aldehyde in an Ar matrix at 11 K via a proton tunneling mechanism. Tunneling is a slow process, and the energy barrier for the kinetic transformation path from the hydroxy carbene to the aldehyde is not always the most facile process compared to the route to the insertion to the neighboring C-H bond.[h,i]; (a) J. H. Plonka, P.S. Skell, *Tetrahedron Lett.* 1970, **52**, 4557-4560; (b) B. R. Weiner, R. N. Rosenfeld, *J. Org. Chem.* 1983, **48**, 5362-5364; (c) V. G. Kiselev, S. Swinnen, V. S. Nguyen, N. P. Gritsan, M. T. Nguyen, *J. Phys. Chem. A* 2010, **114**, 5573-5579; (d) P. R. Schreiner, H. P. Reisenauer, F. C. Pickard IV, A. C. Simmonett, W. D. Allen, E. Mátyus, A. G. Császár, *Nature* 2008, **453**, 906-909; (e) G. Bucher, *Angew. Chem. Int. Ed.* 2008, **47**, 6957-6958; (f) D. Gerbig, H. P. Reisenauer, C. H. Wu, D. Ley, W. D. Allen, P. R. Schreiner, *J. Am. Chem. Soc.* 2010, **132**, 7273-7275; (g) D. Ley, D. Gerbig, J. P. Wagner, H. P. Reisenauer, P. R. Schreiner, *J. Am. Chem. Soc.* 2011, **133**, 13614-13621; (h) P. R. Schreiner, H. P. Reisenauer, D. Ley, D. Gerbig, C. H. Wu, W. D. Allen, *Science* 2011, **332**, 1300-1303; (i) D. Gerbig, D. Ley, H. P. Reisenauer, P. R. Schreiner, *Beilstein J. Org. Chem.* 2010, **6**, 1061-1069.

26 It is well known that the opening of the 2-phenyl cyclopropane carbinyl radical ($k = 1.3 \times 10^8\ s^{-1}$) is a more rapid process than intermolecular delivery of a hydrogen, which would lead to a more thermodynamically stable benzyl radical in our case. Here the absence of the opening of cyclopropane disagrees with the formation of an acyl radical intermediate. B. Maillard, D. Forrest, K. U. Ingold, *J. Am. Chem. Soc.* **1976**, *98*, 7024-7026.

27 Hydroxy carbene is known to have a high intersystem crossing and exists solely in the singlet form.[25d]

28 F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1987, S1.

29 The reactivity of a similar singlet carbene species, siloxy carbene, has been well documented.[a-c] Alcohols to react with siloxy carbene via the protonation followed by a combination of the resulting alkoxide and carbocation. Pyridines are also known to react rapidly ($k > 5.0 \times 10^6\ s^{-1}$ at 20 °C)[d] to give the ylide intermediate. The reaction between the carbene intermediate and alcohol functionality should be involved in the mechanism for the traditional McFadyen-Stevens reaction performed in ethylene glycol as a solvent.[e-h] (a) M. E. Scheller, G. Iwasaki, B. Frei, *Helv. Chim. Acta* 1986, **69**, 1378-1394; (b) M. E. Scheller, B. Frei, *Helv. Chim. Acta* 1984, **67**, 1734-1747; (c) K. Ito, H. Tamashima, N. Iwasawa, H. Kusama, *J. Am. Chem. Soc.* 2011, **133**, 3716-3719; (d) H. M. Perrin, W. R. White, M. S. Platz, *Tetrahedron Lett.* 1991, **32**, 4443-4446; (e) J. P. Pezacki, P. D. Wood, T. A. Gadosy, J. Lusztyk, J. Warkentin, *J. Am. Chem. Soc.* 1998, **120**, 8681-8691; (f) J. P. Pezacki, *Can. J. Chem.* 1999, **77**, 1230-1240; (g) S. Celebi, S. Leyva, D. A. Modarelli, M. S. Platz, *J. Am. Chem. Soc.* 1993, **115**, 8613-8620; (h) C.-S. Ge, E. G. Jang, E. A. Jefferson, W. Liu, R. A. Moss, J. Włostowska, S. Xue, *J. Chem. Soc., Chem. Commun.* 1994, 1479-1480.

30 All attempts of the reaction of the carbene intermediate via intramolecular cyclopropanation or C-H insertion as well as the intermolecular trapping with stylene, allylsulfide, or elemental sulfur were unsuccessful in our case.

31 M. J. Frisch, *et al.* Gaussian 09, revision C.01; Gaussian, Inc., Wallingford CT, 2009. Full citation within the Supporting Information.

32 (a) K. Ohno and S. Maeda, *Chem. Phys. Lett.*, 2004, **384**, 277-282; (b) S. Maeda and K. Ohno, *J. Phys. Chem. A*, 2005, **109**, 5742-5753; (c) X. Yang, S. Maeda and K. Ohno, *J. Phys. Chem. A*, 2005, **109**, 7319-7328; (d) K. Ohno and S. Maeda, *J. Phys. Chem. A*, 2006, **110**, 8933-8941; (e) X. Yang, S. Maeda and K. Ohno, *Chem. Phys. Lett.* 2006, **418**, 208-216; (f) S. Maeda and K. Ohno, *J. Phys. Chem. A*, 2007, **111**, 4527-4534; (g) Y. Watanabe, S. Maeda and K. Ohno, *Chem. Phys. Lett.*, 2007, **447**, 21-26; (h) X. Yang, S. Maeda and K. Ohno, *J. Phys. Chem. A*, 2007, **111**, 5099-5110.

33 (a) Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215-241; (b) Y. Zhao and D. G. Truhlar, *Acc. Chem. Res.*, 2008, **41**, 157-167.

34 (a) K. Fukui, *Acc. Chem. Res.*, 1981, **14**, 363-368; (b) K. Ishida, K. Morokuma and A. Komornicki, *J. Chem. Phys.*, 1977, **66**, 2153-2156; (c) C. Gonzalez and H. B. Schlegel, *J. Chem. Phys.*, 1989, **90**, 2154-2161; (d) C. Gonzalez and H. B. Schlegel, *J. Phys. Chem.*, 1990, **94**, 5523-5527.