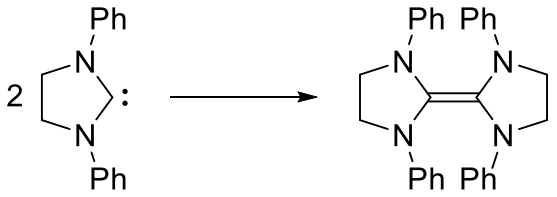
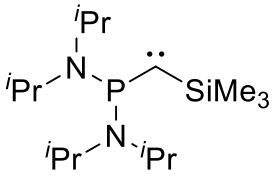
Generation and Reactivity of Hydroxycarbenes in Solution

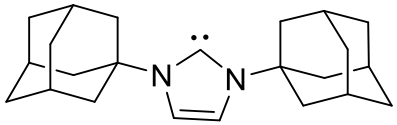
555th group seminar presented by
Felix Keul

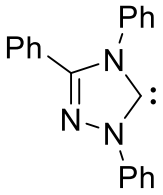
July 16th, 2021

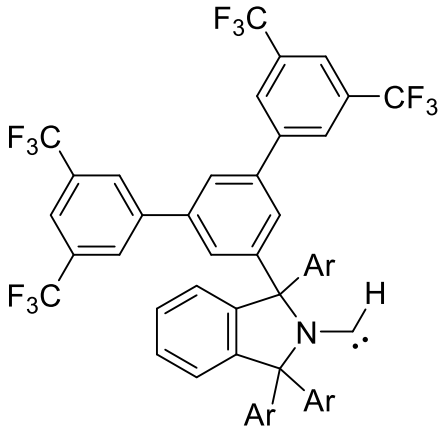
Institute of Organic Chemistry
Justus-Liebig University Giessen





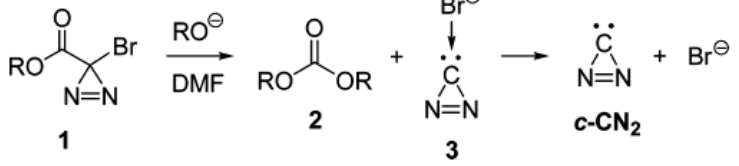


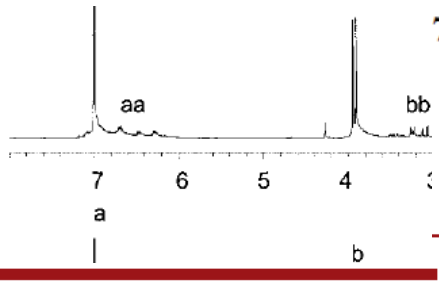


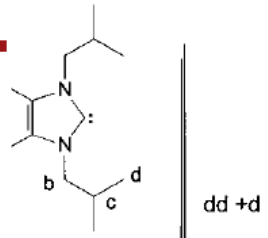


H. W. Wanzlick, *Angew. Chem. Int. Ed.*, **1962**, *74*, 129-134; A. Igau, H. Grützmacher, A. Baceiredo, G. Bertrand, *J. Am. Chem. Soc.*, **1988**, *110*, 6463-6466; A. J. Arduengo III, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.*, **1991**, *113*, 361-363; D. Enders, K. Breuer,G. Raabe, J. Runsink,J. H. Teles, J. P. Melder, K. Ebel, S. Brode, *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 1021-1023; R. Nakano, R. Jazzar, G. Bertrand, *Nature Chem.*, **2018**, *10*, 1196-1200

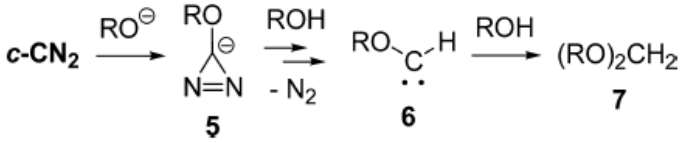
Scheme 1. Reaction of Esters 1 with Alkoxide Ions



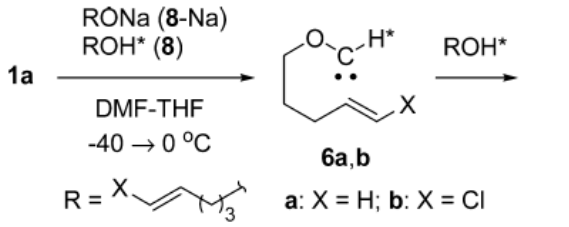


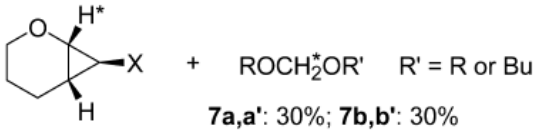


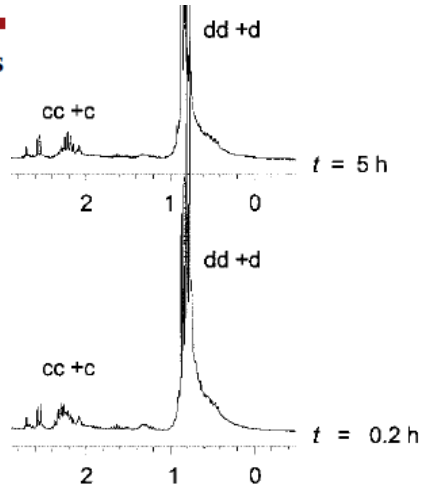
Scheme 2. Proposed Mechanism of the Formation of Acetals 7 in the Presence of Alcohols



Scheme 3. Proposed Mechanism of the Formation of Acetals 7 and Bicycles 9 in the Presence of Pentenols 8

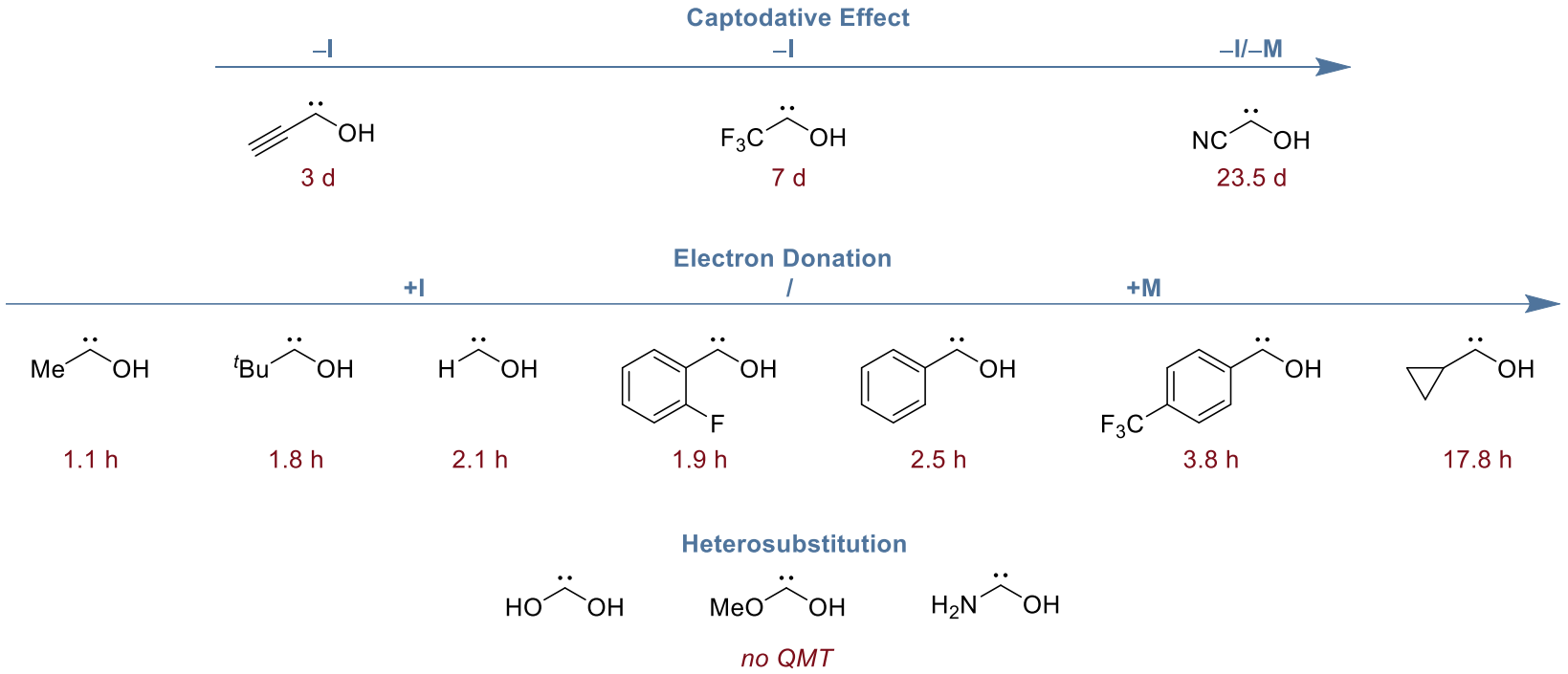






tra (200 MHz, [D8]toluene) of (**3 d**)2

W. M. Jones, *Accounts Chem. Res.*, **1977**, *10*, 353-359; F. Ekkehardt Hahn, L. Wittenbecher, D. Le Van, R. Fröhlich, *Angew. Chem. Int. Ed.*, **2000**, *39*, 541-544; E. Hanzlocá, R. Navrátil, Jan Cejka, S. Böhm, T. Martinu, Org. Lett., **2014**, *16*, 852-855



P. R. Schreiner, H. P. Reisenauer, F. C. Pickard IV, A. C. Simmonett, W. D. Allen, E. Mátys, A. G. CSászár, *Nature*, **2008**, *453*, 906-909; P. R. Schreiner, H. P. Reisenauer, D. Ley, D. Gerbig, C.-H. Wu, W. D. Allen, *Science*, **2011**, *332*, 1300-1303; D. Ley, D. Gerbig, P. R. Schreiner, *Chem. Sci.*, **2013**, *4*, 677-684; D. Ley, D. Gerbig, J. P. Wagner, H. P. Reisenauer, P. R. Schreiner, *J. Am. Chem. Soc.*, **2011**, *133*, 13614-13621; A. Mardyukov, H. Quanz, P. R. Schreiner, *Nature Chem.*, **2017**, *9*, 71-76; D. Gerbig, H. P. Reisenauer, C. H. Wu, D. Ley, W. D. Allen, P. R. Schreiner; *J. Am. Chem. Soc.*, **2010**, *132*, 7273-7275; P. R. Schreiner, H. P. Reisenauer, *Angew. Chem. Int. Ed.*, **2008**, *47*, 7071-7074; A. K. Eckhardt, P. R. Schreiner, *Angew. Chem. Int. Ed.*, **2018**, *57*, 5248-5252; A. K. Eckhardt, F. R. Erb, P. R. Schreiner, *Chem. Sci.*, **2018**, *10*, 802-808

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Modified McFadyen–Stevens reaction for a versatile synthesis of aliphatic/aromatic aldehydes: design, optimization, and mechanistic investigations†

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Yuri Iwai, Takashi Ozaki, Ryo Takita, Masanobu Uchiyama, Jun Shimokawa and Tohru Fukuyama*

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.

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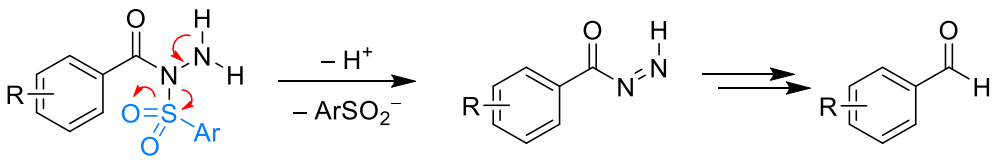
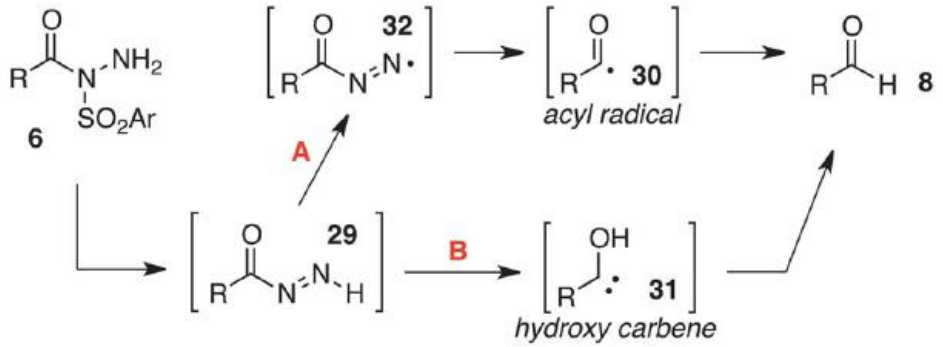
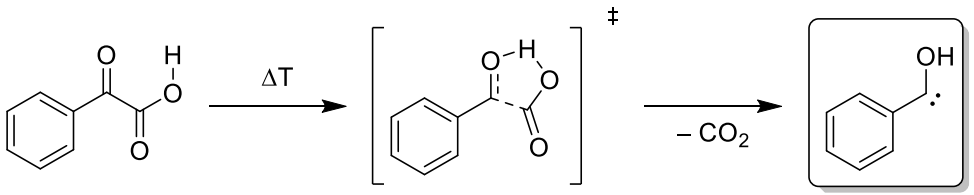


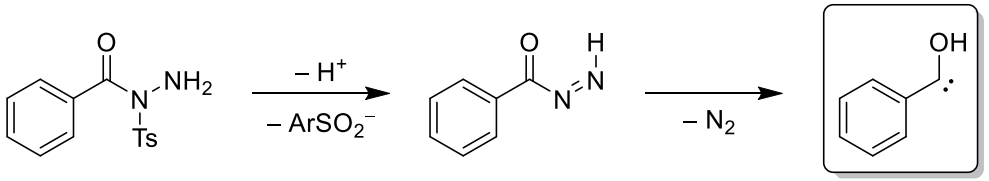


Scheme 4 Possible reaction pathway of our modified McFadyen–Stevens reaction.

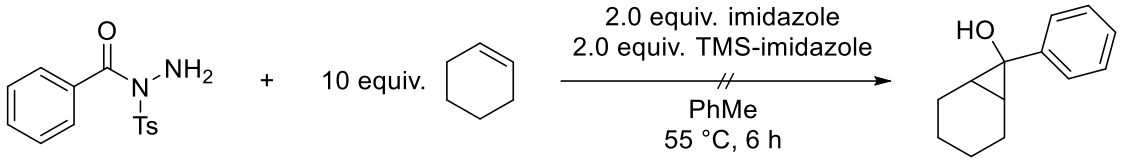
Method for preparation of hydroxycarbenes in gas-phase



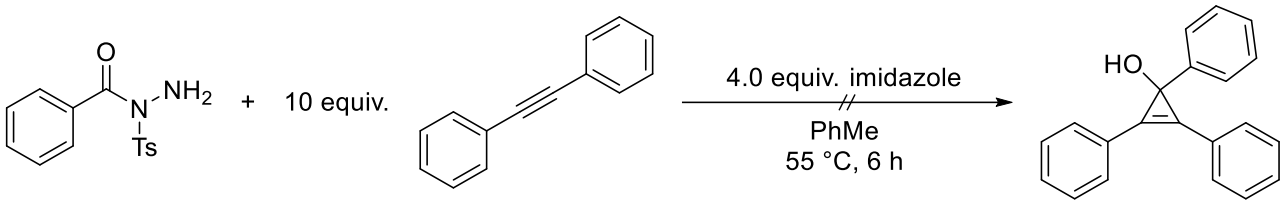
Method for preparation of hydroxycarbenes in solution

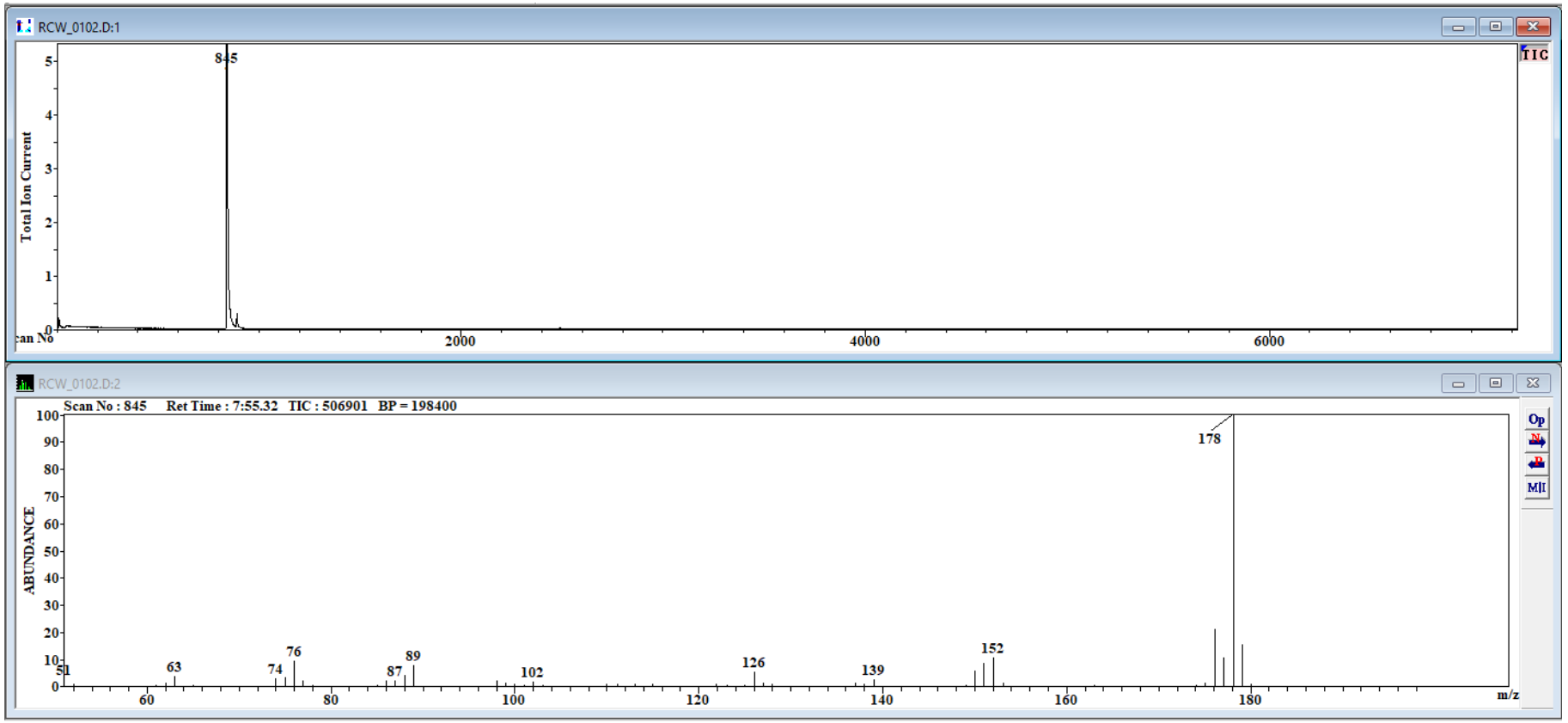


- Cyclohexene

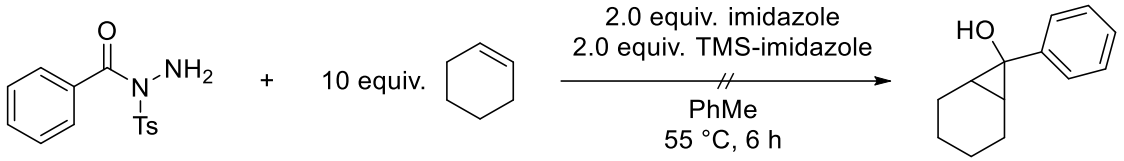


Trapping with cyclopropylation reaction

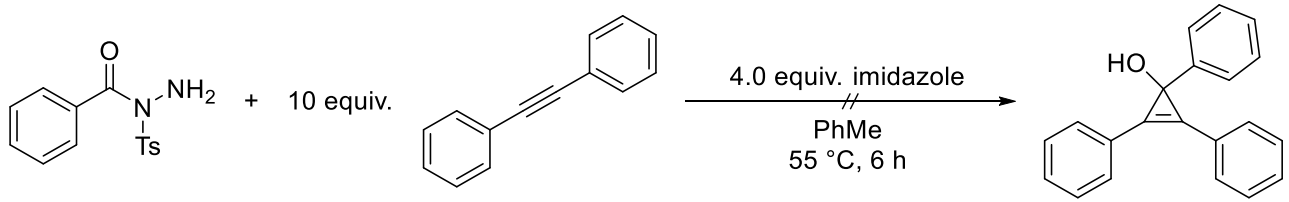




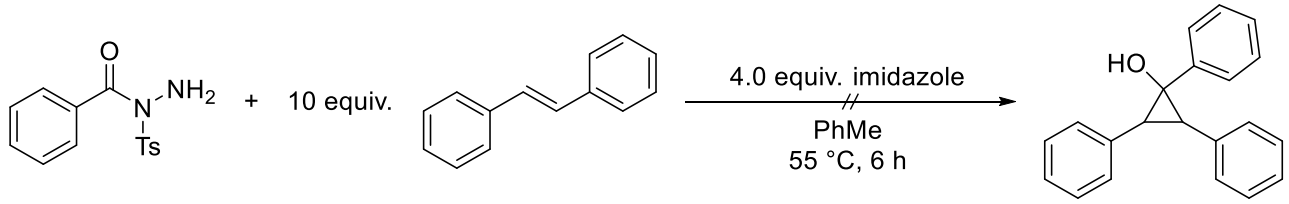
- Cyclohexene



- Diphenylacetylene



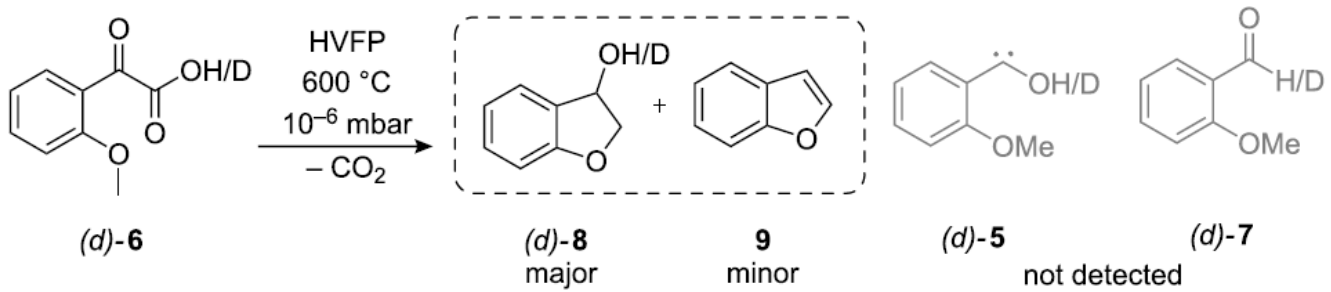
- Stilbene



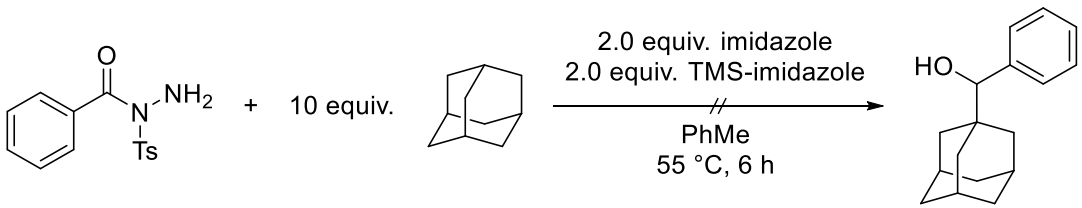
Beilstein Journal of Organic Chemistry

Intramolecular hydroxycarbene C–H-insertion: The curious case of (*o*-methoxyphenyl)hydroxycarbene

Dennis Gerbig, David Ley, Hans Peter Reisenauer and Peter R. Schreiner*



Scheme 3: Attempted generation of **5** and *d*-**5** as well as their corresponding insertion products.


O
NH2
N
Ts
+
10 equiv.
2.0 equiv. imidazole
2.0 equiv. TMS-imidazole
PhMe
55 °C, 6 h
HO

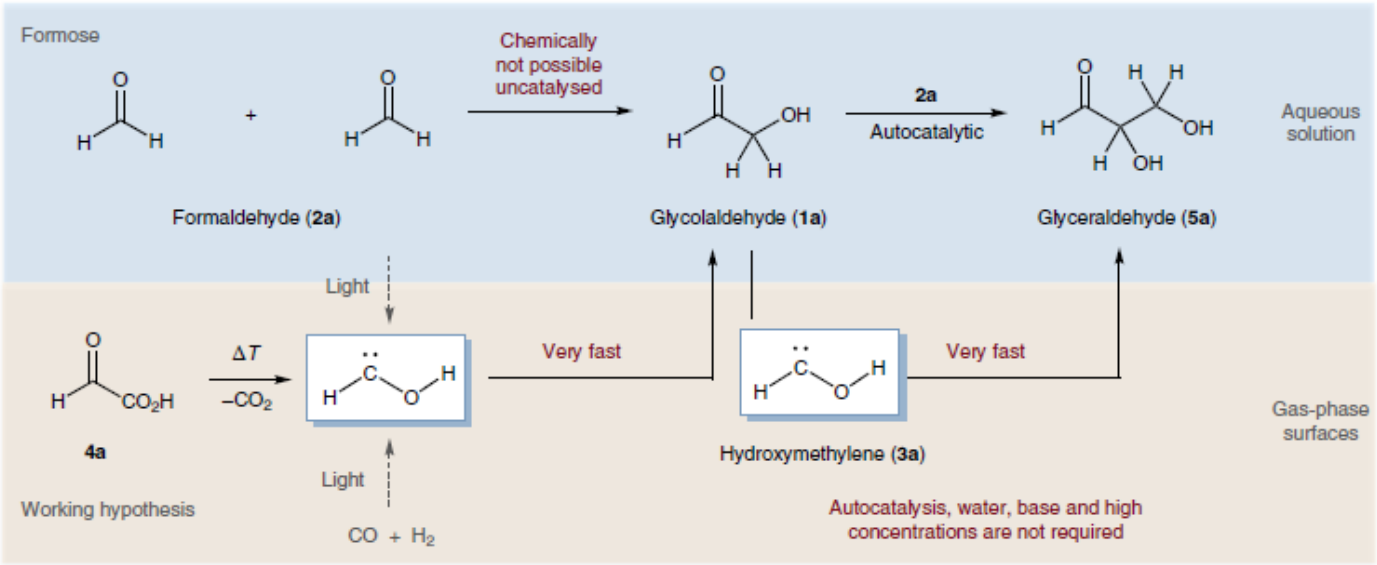


Fig. 1 | Mechanistic hypotheses related to sugar formation from formaldehyde. Simplified depiction of the traditional autocatalytic (with glycolaldehyde (**1a**)) formose reaction (top half) in aqueous media in the presence of base at ambient temperatures, and the proposed new reaction path via hydroxymethylene (**3a**) (bottom half) in the gas phase or on surfaces. Note that the initiation step in the formose reaction for the formation of the first molecule of **1a** is chemically not possible in an uncatalysed fashion.

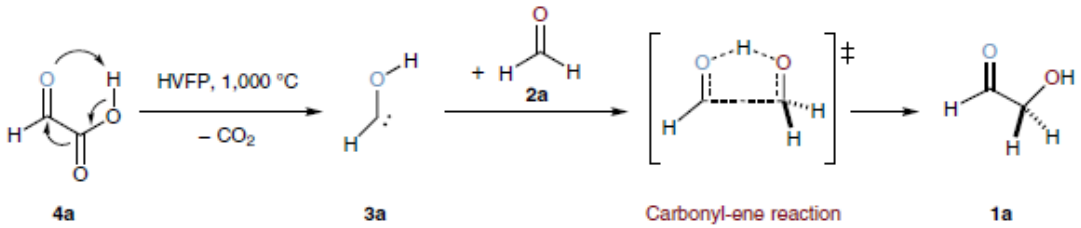
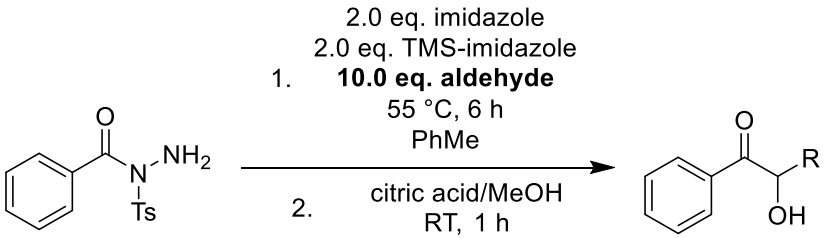
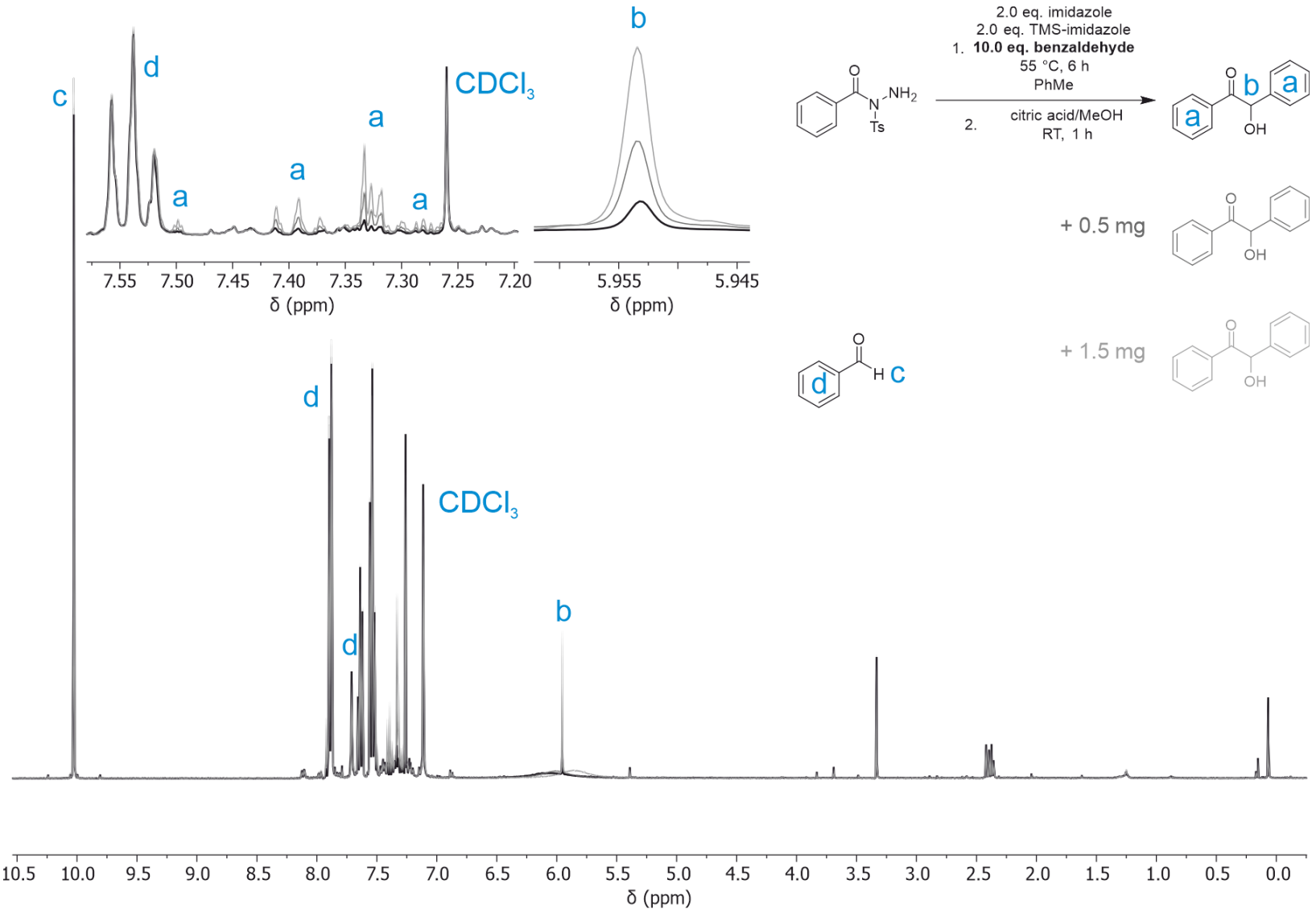


Fig. 2 | Mechanistic hypothesis for the uncatalysed 'carbonyl–ene' reaction. Formaldehyde (**2a**) reacts with hydroxymethylene (**3a**), generated from glyoxylic acid (**4a**) via CO_2 extrusion, to give glycolaldehyde (**1a**). Note the exchange of atoms from starting materials to products. The C=O and C–OH oxygen atoms have changed places. HVFP, high-vacuum flash pyrolysis.

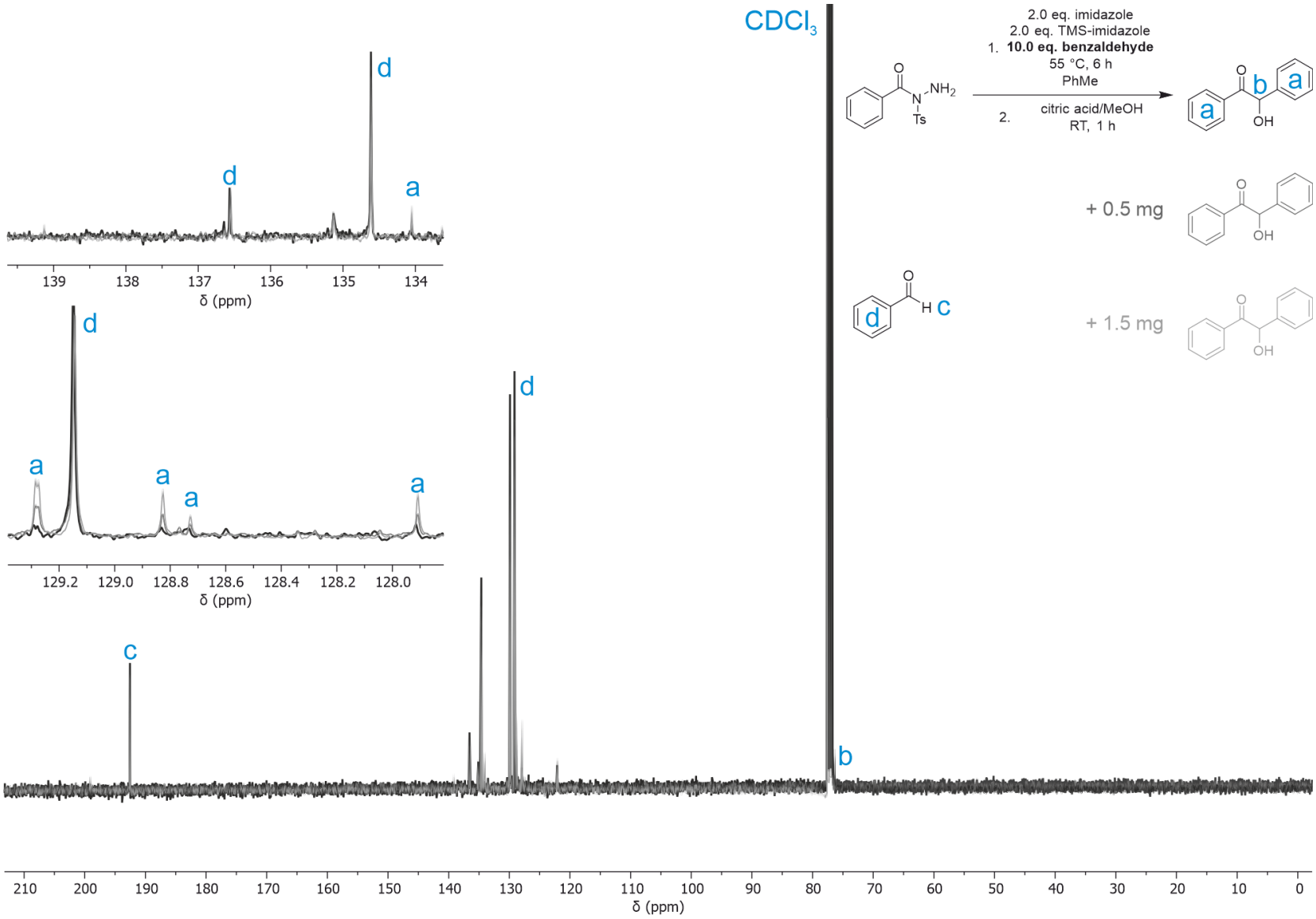

2.0 eq. imidazole
2.0 eq. TMS-imidazole
1. 10.0 eq. aldehyde
55 °C, 6 h
PhMe
2. citric acid/MeOH
RT, 1 h
O
NH2
N
Ts
O
R
OH

Trapping with benzaldehyde

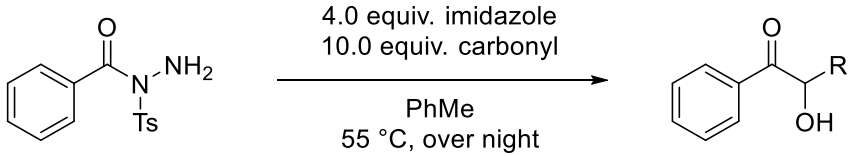


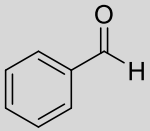
^{1}H-NMR 400 MHz

Trapping with benzaldehyde

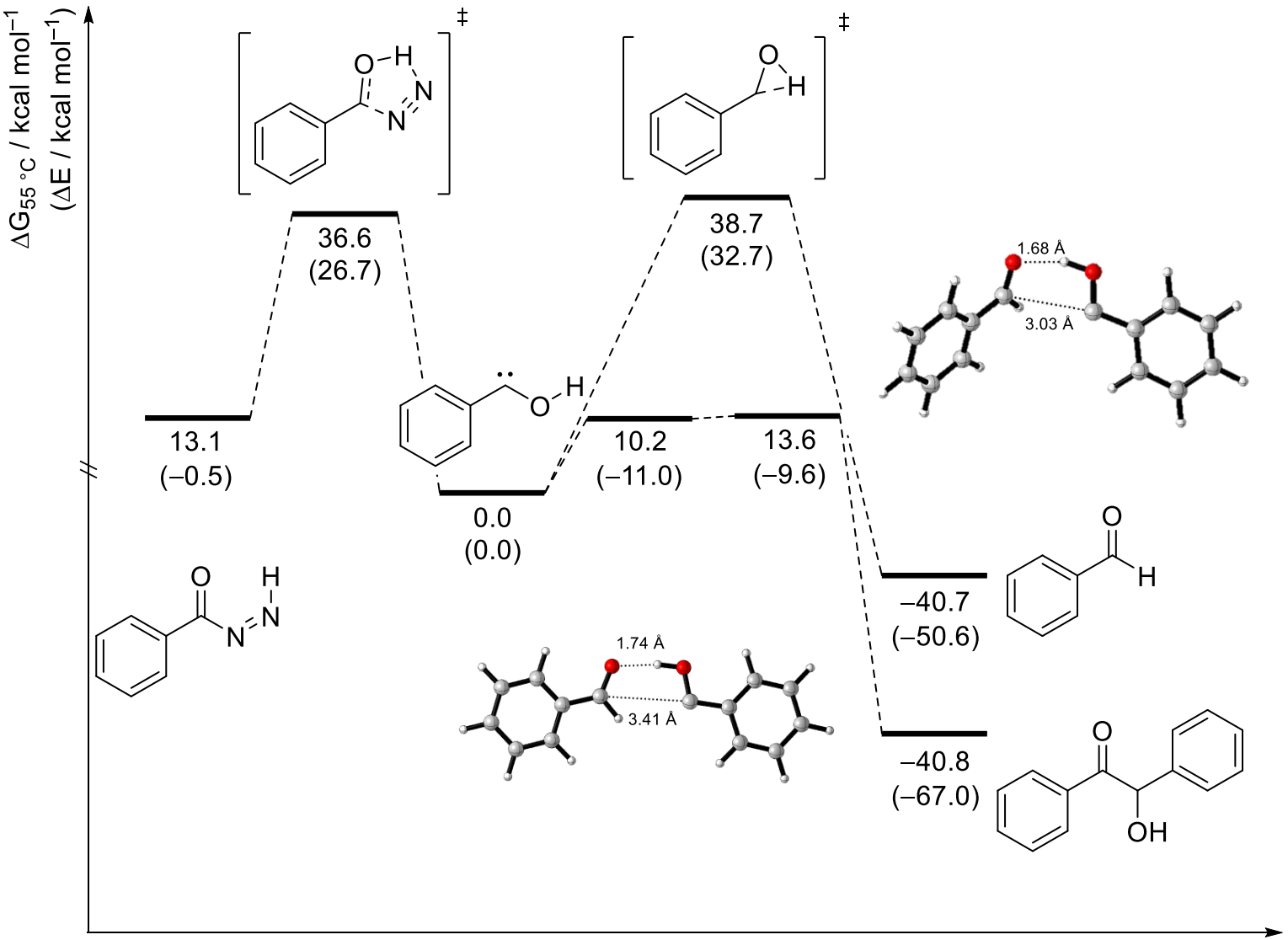


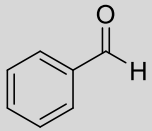
^{13}C-NMR 100 MHz



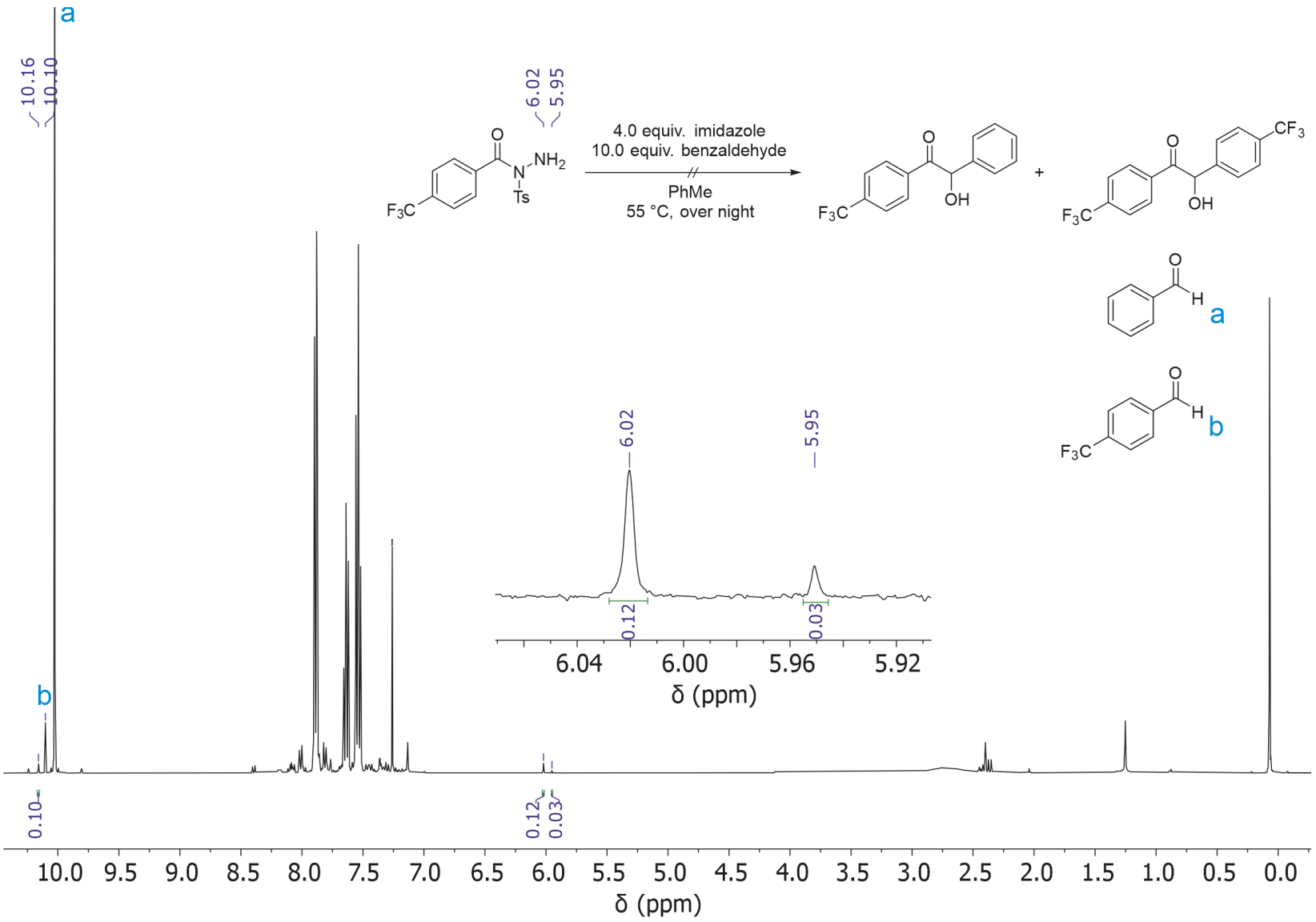
Carbonyl source	yield[a]
	6%
	15%
	-
	-

[a]yields determined with *p*-nitrobenzaldehyde as internal standard (0.1 equiv., 0.034 mmol)

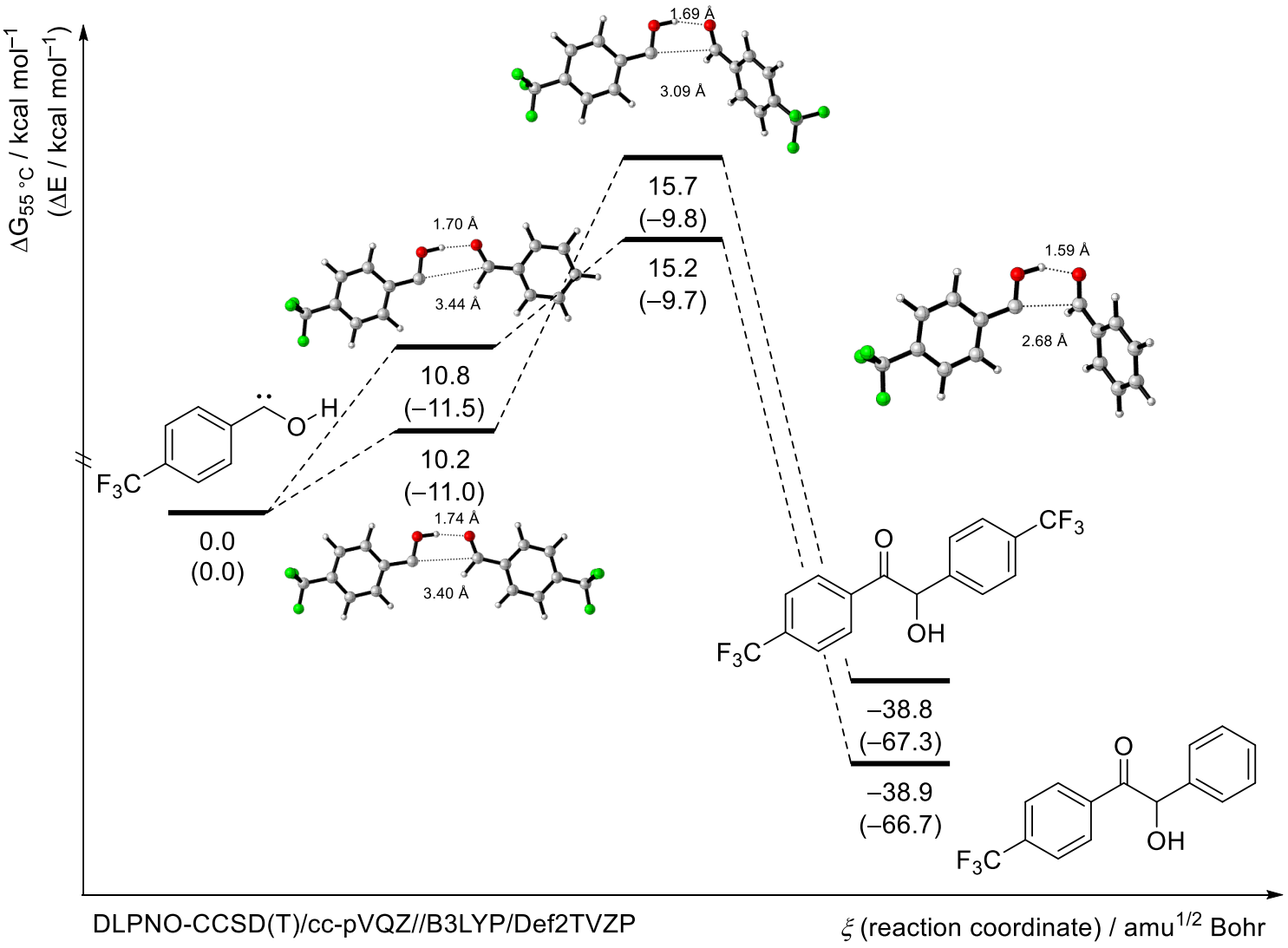

ΔG55 °C / kcal mol−1
(ΔE / kcal mol−1)
36.6
(26.7)
38.7
(32.7)
13.1
(–0.5)
0.0
(0.0)
10.2
(–11.0)
13.6
(–9.6)
–40.7
(–50.6)
–40.8
(–67.0)
1.68 Å
3.03 Å
1.74 Å
3.41 Å
DLPNO-CCSD(T)/cc-pVQZ//B3LYP/Def2TVZP
ξ (reaction coordinate) / amu1/2 Bohr

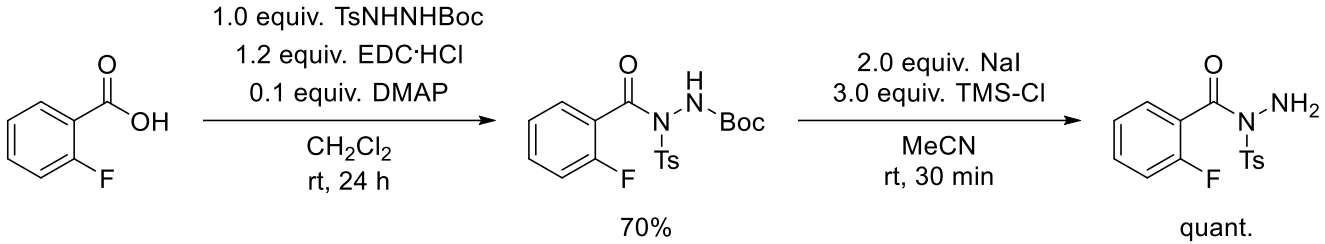
Carbonyl source	C_s-complex	Transition State	$\Delta\Delta G_{55°C}$
	10.2	13.6	3.4
	10.8	-	-
	10.3	12.7	2.4

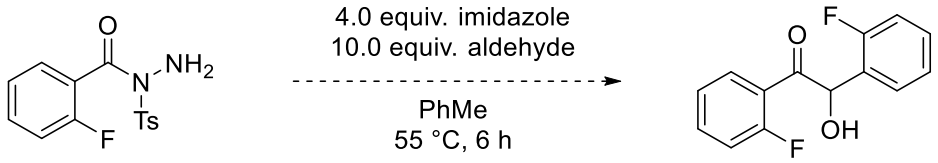
DLPNO-CCSD(T)/cc-pVQZ//B3LYP/Def2TZVP

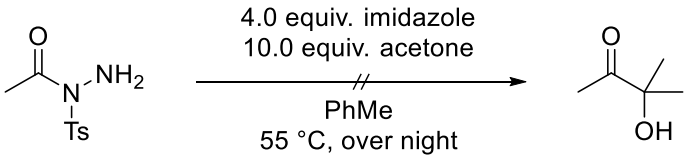


^{1}H-NMR 400 MHz


ΔG55 °C / kcal mol−1
(ΔE / kcal mol−1)
1.69 Å
3.09 Å
15.7
(–9.8)
15.2
(–9.7)
1.70 Å
3.44 Å
1.59 Å
2.68 Å
10.8
(–11.5)
10.2
(–11.0)
F3C
O
H
0.0
(0.0)
1.74 Å
3.40 Å
CF3
O
OH
F3C
–38.8
(–67.3)
–38.9
(–66.7)
O
OH
F3C
DLPNO-CCSD(T)/cc-pVQZ//B3LYP/Def2TVZP
ξ (reaction coordinate) / amu1/2 Bohr


1.0 equiv. TsNHNHBoc
1.2 equiv. EDC·HCl
0.1 equiv. DMAP
CH2Cl2
rt, 24 h
70%
2.0 equiv. NaI
3.0 equiv. TMS-Cl
MeCN
rt, 30 min
quant.


4.0 equiv. imidazole
10.0 equiv. aldehyde
PhMe
55 °C, 6 h



- Trapping as acetoine was not successful
- Acetone as solvent

- Tunneling half life of 1.1 h
- Low boiling point of carbene?

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Spectroscopic identification of the phenyltelluryl radical and its reactivity toward molecular oxygen†

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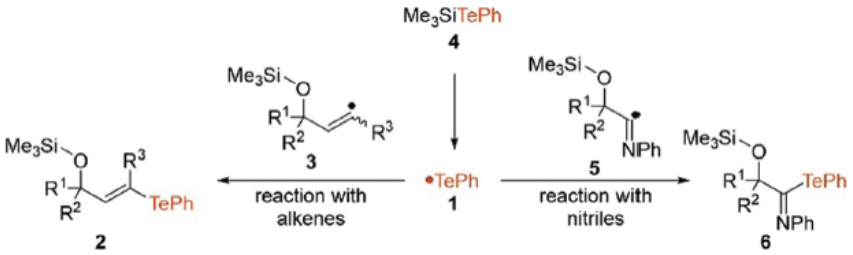
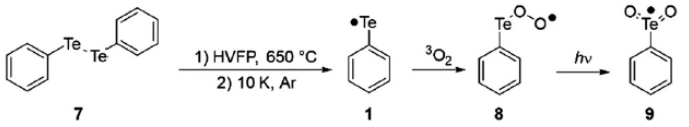
The phenyltelluryl radical was prepared by high-vacuum flash pyrolysis of diphenyl ditelluride and was chacracterized by matrix isolation IR and UV/Vis spectroscopy. After doping the matrix with molecular oxygen and allowing bimolecular reactions, the hitherto unkown phenyltelluro peroxy radical formed and was identified *via* IR spectroscopy. Irradiation with light at λ = 436 nm leads to isomerization to the thermodynamically more stable novel phenyltelluroyl radical. All experimental findings agree well with density functional theory (UB3LYP/Def2QZVPP and UM06-2X/Def2QZVPP) computations.



Scheme 1 A selection of synthetic applications of reactions with organotellurium compounds.



Scheme 2 The phenyltelluryl radical **1** generated by high-vacuum flash pyrolysis (HVFP) of diphenyl ditelluride **7** and subsequent trapping and isolation in an inert argon matrix 10 K. Warming in a matrix doped with molecular oxygen leads to the phenyltelluride peroxy radical **8** that photochemically isomerizes to the phenyltelluroyl radical **9**.

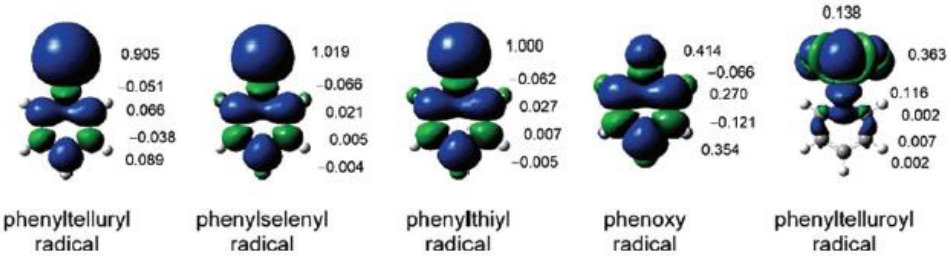
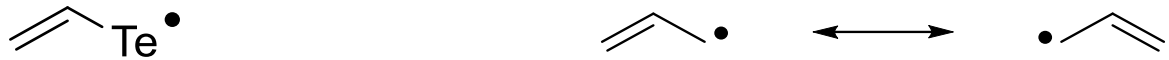
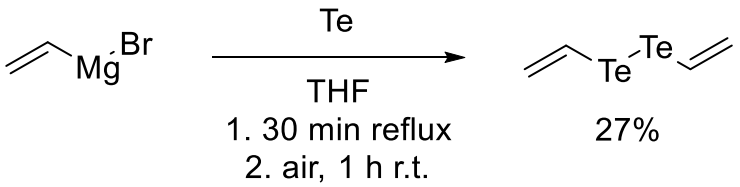


Fig. 3 Computed spin densities of **1**, the phenylselenyl, phenylthiyl, phenoxy, and phenyltelluroyl radicals at UB3LYP/Def2QZVPP. The chalcogen atom is at the top in all cases.





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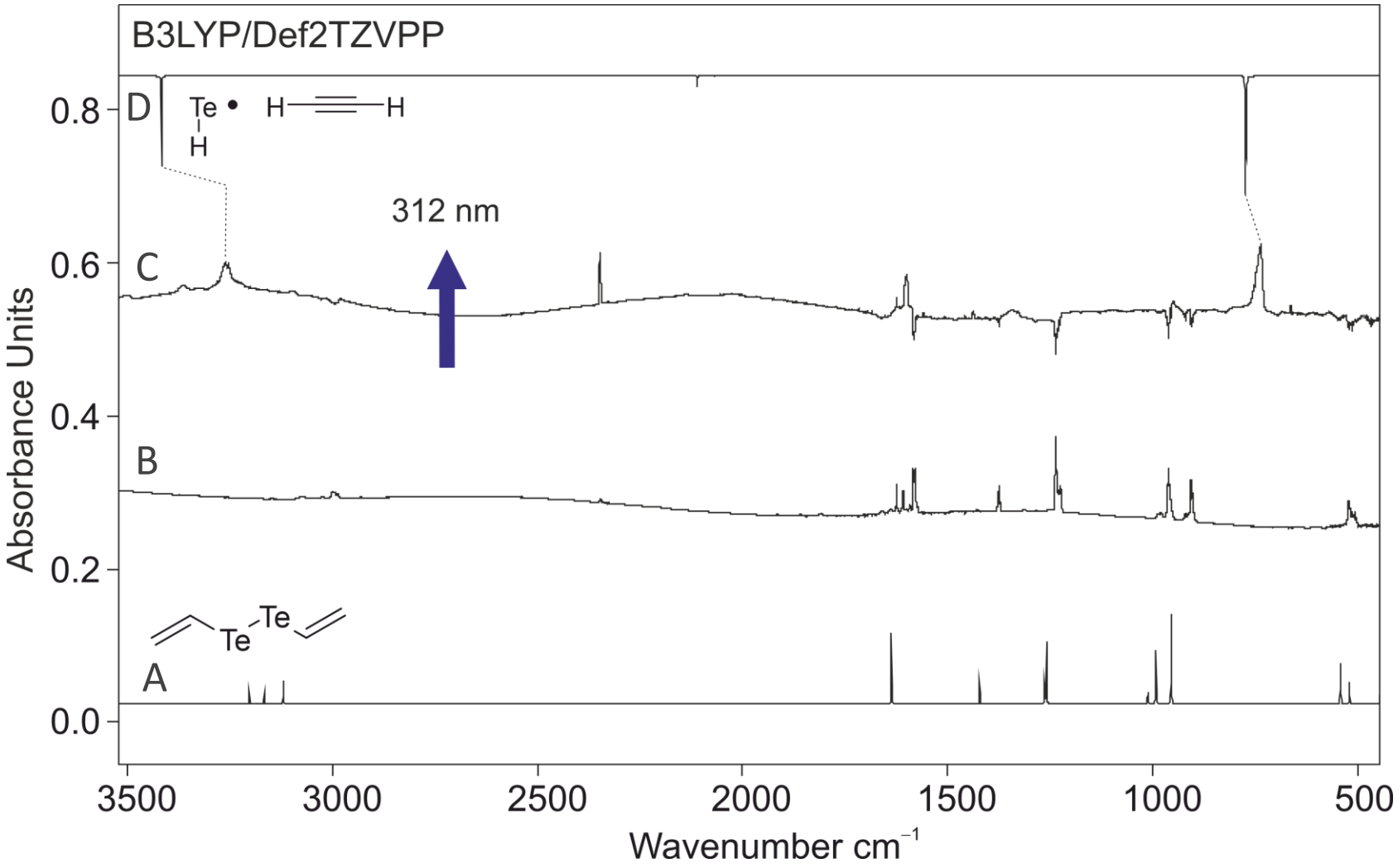
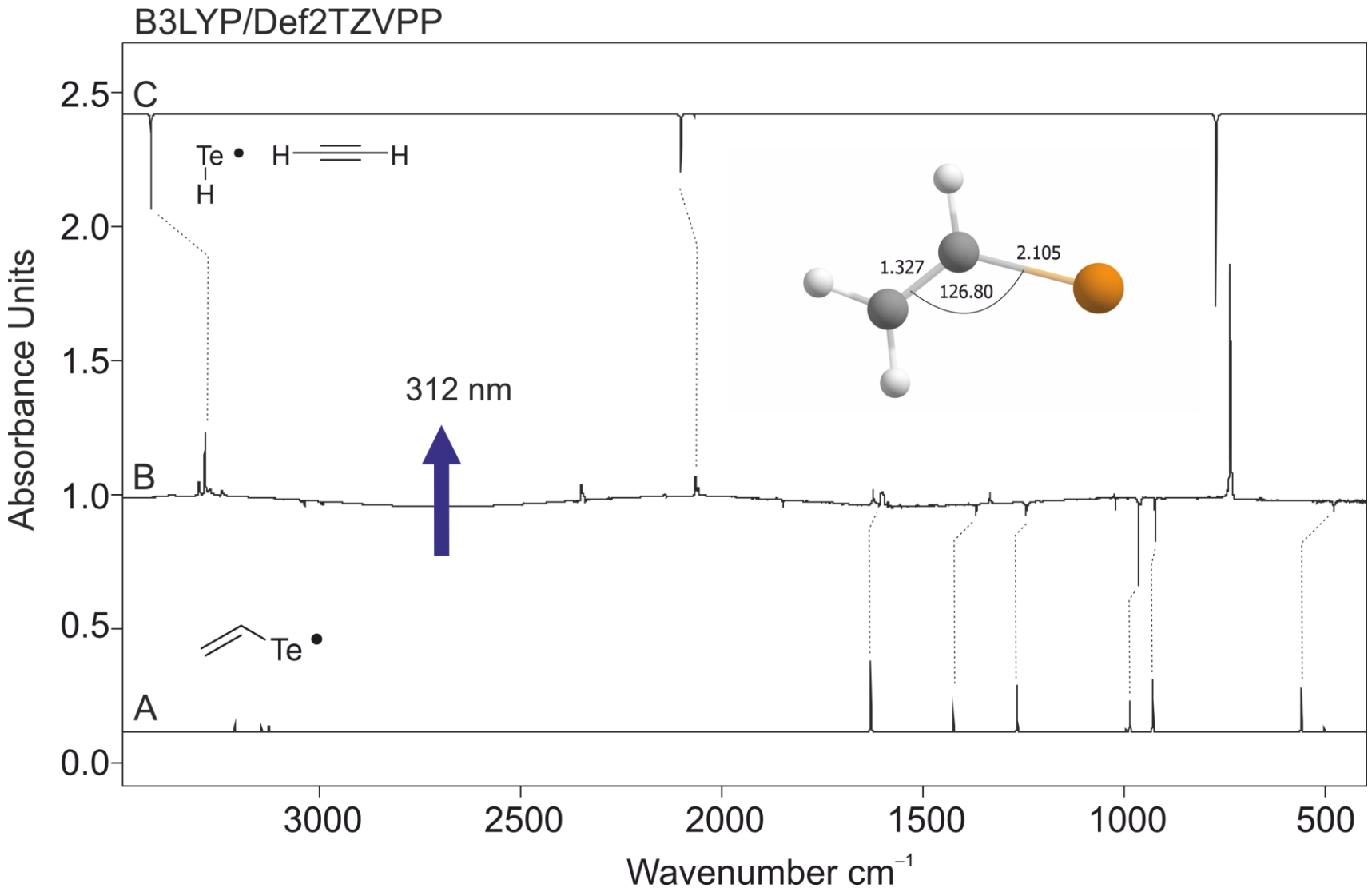
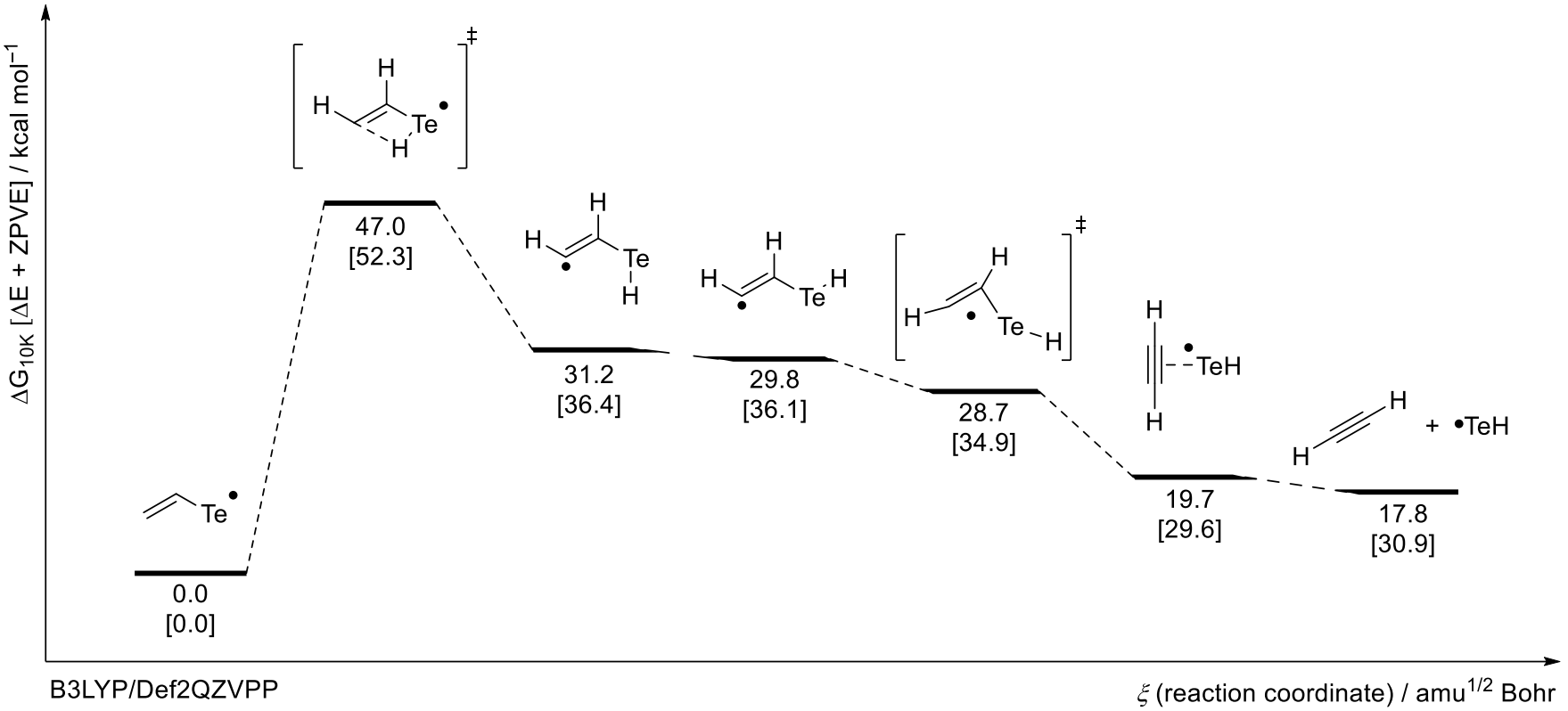
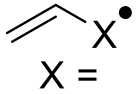

B3LYP/Def2TZVPP
D
Te
H
H
H
312 nm
C
B
A
Te
Te
Absorbance Units
0.0
0.2
0.4
0.6
0.8
3500
3000
2500
2000
1500
1000
500
Wavenumber cm⁻¹


B3LYP/Def2TZVPP
C
B
A
Te
H
H
H
312 nm
1.327
2.105
126.80
Te
Absorbance Units
2.5
2.0
1.5
1.0
0.5
0.0
3000
2500
2000
1500
1000
500
Wavenumber cm⁻¹


ΔG10K [ΔE + ZPVE] / kcal mol−1
0.0
[0.0]
47.0
[52.3]
31.2
[36.4]
29.8
[36.1]
28.7
[34.9]
19.7
[29.6]
17.8
[30.9]
+ •TeH
B3LYP/Def2QZVPP
ξ (reaction coordinate) / amu1/2 Bohr

 X =	BDE [kcal mol^{-1}]	Spin density[a]
Te	47.2	1.014
Se	51.3	1.008
S	56.6	0.985
O	–16.0	0.348

[a]located at the chalcogen radical

X	ΔH_r [kcal mol^{-1}]
Te	14.3
Se	6.0
S	- 1.6
O	3.3
CH_2	0.0

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